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Doctoral Dissertation

Effectiveness of an educational training program on skin reactions induced by immunotherapies, Epidermal Growth Factor Inhibitors (EGFRI) treatments, and chemotherapies: A pilot study

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Limassol, 2023

CYPRUS UNIVERSITY OF TECHNOLOGY

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DEPARTMENT OF NURSING

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Approval Form

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ABSTRACT

Introduction: Pruritus, rash, and photosensitivity are among the most prevalent skin reactions observed to individuals undertaking immunotherapies, Epidermal Growth Factor Receptor Inhibitor (EGFRI) treatments and chemotherapies. The incidence of immunotherapy-induced pruritus to this group ranges from 3.0% to 30.7%, while skin rash occurs in 50–100% of patients treated with EGFRI. In the same pattern, the percentage of skin photosensitivity ranges from 22.2% to 66.7% in patients treated with chemotherapeutic drugs.

These three types of skin reactions, have both a physical and a psychological impact on the patients, affect their Quality of Life (QoL) and in severe cases can lead to either a treatment dose reduction or delay in treatment dose optimization or even discontinuation of cancer treatment.

Numerous medications are used to manage and/or treat pruritus, rash, and photosensitivity with primary pharmacological choices being the corticosteroids and antibiotics. A large gap in the scientific literature exists though regarding non-pharmaceutical methods, products and practices that are used for the management of the aforementioned skin reactions. Such options, i.e. an effective personalized educational/training program could benefit cancer patients treated with immunotherapy, EGFRI treatment and chemotherapy that suffer from skin reactions and for any reason cannot receive a conventional pharmacological intervention.

Aim: The present study aims to evaluate the effectiveness of an individualized educational program for cancer patients who developed skin reactions (pruritus, rash or photosensitivity) induced by chemotherapy, EGFRI treatment, or immunotherapy.

Sample and Method: This was a pilot study designed to determine the effectiveness of the intervention - here the educational program - for cancer patients who developed pruritus, rash or photosensitivity induced by chemotherapy, EGFRI treatment, or immunotherapy. The study was conducted between 01/2019 and 12/2020 and included 40 patients undertaking chemotherapy, EGFRI treatment or immunotherapy treatment, that were at the onset of the symptoms of pruritus, rash or photosensitivity. The patients were randomly allocated into two groups, the intervention and the control group, and their progress was monitored.

Induction day to the study for each participant was considered the day of symptoms initiation and this day marked the start of week zero to the program for each patient. During this week, the patients in the intervention group, signed the program's consent form and received written educational material (in the form of a booklet) and had their first educational training session, conducted by one of the researchers. The same patients were assigned to attend the educational program individually once weekly, for a total of four consecutive weeks. On the other hand, patients in the control group did not receive the educational material or the training session. Instead they received the standard information provided to any cancer patient who is about to initiate a therapeutic scheme such as chemotherapy, EGFRI treatment or immunotherapy treatment.

For this study's primary endpoint, repeated measurements were taken weekly (starting from week zero) regarding the grade of skin reaction according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v 5.0).

For the secondary objectives of the study, the health-related quality of life (HR-QoL) of the patients were evaluated. This was achieved via the use of questionnaires; the generic Short Form 36 questionnaire (SF-36 questionnaire) and the more targeted Dermatology Life Quality Index questionnaire (DLQI questionnaire). More specifically, the SF-36 questionnaire was utilized from week zero up to the end of week three, while the DLQI questionnaire was filled from week one and onward. Additionally, information regarding emergency admissions of the patients and possible treatment dose reductions were collected from week one and onward via the treatment information form.

Mixed-effects model was used to analyze the results. The statistical analysis was performed with the SPSS v.28 software and the level of statistical significance was set at a p-value of <0.05.

Results: Data analysis indicated that intervention-group participants demonstrated better results regarding the severity of the examined adverse skin reactions (pruritus, rash and photosensitivity) compared to the participants at control group. At baseline (week zero), 50% of the control group patients presented grade one pruritus with the same percentage applying for grade two pruritus cases. At the same time, in the intervention group 42.9% of the patients experienced grade one pruritus and 57.1% grade two. During the fourth week of follow-up (week three), patients in the control

group presented deterioration as 50% of them experienced grade two and 50% grade three pruritus, opposingly to 85.7% of the intervention group patients presenting grade one pruritus and 14.3% grade two. In regards to patients experiencing skin rash, the baseline percentage in the control group was 50% for participants experiencing grade one rash and grade two respectively, while intervention group participants presented 83.3% grade one rash and 16.7% for grade two. During the fourth week of follow-up (week three) the percentages changed to 33.3% for patients in the control group experiencing grade one rash, 50% grade two, and 16.7% escalated to grade four rash. During the same week, 40% of the intervention group patients presented grade one rash and 60% presented grade two. Skin photosensitivity was present to 37.5% of control group patients at grade one and 62.5% at grade two. At the intervention group 42.9% of patients presented grade one photosensitivity and 57.1% grade two. During the fourth week of follow-up (week three), 85.7% of the patients in the control group presented grade two photosensitivity and 14.3% escalated to grade three while all patients in the intervention group experienced grade one photosensitivity.

The weekly measurements of the grades of pruritus, rash and photosensitivity, representing the spreading and severity of the skin reaction, showed a statistically significant improvement to the intervention group compared to the control group (Walds X2 = 19,25, p = 0.004). In regards to the severity of pruritus recorded at the control group patients, is obvious that baseline measurements were clearly better, compared to the end results at week three (baseline: 50% grade one & 50% grade two vs week three: 50% grade two & 50% grade three). The same interpretation applies for the results recorded to the control groups for people experiencing rash (baseline: 50% grade one & 50% grade two vs week three: 33.3% grade one & 50% grade two & 16.7% grade four) and photosensitivity (baseline: 37.5% grade one & 62.5% grade two vs week three: 85.7% grade two & 14.3% grade three) skin reactions. Patients participating at the intervention groups for pruritus (baseline: 42.9% grade one & 57.1% grade two vs week three: 85.7% grade one & 14.3% grade two) and photosensitivity (baseline: 42.9% grade one & 57.1% grade two vs week three: 100% grade one) experienced improvement regarding the severity of their skin condition from baseline week to week three. On the other hand, participants at the intervention group regarding the severity of rash, experienced the opposite situation; their results were better at week zero (baseline)

rather than in week three (baseline: 83.3% grade one & 16.7% grade two vs week three: 40% grade one & 60% grade two).

For the secondary endpoints of the study, the SF-36 questionnaire was utilized in order to evaluate the patients' health-related quality of life (HR-QoL). The retrieved data from the SF-36 questionnaire illustrated that intervention group patients presented a higher score in all dimensions tested by the SF-36, compared to control group patients, although a significant interaction between Group and Time over the weekly measurements was not indicated for any of the questionnaire parameters. The DLQI questionnaire, a tool used to define the health-related quality of life (HR-QoL) of adult patients suffering from skin conditions, was also used for the secondary endpoints of the study. It is important to note that this questionnaire's results define how much the skin problem has affected the patient's life over the last week. So, as per the results of the DLQI, the beneficial effect of the intervention was obvious between the intervention and control groups at week three (d= 0.44), despite the fact that the results from week one indicated better results regarding the HR-QoL for the control group compared to intervention group (d= -0.12). Furthermore, for the secondary endpoints of the study, dose reduction of the appropriate treatment and emergency admissions of the patients were also reviewed. Regarding emergency admissions, in week one, the percentage of the patients in the control group who required to be admitted reached 15.8% while the percentage in the intervention group was recorded at 10% (Relative Risk (RR) = 0.66). In week three, that percentage changed to 21.10% for control group patients and 31.6% for patients in intervention group (RR=1.50). Regarding the data for the patients who required dose reduction of their treatment, in week one the percentage of control group patients was 21.10% whereas the percentage in the intervention group was only 10% (RR=0.5). At week three, that percentage changed to 31.6% for the control group and remained at the same level 10.5%, for intervention group patients (RR= 0.33).

Conclusion: Patients in the intervention group presented better results regarding the severity of the examined skin reaction of pruritus, rash and photosensitivity, compared to the participant of the control group. The results of this pilot study provide preliminary evidence on the effectiveness of the educational program regarding the severity of reviewed skin reactions in cancer patients. Additionally to that, this pilot study illustrated the effectiveness of the educational program regarding the improvement of

HR-QoL as well as the reduction of emergency admissions and appropriate treatment dose reductions.

Further research is currently needed in order to allow this educational program to be refined and a randomized controlled trail to be planned and contacted.

Keywords: rash, photosensitivity, pruritus, educational, chemotherapy, EGFRI, immunotherapy

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι φαρμακευτικές θεραπείες κατά του καρκίνου όπως ανοσοθεραπείες, θεραπείες με αναστολείς του υποδοχέα του επιδερμικού αυξητικού παράγοντα (EGFRI) και χημειοθεραπείες μπορούν να προκαλέσουν ανεπιθύμητες δερματικές αντιδράσεις. Οι πιο συχνές ανεπιθύμητες δερματικές αντιδράσεις που καταγράφονται είναι τρείς : ο κνησμός, το δερματικό εξάνθημα και η φωτοευαισθησία.

Η συχνότητα εμφάνισης κνησμού σε ασθενείς που λαμβάνουν ανοσοθεραπεία κυμαίνεται από 3% μέχρι 30,7%, ενώ δερματικά εξανθήματα εκδηλώνονται στο 50% έως και το 100% των ασθενών που υποβάλλονται σε θεραπεία με EGFRI. Φωτοευαισθησία εκδηλώνεται κυρίως σε ασθενείς που υποβάλλονται σε θεραπεία με χημειοθεραπεία και το ποσοστό εμφάνισης της κυμαίνεται από 22,2% μέχρι 66,7% σε καρκινοπαθείς που λαμβάνουν θεραπεία με φάρμακα που επιφέρουν ευαισθησία στην υπεριώδη ακτινοβολία.

Οι τρεις προαναφερόμενοι τύποι ανεπιθύμητων δερματικών αντιδράσεων (κνησμός, εξάνθημα, φωτοευαισθησία), προκαλούν τόσο σωματικές όσο και ψυχολογικές επιπτώσεις στη ζωή των ασθενών επηρεάζοντας έτσι την ποιότητα ζωής (QoL) τους. Επιπλέον, οι εν λόγω ανεπιθύμητες δερματικές αντιδράσεις μπορεί να οδηγήσουν σε μείωση της απαιτούμενης δόσης θεραπείας, καθυστέρηση στην χορήγηση της απαιτούμενης θεραπείας (ανοσοθεραπεία, θεραπεία με EGFRI και χημειοθεραπεία) ή ακόμη και διακοπή της θεραπείας.

Οι πιο ευρέως χρησιμοποιούμενες επιλογές θεραπείας για τον κνησμό, τα δερματικά εξανθήματα και της φωτοευαισθησίας είναι τα κορτικοστεροειδή και τα αντιβιοτικά. Πέραν από τη χρήση αυτών των θεραπευτικών επιλογών, η επιστημονική βιβλιογραφία παρουσιάζει ένα κενό όσον αφορά εκπαιδευτικά προγράμματα βασισμένα σε μη φαρμακευτικές μεθόδους για την θεραπεία των ανεπιθύμητων αυτών δερματικών αντιδράσεων που επέρχονται από τη χορήγηση ανοσοθεραπείας, θεραπείας με EGFRI και χημειοθεραπείας.

Ως εκ τούτου, υπάρχει ανάγκη για τη δημιουργία εκπαιδευτικών προγραμμάτων για ασθενείς με καρκίνο που υποφέρουν από δερματικές ανεπιθύμητες αντιδράσεις όπως ο κνησμός, το δερματικό εξάνθημα και η φωτοευαισθησία που προέρχονται στη χορήγηση ανοσοθεραπείας, θεραπείας με EGFRI και χημειοθεραπείας.

Σκοπός: Η παρούσα μελέτη φιλοδοξεί να διερευνήσει την αποτελεσματικότητα ενός εκπαιδευτικού προγράμματος για καρκινοπαθείς που παρουσιάζουν ανεπιθύμητες δερματικές αντιδράσεις (κνησμό, εξάνθημα ή φωτοευαισθησία) ως αποτέλεσμα της χορηγούμενης ανοσοθεραπείας, θεραπείας EGFRI ή χημειοθεραπείας.

Δείγμα και Μέθοδος: Αφορά μια πιλοτική μελέτη για τη διερεύνηση της αποτελεσματικότητας της παρέμβασης (εκπαιδευτικό πρόγραμμα) σε καρκινοπαθείς που παρουσιάζουν ανεπιθύμητες δερματικές αντιδράσεις (κνησμό, εξάνθημα ή φωτοευαισθησία) που προκλήθηκαν από τη χορήγηση ανοσοθεραπείας, θεραπείας με EGFRI ή χημειοθεραπείας.

Η μελέτη διεξήχθη μεταξύ 01/2019 και 12/2020 και περιλάμβανε 40 ασθενείς που παρουσίασαν κνησμό, δερματικά εξανθήματα ή φωτοευαισθησία λόγω ανοσοθεραπείας, θεραπείας με EGFRI ή χημειοθεραπείας και βρίσκονταν στην αρχή της έναρξης των ανεπιθύμητων δερματικών αντιδράσεων. Οι ασθενείς τυχαιοποιήθηκαν σε δύο ισόποσες ομάδες (την ομάδα παρέμβασης και την ομάδα ελέγχου), ενώ τα δεδομένα που συλλέχθηκαν την ημέρα εισδοχής των ασθενών στη μελέτη αντιστοιχούν στη τιμή αναφοράς (εβδομάδα μηδέν).

Η πρώτη εκπαιδευτική συνεδρία και η διανομή του εκπαιδευτικού υλικού (βιβλιάριο) στους ασθενείς της ομάδας παρέμβασης, πραγματοποιήθηκαν κατά την πρώτη μέρα εισδοχής τους στη μελέτη. Η εφαρμογή της παρέμβασης (εκπαιδευτικό πρόγραμμα) γινόταν ατομικά και επαναλαμβανόταν μία φορά την εβδομάδα. Συνολικά η παρέμβαση διήρκεσε τέσσερις συνεχόμενες εβδομάδες (από την εβδομάδα μηδέν μέχρι την εβδομάδα τρία). Οι ασθενείς που κατανεμήθηκαν στην ομάδα ελέγχου δεν έλαβαν τις πληροφορίες σχετικά με το εκπαιδευτικό πρόγραμμα. Ωστόσο, τους παρασχέθηκαν οι συνήθεις πληροφορίες, όπως σε κάθε καρκινοπαθή ασθενή, κατά την έναρξη της ανοσοθεραπείας, θεραπείας με EGFRI ή χημειοθεραπείας.

Για την αξιολόγηση της σοβαρότητας των ανεπιθύμητων δερματικών αντιδράσεων (κνησμός, δερματικό εξάνθημα, φωτοευαισθησία) πραγματοποιούνταν επαναλαμβανόμενες μετρήσεις εβδομαδιαίως (από την εβδομάδα μηδέν μέχρι την τρίτη εβδομάδα) σύμφωνα με τις οδηγίες της έκδοσης 5.0 της κλίμακας Κοινών Κριτηρίων Ορολογίας για Ανεπιθύμητα Συμβάντα, (CTCAE v 5.0). Για τους επιμέρους στόχους της πιλοτικής μελέτης χρησιμοποιήθηκαν δυο εργαλεία: το ερωτηματολόγιο Short Form 36 (ερωτηματολόγιο SF-36) και το ερωτηματολόγιο Δερματολογικού Δείκτη Ποιότητας Ζωής (ερωτηματολόγιο DLQI). Το ερωτηματολόγιο SF-36 (γενικό) χρησιμοποιήθηκε για την αξιολόγηση της ποιότητας ζωής των ασθενών και κατανεμόταν στους ασθενείς μια φορά εβδομαδιαίως (από την εβδομάδα μηδέν έως την εβδομάδα τρία). Η σχετιζόμενη με την υγεία ποιότητα ζωής (HR-QoL) των ασθενών μετρήθηκε μέσω του ερωτηματολογίου DLQI (ειδικό) που συμπληρωνόταν μια φορά την εβδομάδα (από την εβδομάδα ένα μέχρι την εβδομάδα τρία). Επιπλέον, τα δεδομένα σχετικά με τις επείγουσες εισαγωγές των ασθενών και τη μείωση της απαιτούμενης δόσης της παρεχόμενης θεραπείας συλλέγονταν στη φόρμα πληροφοριών θεραπείας από την εβδομάδα ένα μέχρι την εβδομάδα τρία.

Η στατιστική ανάλυση των αποτελεσμάτων πραγματοποιήθηκε μέσω του στατιστικού λογισμικού SPSS v.28. Η τιμή $p < 0,05$ τέθηκε ως το επίπεδο στατιστικής σημαντικότητας.

Αποτελέσματα: Σύμφωνα με την ανάλυση των αποτελεσμάτων, οι ασθενείς στην ομάδα παρέμβασης παρουσίασαν καλύτερα αποτελέσματα όσον αφορά το βαθμό σοβαρότητας των ανεπιθύμητων δερματικών αντιδράσεων (κνησμός, εξάνθημα και φωτοευαισθησία) συγκριτικά με τους ασθενείς της ομάδας ελέγχου.

Συγκεκριμένα, την εβδομάδα μηδέν (τιμή αναφοράς), ποσοστό 50% των ασθενών της ομάδας ελέγχου παρουσίασε κνησμό πρώτου βαθμού και 50% κνησμό δευτέρου βαθμού, ενώ ποσοστό 42,9% και ποσοστό 57.1% των ασθενών της ομάδας παρέμβασης εμφάνισε κνησμό πρώτου και δευτέρου βαθμού αντίστοιχα. Την τέταρτη εβδομάδα παρακολούθησης (εβδομάδα τρία), ποσοστό 50% των ασθενών της ομάδας ελέγχου εμφάνισε κνησμό δευτέρου και αντίστοιχα τρίτου βαθμού ενώ ποσοστό 85.7% της ομάδας παρέμβασης εκδήλωσε κνησμό πρώτου βαθμού και 14.3% δευτέρου βαθμού. Όσον αφορά τα ποσοστά εκδήλωσης δερματικού εξανθήματος, το ποσοστό των

ασθενών της ομάδας ελέγχου κατά την εβδομάδα μηδέν ήταν 50% για ασθενείς που εκδήλωσαν εξάνθημα πρώτου και αντίστοιχα δευτέρου βαθμού, ενώ τα ποσοστά των ασθενών της ομάδας παρέμβασης ήταν 83,3% και 16.7% αναλόγως. Την τέταρτη εβδομάδα παρακολούθησης (εβδομάδα τρία), το 33,3% των ασθενών της ομάδας ελέγχου εμφάνισε δερματικό εξάνθημα πρώτου βαθμού, το 50% ανέπτυξε εξάνθημα δευτέρου βαθμού και το 16,7% ανέπτυξε εξάνθημα τετάρτου βαθμού. Κατά την ίδια εβδομάδα, ποσοστό 40% των ασθενών της ομάδας παρέμβασης εμφάνισε δερματικό εξάνθημα πρώτου βαθμού ενώ 60% των ασθενών στην ίδια ομάδα παρουσίασε εξάνθημα δευτέρου βαθμού. Όσον αφορά τη φωτοευαισθησία, κατά την εβδομάδα αναφοράς ποσοστό 37.5% και ποσοστό 62.5% των ασθενών της ομάδας ελέγχου παρουσίασε φωτοευαισθησία πρώτου βαθμού και δευτέρου βαθμού αντίστοιχα, ενώ ποσοστό 42,9% και 57.1% των ασθενών της ομάδας παρέμβασης εμφάνισε φωτοευαισθησία πρώτου και δευτέρου βαθμού αντίστοιχα. Την τέταρτη εβδομάδα παρακολούθησης, ποσοστό 85,7% των ασθενών της ομάδας ελέγχου εκδήλωσε φωτοευαισθησία δευτέρου βαθμού και ποσοστό 14,3% εμφάνισε φωτοευαισθησία τρίτου βαθμού. Την ίδια εβδομάδα παρακολούθησης όλοι οι ασθενείς της ομάδας παρέμβασης εκδήλωσαν φωτοευαισθησία πρώτου βαθμού.

Σύμφωνα με τις εβδομαδιαίες μετρήσεις, η ομάδα παρέμβασης παρουσίασε στατιστικά σημαντική βελτίωση στο βαθμό σοβαρότητας του κνησμού, του δερματικού εξανθήματος και της φωτοευαισθησίας συγκριτικά με τους ασθενείς της ομάδας ελέγχου (Walds $X^2 = 19,25$, $p = 0,004$).

Για τους επιμέρους στόχους της πιλοτικής μελέτης χρησιμοποιήθηκαν δύο ερωτηματολόγια: το ερωτηματολόγιο SF-36 και το ερωτηματολόγιο DLQI. Σύμφωνα με τις μετρήσεις του ερωτηματολογίου SF-36, διαφάνηκε ότι οι ασθενείς της ομάδας παρέμβασης παρουσίασαν καλύτερη ποιότητα ζωής σε σύγκριση με τους ασθενείς της ομάδας ελέγχου. Επιπλέον, όπως μετρήθηκε μέσω του ερωτηματολογίου DLQI, οι ασθενείς της ομάδας παρέμβασης βρέθηκαν να παρουσιάζουν καλύτερη σχετιζόμενη με την υγεία ποιότητα ζωής (HR-QoL) κατά την τρίτη εβδομάδα παρακολούθησης σε σύγκριση με τους ασθενείς της ομάδας ελέγχου ($d= 0,44$).

Επιπλέον, σύμφωνα με τα δεδομένα που ανακτήθηκαν από το έντυπο πληροφοριών θεραπείας, την πρώτη εβδομάδα παρακολούθησης, μεγαλύτερο ποσοστό ασθενών της

ομάδας ελέγχου χρειάστηκαν επείγουσα νοσηλεία (15.8%) σε σύγκριση με τους ασθενείς της ομάδας παρέμβασης (10%) [Σχετικός Κίνδυνος (RR) = 0,66]. Αντίθετα όμως, κατά την τρίτη εβδομάδα παρακολούθησης το ποσοστό επείγουσας νοσηλείας στους ασθενείς της ομάδας ελέγχου ήταν μικρότερο (21.10%) σε σύγκριση με τους ασθενείς της ομάδας παρέμβασης (31.6%) (RR=1,50). Επιπλέον, δεδομένα σχετικά με την μείωση της δόσης της απαιτούμενης θεραπείας συλλέχθηκαν μέσω του εντύπου πληροφοριών θεραπείας. Σύμφωνα με τα δεδομένα, κατά την πρώτη και τρίτη εβδομάδα παρακολούθησης η ομάδα ελέγχου παρουσίασε σε μεγαλύτερο ποσοστό ανάγκη για μείωσης της απαιτούμενης δόσης θεραπείας σε σύγκριση με την ομάδα παρέμβασης. Λεπτομερώς, την πρώτη εβδομάδα παρακολούθησης, ποσοστό 21.10% των ασθενών της ομάδας ελέγχου χρειάστηκε μείωση της δόσης θεραπείας ενώ το αντίστοιχο ποσοστό των ασθενών της ομάδας παρέμβασης ήταν 10% (RR=0,5). Την τρίτη εβδομάδα παρακολούθησης, ποσοστό 31.6% των ασθενών της ομάδας ελέγχου χρειάστηκε μείωση της απαιτούμενης δόσης της θεραπείας ενώ το ποσοστό της ομάδας παρέμβασης ήταν 10,5% (RR= 0,33).

Συμπεράσματα: Τα αποτελέσματα αυτής της πιλοτικής μελέτης παρέχουν θετικά στοιχεία όσον αφορά την αποτελεσματικότητα του εκπαιδευτικού προγράμματος έναντι στο βαθμό σοβαρότητας των ανεπιθύμητων δερματικών αντιδράσεων (κνησμός, εξάνθημα, φωτοευαισθησία) σε ασθενείς με καρκίνο που υποβάλλονται σε ανοσοθεραπεία, θεραπεία με EGFRI και χημειοθεραπεία.

Επιπρόσθετα, αυτή η πιλοτική μελέτη κατέδειξε την αποτελεσματικότητα του εκπαιδευτικού προγράμματος όσον αφορά την σχετιζόμενη με την υγεία ποιότητας ζωής, τη μείωση της απαιτούμενης δόσης της θεραπείας και τις επείγουσες εισαγωγές.

Περαιτέρω έρευνα απαιτείται όμως προκειμένου να βελτιστοποιηθεί το εκπαιδευτικό πρόγραμμα και να ολοκληρωθεί η τυχαιοποιημένη κλινική δοκιμή.

Λέξεις κλειδιά: εξάνθημα, φωτοευαισθησία, κνησμός, εκπαιδευτικό πρόγραμμα, χημειοθεραπεία, EGFRI, ανοσοθεραπεία.

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CTCAE: Common Terminology Criteria for Adverse Events

DLQI: Dermatology Life Quality Index

EGFRI: Epidermal Growth Factor Receptor Inhibitor

EGFRIr: Rash due to Epidermal Growth Factor Receptor Inhibitor

HR-QoL: Health Related Quality of Life

IARC: International Agency for Research on Cancer

PD-1: Programmed death 1

PD-L1: Programmed death ligand 1

QoL: Quality of Life

SF-36: Short Form – 36

WHO: World Health Organization

GENERAL SECTION

1 INTRODUCTION

Cancer is currently one of the leading causes of death worldwide, with negative predictions noting that it might be declared as the most important cause within the following years (Bray et al., 2021). The burden of cancer is substantial and rapidly rising worldwide in countries of all income levels (Bray et al., 2021). According to the study of Sung et al., (2021) there were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020 when in Europe the percentage of the total cancer cases was 22.8% and of percentage of the cancer deaths was 19.6%.

These days, there are several approaches in pharmaceutical cancer treatments such as chemotherapy, EGFRI cancer treatments and immunotherapy (Debela et al., 2021). The pool of chemotherapeutic drug options is vast including taxanes, cyclophosphamide and ifosphamide, 5- fluorouracil (5-FU), doxorubicin and platinum-based anticancer drugs such as cisplatin, carboplatin, and oxaliplatin (Belachew et al., 2016). EGFRI treatment regimens include cetuximab, panitumumab, gefitinib, erlotinib, lapatinib, and afatinib (Clabbers et al., 2016), while immunotherapy drug regimens are based on ipilimumab, nivolumab and pembrolizumab (Steven, Fisher and Robinson, 2016).

Adverse dermatologic events can unfortunately occur due to use of the aforementioned anti-cancer treatments (Lacouture et al., 2010). Pruritus (Wang et al., 2019), rash (Lacouture et al., 2010), and photosensitivity (Sibaud, 2022) are among the most common skin reactions reported during the use of above cancer treatments. These adverse skin reactions can have a major impact on the well-being and quality of life of cancer patients (Sibaud, 2022) and in severe cases, may lead to a reduction in treatment dose, a delay in treatment dose optimization, or even discontinuation of treatment (Lacouture et al., 2010).

Corticosteroids and antibiotics are the most commonly used pharmacological interventions for the treatment and management of pruritus, rash and photosensitivity (Ensslin et al., 2013; Gerber et al., 2012; Melosky et al., 2015; Sibaud, 2022). Both drug groups have been the subject of extensive research that showed how both types are

effective against these types of skin conditions (Ensslin et al., 2013; Gerber et al., 2012; Melosky et al., 2015; Sibaud, 2022).

On the other hand, the use of antibiotics and steroids over a long period of time is not indicatory due to side effects (Buchman, 2001; Fischer et al., 2013; Mihai et al. 2021). Long-term use of topical corticosteroids for example, can cause skin atrophy (Fischer et al., 2013). Similarly, long-term intravenous corticosteroids have been associated with osteoporosis, adrenal insufficiency, gastrointestinal problems, adverse ocular eye effects, and hyperlipidemia (Buchman, 2001). In addition, as per Mihai et al. (2021), prolonged use of antibiotics can also cause esophageal ulceration, heartburn, gastritis, nausea, vomiting, diarrhea, and bacterial or antibiotic resistance.

Several publications provide recommendations or algorithms for pharmaceutical treatments, but non-pharmacological skin care approaches have yet to be studied thoroughly (Bensadoun et al., 2013). Such approaches though could prove helpful for the treatment of adverse skin reactions in patients undergoing cancer treatments that causes dermatological problems, and study towards that field is necessary (Bensadoun et al., 2013). According to the study of Martin et al. from 2012, education of cancer patients has become a standard component of non-pharmacological cancer care. According to Faller et al., (2009) providing adequate information during patient education aims at improving symptoms management and coping with illness. Educational interventions should be an essential part of daily clinical practice (Martin et al., 2012) because patient education is associated with involvement in decision-making, greater satisfaction with treatment choices and improved knowledge (Faller et al., 2009). Thus, early education regarding the management of skin adverse reactions contributes significantly into improved management of the symptoms (Bensadoun et al., 2013).

Taking into consideration all the above, effective educational programs with evidence-based guideline recommendations seem required for all types of cancer patients (Martin et al., 2012). However, and according to our knowledge, there is a gap in scientific literature regarding the existence of educational training programs for the management of skin adverse side effects caused by chemotherapy, EGFRI treatments, and immunotherapies.

This dissertation consists of two parts: the general section and the specific (research) section. The general section consists of the theoretical part where the research problem is explained and definitions and epidemiological data on pruritus, skin rash, and photosensitivity are provided. The pathophysiology of the studied skin reactions is also analyzed. In addition, to this section we describe how evaluation of the aforementioned skin reactions is performed using the CTCAE v. 5.0 and outline the current guidelines for the treatment of pruritus, rash and photosensitivity using bibliographic references. The theoretical section also introduces new treatment options such as vitamin K cream and topical retinoids, while it notes the importance of patient education and describes already published educational measures for the studied skin conditions. In addition, a systematic literature review is presented, based on studies published in the past decade, regarding the effectiveness of various interventions (excluding antibiotics and steroid products) as prevention and treatment of the EGFRI treatment-induced rash (EGFRIr).

The same chapter presents the objective of the systematic review, methodology, inclusion and exclusion criteria, screening method, and quality assessment of the included studies. To this chapter, are also presented the study findings and the analysis and interpretation of results. The discussion of the systematic review is divided into three subchapters: acceptance of studies, results comparison with other studies; and results comparison with recently published studies. Lastly, the systematic review's limitations are discussed, and a brief summary of its findings is provided.

The second part of the dissertation (research part) contains information about pilot study regarding an educational training program for cancer patients who developed pruritus, skin rash and photosensitivity due to immunotherapies, EGFRI treatments and chemotherapies. This chapter presents the study's aim, secondary objectives, materials, and methods. There is also a detailed interpretation of the results and discussion follows. Finally, the study's strengths and limitations are discussed, and a synopsis (conclusion) of the study is provided.

2 RESEARCH PROBLEM: TREATMENT-INDUCED ADVERSE SKIN EVENTS IN CANCER PATIENTS

According to the data of World Health Organization (WHO) published in 2022, cancer is one of the leading cause of death worldwide, with the most common lethal cancer types in 2020 being: lung cancer with 1.80 million deaths, colon and rectum cancer causing 916 000 deaths, liver cancer with 830 000 deaths, stomach cancer with 769 000 deaths and breast cancer causing 685 000 deaths (WHO, 2022).

These numbers are dreadful, despite the fact that pharmaceutical agents have been developed and used for the treatment of cancer for years now (Falzone, Salomone and Libra, 2018). According to the study of Falzone, Salomone and Libra, (2018) both chemotherapy and targeted therapy have significantly improved the survival of cancer patients inducing sometimes complete tumor remission. On the other hand, the use of chemotherapy as monotherapy or in combination with surgical removal of cancer and/or radiation therapy has a poor prognosis for many cancer types (i.e. lung cancer) while the disease rarely remains curable (Sun et al., 2007). For this reason, new chemotherapeutic agents and new protocols have developed in oncology, aiming to increase the survival rate and the QoL among cancer patients (Fabbrocini et al., 2012).

Despite the advantages of anti-cancer treatments, they still cause numerous adverse side effects (Fabbrocini et al., 2012). Immunotherapies (ipilimumab, pembrolizumab and nivolumab), EGFRI treatments (Cetuximab, Panitumumab, Erlotinib, Gefitinib) and chemotherapeutic drugs (Capecitabine, 5-FU, Cyclophosphamide, Doxorubicin, and Taxanes) are the causative effects of significant adverse skin reactions (Fabbrocini et al., 2012; Salinas et al., 2021). Pruritus, skin rash and photosensitivity are the most common adverse skin reactions recorded due to the aforementioned drugs (Ensslin et al. 2013; Fabbrocini et al., 2015; Lugović-Mihić et al., 2017; Lembo et al., 2020).

Pruritus is the main adverse skin reaction observed due to immunotherapy administration to cancer patients (Sibaud 2017). A study by Sibaud from 2017, examined the incidence of all grades of pruritus in patients treated with nivolumab and pembrolizumab and demonstrated that the incidence of this side effect was between 13% and 20%. Another study from 2013 by Ensslin et al. which investigated the incidence of pruritus in all grades of severity in 17,368 patients from 141 clinical trials,

showed that the incidence ranged from 3.0% (95% CI: 1.1%–7.8%) to 30.7% (95% CI: 15.9%–51.0%) (Ensslin et al., 2013). The same study examined the incidence of high-grade pruritus in a total of 15,927 patients from 132 clinical trials, finding that the incidence ranged from 0.5% (95% CI: 0.2%-1.5%) to 1.8% (95% CI: 1.5%-2.3%) (Ensslin et al., 2013).

Skin rash has been reported as a side effect in 49% to 75% of patients treated with erlotinib and in up to 90% of patients treated with cetuximab or panitumumab (Fischer et al., 2013). According to another study from Fabbrocini et al. (2015), the incidence of rash in patients receiving treatment with erlotinib ranged at similar percentages from 49% to 67%, while in patients receiving gefitinib, the incidence of the same adverse effect was 24% to 62% and for cetuximab administration at 75% to 95% (Fabbrocini et al., 2015). As per the same data, 32% to 76% of patients under EGFRI regimen had to discontinue or postpone their treatment (Fabbrocini et al., 2015).

Depending on the type of drug and the season in which that is administered, the percentage of photosensitive skin reactions ranges from 22.2% to 66.7% in patients treated with regimens known to cause photosensitivity, (Lembo et al., 2020). Photosensitivity was also reported in more than 15% of women treated with the anti-cancer agent rucaparib, while immunotherapy with nivolumab (medical classification: monoclonal antibodies) has been associated with an all-grade incidence of photosensitivity estimated at 1.5% (95% CI: 0.5%–4.4%) (Sibaud, 2022).

According to the study of Naing et al., (2020) patient education is an essential element for the management of skin adverse side events. In a survey conducted by the non-profit network Cancer Support Community, patients stated their difficulty in obtaining information on managing side effects and emphasized that this was the most important educational need (Naing et al., 2020). Educating patients is an important component of cancer care as it increases patients' ability to make informed decisions about their therapy and helps them to adhere to their medical treatment (Kaupp et al., 2019). Furthermore, educated patients tend to develop a sense of control over their treatment something that eventually decreases their depression and anxiety levels (Kaupp et al., 2019).

Many oncological societies, pharmaceutical companies, the American Cancer Society and other non-profit organizations have created patient education programs via the

provision of online information and printed information via brochures, blogs, and testimonials (Naing et al., 2020). Guidelines have also been published by influential oncology societies (American Society of Clinical Oncology (ASCO), Society for Immunotherapy of Cancer (SITC), National Comprehensive Cancer Network, and European Society for Medical Oncology) however these guidelines are not based on tested approaches, but they are recommendations by experts' panels, algorithms and suggestions (Naing et al., 2020) thus their effectiveness is not proved.

Patient education programs for other cancer related side effects, such as fatigue (Du et al., 2015) or pain (Lovell et al., 2014), have already been studied and published. To our knowledge though, no other studies have been published to date, investigating the effectiveness of educational programs for the management of the adverse skin side effects (pruritus, skin rash and photosensitivity) in patients treated with immunotherapies, EGFRI treatments and chemotherapies.

Therefore, the research part of this doctoral dissertation focuses on a pilot study regarding the development and effectiveness of an educational program for cancer patients who developed pruritus, skin rash or photosensitivity due to anti-cancer treatments (chemotherapies, EGFRI treatments, or immunotherapies).

3 DEFINITIONS

3.1 Adverse drug event

As per the National Cancer Institute, an adverse event, defined by the abbreviation AE, is a term that is a unique representation of a specific event used for medical documentation and scientific analyses (National Cancer Institute, U.S., 2017). An adverse drug event (ADE) is defined as: “an unfavorable medical occurrence which is characterized by sign or symptom or an abnormal laboratory finding that happens due to a treatment with a drug” (Shabaruddin et al., 2013). ADE is a descriptive terminology that has been widely used for reporting adverse events (AEs) (Chen et al., 2012), while the term is also a standard approach for documenting adverse events (AEs) in cancer clinical trials (Basch et al., 2014).

Different chemotherapy drugs and regimens can cause different ADEs at a different severity level (Shabaruddin et al., 2013). The standard approach for documenting AEs in cancer clinical trials involves investigator reporting by utilizing the National Cancer Institute’s (NCI’s) Common Terminology Criteria for Adverse Events (CTCAE) (Basch et al., 2014). Via the NCI- CTCAE scoring system different grades of ADEs categorize according to severity (Shabaruddin et al., 2013). Grade one and grade two drug-related adverse events are considered mild opposing to grades three and grade four which are considered severe ADEs (Shabaruddin et al., 2013).

The NCI published the first (v 1.0) and the second (v 2.0) versions of the Common Terminology Criteria (CTC) in 1982 and 1998 respectively, whereas the third version (v 3.0) was launched on June 10, 2003, and contains 28 categories and 1056 adverse event terminologies, compared to 24 categories and 395 adverse event terms of the CTC version 2 (Colevas and Setser, 2004). In 2010, version 4.03 (v4.03) replaced version 4.0, whereas on November 27, 2017, the NCI published the NCI-CTCAE version 5.0 (National Cancer Institute, U.S., 2017). Version 5.0 describes 54 new/updated algorithms and 19 lab parameters (Zhong, 2020).

According to the findings of Shabaruddin et al. from 2013, ADEs can lead to increased morbidity, have an impact on patients’ health-related quality of life (HR-QOL) and decrease the effectiveness of the appropriate treatment. Thus, clinical research requires

the consistent reporting of adverse events (AEs) in order to ensure patients' safety and comprehend the toxicity profile of various therapies (Basch et al., 2014).

3.2 Self-management

Self-management has gained popularity as a descriptor for both healthy behaviors and behavioral interventions (Lorig and Holman, 2003). It is currently a common term used in health education and is associated with many health promotion and patient educational programs (Lorig and Holman, 2003). The term denotes that the patient is an active participant in his/her treatment and therefore is a significant term for the patient education programs (Lorig and Holman, 2003).

Historically, the term "self-management" appeared in the mid-1960s with one of the first appearances of it, being in Thomas Creer's book referring to the rehabilitation of chronically ill children (Lorig and Holman, 2003). Afterwards, Thomas Creer and his colleagues re-used the term "self-management" during a study regarding asthmatic juvenile patients from the pediatric Asthma program of The Children's Asthma Research Institute and Hospital (Creer and Yoches, 1971). Since then, self- management term has been established as a term and is used during patient education programs (Lorig and Holman, 2003).

Self- management consists of three independent self-management tasks (Lorig and Holman, 2003). First task set, is the medical management where patients should adhere to taking their medication and following a special diet; second task is the role management where they should maintain, change and create new meaningful behaviors or life roles, while for task three, the emotional management, the patients should learn how to manage emotions such as fear and depression (Lorig and Holman, 2003).

Beyond the tasks, self-management also consists of six management skills (Lorig and Holman, 2003). Problem solving and decision making are two of the first self-management skills patients are anticipated to develop through an educational program. The former means that the patients are taught basic problem-solving techniques and is expected to apply them to address matters/effects deriving from treatment, while the latter denotes that they are expected to make day-to-day decisions in response to

changes in their disease condition (Lorig and Holman, 2003). The third self-management skill is the “resource utilization”, that within this frame translates as teaching patients the way to find and utilize resources opposing to simply provide them with resources but not teach them how to use them (Lorig and Holman, 2003). The formation of a patient-provider partnership is the fourth self-management skill anticipated patients to cultivate via an educational program, while the fifth skill is “action planning” meaning that patients learn how to make informed choices about treatment and discuss these with their health care provider (Lorig and Holman, 2003). Finally, the sixth self-management skill developed is the ability to take action, for example, to make a short-term action plan and carry it out (Lorig and Holman, 2003).

Effective self-management is not just participation in programs (Howell et al., 2020). Another definition for the term is “the individual’s ability to manage the symptoms, treatment, physical and psychosocial consequences and lifestyle changes inherent in living with a chronic condition” (Howell et al., 2020). In other words, self-management for cancer patients means self-monitoring their illness and symptoms, recognizing any adverse events, reporting to their doctor and achieving effective management and treatment of the symptoms with final aim to achieve improvement of overall functional status and quality of life (Howell et al., 2020, Hammer et al., 2015).

3.3 Patient education

Patient education by definition is the education managed by trained, highly qualified healthcare providers, able to train a single or a group of patients (and/or their families) in order to qualify them so as to manage their condition's treatment and prevent preventable complications, while maintaining or improving their QoL (Jotterand, Amodio and Elger, 2016).

Patient education is the contrary to the tactic of simply informing patients, as it aims to educate patients on how to self-manage and adjust treatment to their condition as well as it enhances their or teaches them processes and skills to cope with disease (Jotterand, Amodio and Elger, 2016).

Through this type of education, patients acquire a framework through which they comprehend the available treatment options, how the disease is managed and its behavioral impact over a potential successful outcome (Jotterand, Amodio and Elger,

2016). The four main goals of patient education is firstly to improve disease management, secondly to increase treatment adherence, thirdly to promote healthy behaviors and finally to empower patients and increase their participation through healthcare decision-making (Jotterand, Amodio and Elger, 2016).

Historically, nurses were the first healthcare professionals to act as "educators" in the clinical context since the early twentieth century (Jotterand, Amodio and Elger, 2016). They were the people explaining the various medical procedures and providing advice over hygiene, nutrition, and health promotion to patients and their families (Jotterand, Amodio and Elger, 2016).

In the 1960s and 1970s, a gradual emphasis on patient education took place in Europe, with the Netherlands leading the way on the continent, while in the United States educational programs were developed in the 1990s to allow patients to self-regulate and manage their medical conditions (Jotterand, Amodio and Elger, 2016).

Advancements in patient education at the oncology field have increased the proportion of treatment-eligible patients and improved the survival rate for many cancer types (Kaupp et al., 2019). Patient education is critical in oncology as it assists patients to understand the provided therapeutic drugs, potential ADEs resulting from their use and possible drug interactions. This way, potentially life-threatening complications are avoided (Kaupp et al., 2019). Typically, the oncologist is the professional to provide this information upon diagnosis while nurses are informing patients during anti- cancer treatment (Kaupp et al., 2019).

Patient education is an important component of oncological care as it increases patients' ability to make informed decisions regarding treatment and helps them to adhere to their therapeutic plan (Kaupp et al., 2019). Furthermore, educated patients tend to develop a sense of control over their treatment, something that eventually decreases depression and anxiety levels (Kaupp et al., 2019).

3.4 Quality of Life (QoL)

Quality of life (QoL) is established as a significant concept and an important target for research and practice in the fields of health and medicine (Haraldstad et al., 2019). Over

the past decades, more research focused towards patients' QoL, while the use of QoL assessments also increased (Haraldstad et al., 2019).

Despite the fact that in 1947 WHO interpreted the term QoL as the: "state of complete physical, mental, and social well-being, and not merely the absence of disease and infirmity", a uniform definition for QoL does not exist (Haraldstad et al., 2019).

Defining QoL has proven challenging, allowing a number of definitions for it to be released (Karimi and Brazier, 2016). The study of Post, (2014) collected and presented various definitions of QoL appearing in the literature: "The degree of need and satisfaction within the physical, psychological, social, activity, material, and structural area " (Hörnquist, 1982); "…the individuals' perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns" (The WhoQoL Group, 1998); "Subjective quality of life reflects an individual's overall perception of and satisfaction with how things are in their life." (Wood-Dauphinée et al., 2002).

Regardless the variety of existing definitions for the term, the impact of QoL is what is really important as this will result in improving symptoms relief, care and rehabilitation for patients (Haraldstad et al., 2019). QoL is also taken into consideration during crucial medical decision-making because of its prognostic importance, as it plays the role of a treatment-success predictor (Haraldstad et al., 2019)

3.5 Health- related Quality of Life (HR-QoL)

Health-related Quality of Life (HR-QOL) is often described as: "A term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning" (Haraldstad et al., 2019).

At least four definitions of HR-QoL can be identified in the literature (Karimi and Brazier, 2016). The first definition concerns to ''how well a person functions in their life and his or her perceived wellbeing in physical, mental, and social domains of health'' (Stenman U, 2010); the second definition denotes that ''quality of life is an all-inclusive concept incorporating all factors that impact upon an individual's life. Health-related quality of life includes only those factors that are part of an individual's health'' (Torrance, 1987). A third definition refers to ''those aspects of self-perceived well-

being that are related to or affected by the presence of disease or treatment''(Ebrahim, 1995), with the fourth definition describing HR-QoL as the ‘‘values assigned to different health states''(Gold et al., 1996).

Through the last decades, information regarding the HR-QoL of cancer patients has played a major role in the context of approval of novel treatment regimens, thus HR-QoL is currently considered an important parameter to study in each cancer trial/study (Oh et al., 2021). Moreover, the attention of oncology professionals grew towards HR-QoL as it serves as prognostic factor for patients' life expectancy (Eichler et al., 2022).

Conclusively, HR-QoL consists of data regarding the somatic and mental health of patients, as well as the impact of health status over quality of life, thus is a multifaceted concept and a valuable indicator of overall health (Yin et al., 2016).

4 PRURITUS

The following sub-chapters describe the definition of skin pruritus (sub-chapter 4.1), the pathophysiology (sub-chapter 4.2), the assessment of pruritus grades according to the NCI-CTCAE v. 5.0 (sub-chapter 4.3), the management of skin pruritus according to bibliographic references (sub-chapter 4.4) and finally new aspects of pruritus treatment according to bibliography (sub-chapter 4.5).

4.1 Definition of pruritus

Pruritus is a condition characterized by severe itchiness that most commonly affects the scalp, head, neck and acral parts (Phillips et al., 2019). Depending on the severity of the adverse event, pruritus is classified into three grades; grade 1, grade 2 and grade 3, while its site of occurrence can be either local or generalized (Phillips et al., 2019, Song et al., 2018). Pruritus is among the most prevalent adverse skin reactions induced by immunotherapies, described as an uncomfortable feeling on the skin, impairing patients' quality of life most of the times (Sibaud, 2017, Song et al., 2018). Immunotherapies are responsible for 14% to 47% of pruritus cases recorded in treated cancer patients with incidents ranging in intensity from mild to severe (Phillips et al., 2019).

4.2 Pathophysiology of pruritus

It is widely assumed that the cause of pruritus-induced itching is extremely complicated, with many factors involved, both internal and external (Song et al., 2018). What is evident though, is that the itching is primarily linked with the free teleneuron, which ramifies in the epidermis' superficial layers (Song et al., 2018).

Immunotherapy is an anticancer treatment which utilizes antibodies in order to halt the action of Programmed cell Death receptor 1 (PD-1) (Allegra et al., 2020). T-cells mediated immune response is blocked when Programmed Death-Ligand 1 (PD-L1) and Programmed Death-Ligand 2 (PD-L2) are bound to PD-1 (Allegra et al., 2020). Monoclonal humanized antibodies (mAbs) such as pembrolizumab and nivolumab (immunotherapies) work by prohibiting the association between PD-1 and PD-Ls. This way, the intermediate cytotoxic activities of T lymphocytes are motivated in order to

ameliorate cancer cells in different tumor types (Alsaab et al., 2017). Figure 1, from the study of Ohaegbulam et al. (2015), depicts the action mechanism of cancer immunotherapy with the use of monoclonal antibodies against PD-1 and PD-Ls.

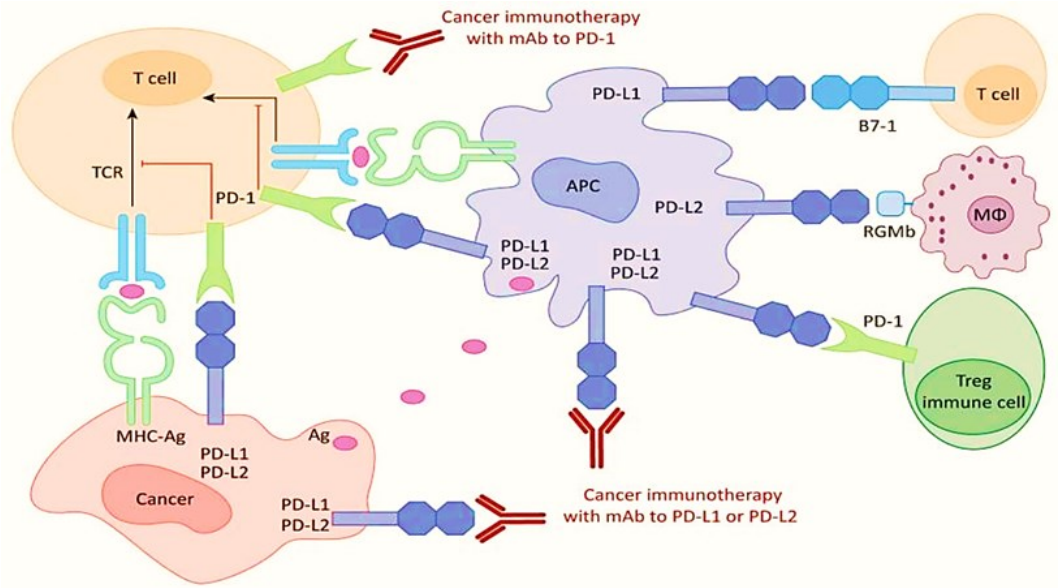


Figure 1 Mechanism of immunotherapy with anti-PD-1 and anti-PD-L1/L2 antibodies

Source: Ohaegbulam et al., (2015)

In contrast to other cancer therapies, antibodies against PD-1 and PD-L1 have demonstrated a greater overall response rate (ORR) and longer progression-free survival (PFS) in the treatment of melanoma, gastric cancer, and liver cancer since 2017 (Allegra et al., 2020). Longer overall patient survival (OS) is achieved by using the monoclonal antibody (mAb) ipilimumab to activate the immune checkpoint by inhibiting CTLA-4 (Allegra et al., 2020). However, the same path has also been connected to a high rate of skin reactions (Buchbinder and Hodi, 2015). Pruritus skin reaction appears to be a direct consequence of CTLA-4 inhibition and immune system response (Ensslin et al., 2013). Figure 2 demonstrates the possible mechanism associating cancer treatments and skin reactions.

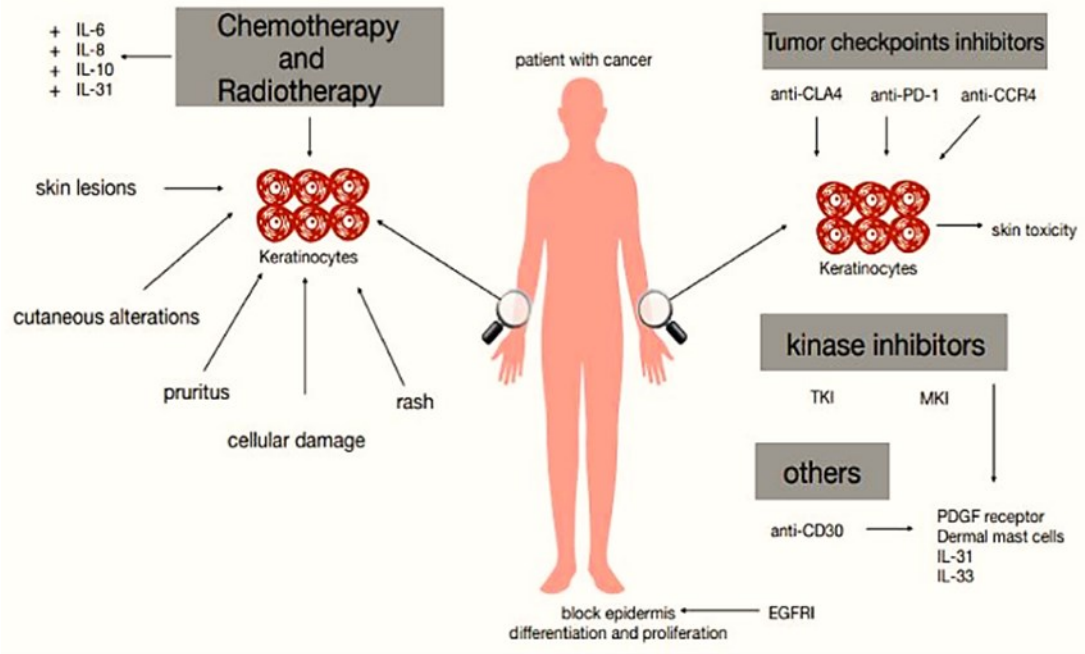


Figure 2 Possible mechanisms of skin pruritus due to cancer treatment.

Source: Allegra et al., (2020)

In summary, numerous studies have been conducted in the last decade aiming to understand the pathophysiology of pruritus (Silva et al., 2020; Ensslin et al., 2013). Some studies indicated that the pathophysiology of pruritus has remained unclear (Silva et al., 2020; Song et al., 2018), while others pointed towards possible pathophysiological mechanisms (Ensslin et al., 2013).

This subchapter denotes the need for further research so as to understand the pathophysiology of pruritus, something that will lead into developing effective measures for the management and treatment of this adverse event.

4.3 Assessment of pruritus grades according to the NCI-CTCAE v. 5.0

According to the NCI-CTCAE v. 5.0 (2017), grade one pruritus, refers to localized or mild pruritus requiring topical intervention. Grade two, is characterized by extensive and intermittent pruritus or skin damage from scratching, such as edema, oozing/crusts, papulation or excoriations (NCI- CTCAE v. 5.0., 2017). Additionally, grade two is considered to affect the activities of daily life (ADL) and thus oral intervention is required (NCI- CTCAE v. 5.0, 2017). Finally, grade three pruritus is characterized by

widespread and constant pruritus symptoms, limiting self-care ADL or affecting the patient's sleep. For that reason, treatment with corticosteroid or immunosuppressive is indicated for this grade (NCI- CTCAE v. 5.0, 2017). Table 1 demonstrates the definition of pruritus and the three grades (CTCAE v5.0, 2017).

Table 1 Definition of pruritus and the grades according to the CTCAE v5.0.

CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self -care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated
Definition: A disorder characterized by an intense itching sensation.			

Source: CTCAE v5.0 – November 27, (2017)

The following figure (Figure 3), as obtained from the article of Ensslin et al., (2013), shows excoriations caused by pruritus due to targeted therapy that affect the patient's chest, abdomen, legs (left side), arms, and wrists (right side). Such severe pruritus symptoms can lead to excessive scratching, which leads to secondary adverse reactions such as infections (Ensslin et al., 2013).

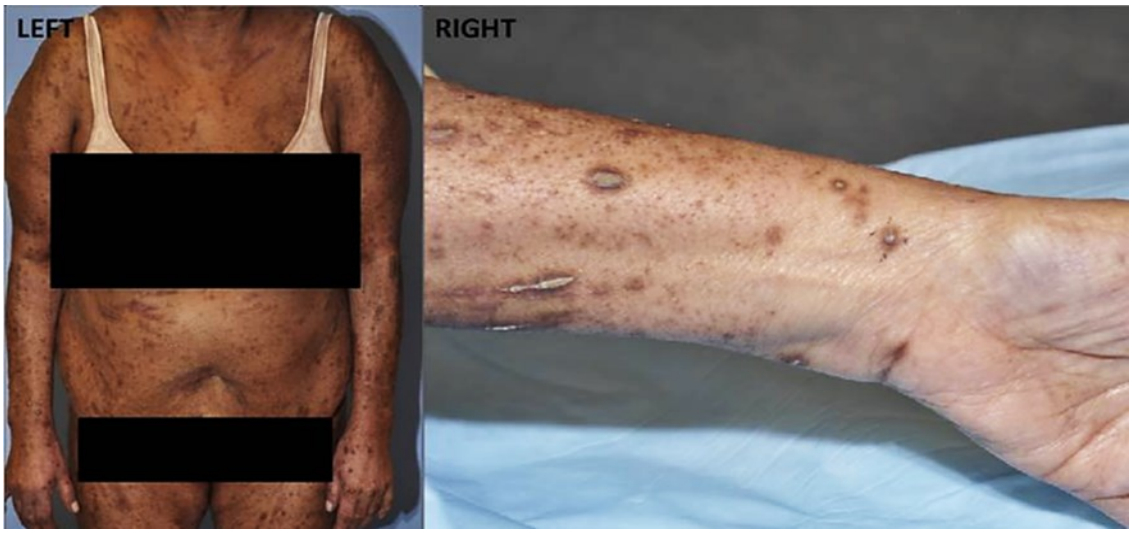


Figure 3 Pruritus-induced excoriations due to target treatment

Source: Ensslin et al., (2013)

4.4 Pruritus management measures using bibliographic references

As the precise process causing pruritus still remains unclear, conventional treatment methods are still used for its management (Song et al., 2018). Antihistamines though, which are typically used to treat pruritus, can fail to reduce itching symptom in some patients (Song et al., 2018). Recent research suggests that various therapeutic options for pruritus have been developed and are analysed below (Song et al., 2018).

The study of Satoh et al., (2021) is a doctoral dissertation that focuses on drug-induced pruritus in cancer patients (drug-induced category) that generated an algorithm (Figure 4) for pruritus management according to the cause of the pruritus symptom.

For cancer patients experiencing grade one pruritus, treatment is continued according to treatment protocol despite the reaction (Fisher et al., 2013). For this grade's management, topical steroids and oral anti-itch medications are recommended such as pramoxine 1%, doxepin 5% cream, and menthol 0.5%, while for small areas of skin presenting itchiness, lidocaine patches are also recommended (Fisher et al., 2013, Elmariah and Lerner, 2011). The physician's or patient's self-assessment for pruritus symptoms is re-evaluated after two weeks, and if the adverse skin reaction does not

improve, grade two pruritus management methods should be applied (Fisher et al., 2013).

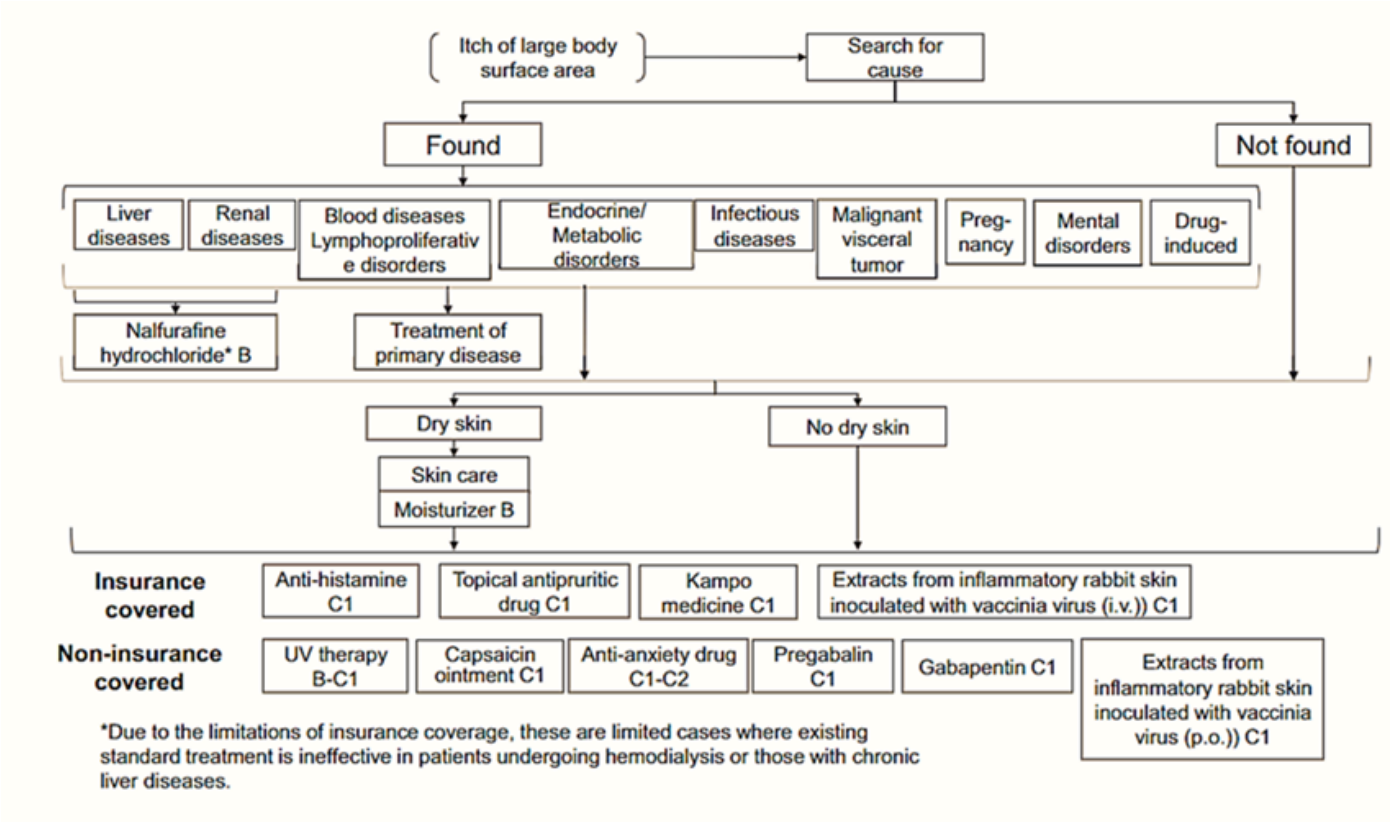


Figure 4 Treatment algorithm for pruritus

Source: Satoh et al., (2021)

For grade two skin pruritus cases, the anticancer regimen is provided regularly without a dose change but with continuous monitoring of pruritus symptom (Fisher et al., 2013). To manage this grade's symptoms, topical steroids or topical antipruritic agents such as pramoxine 1%, doxepin 5% cream and menthol 0.5% are suggested twice daily (Fisher et al., 2013). Furthermore, oral therapy with corticosteroids can be utilized (Fisher et al., 2013). At two weeks of treatment, reassessment of the skin symptoms is mandatory; if the symptoms are still present or worse, grade three pruritus management must be applied (Fisher et al., 2013).

For patients experiencing grade three skin pruritus, treatment dose adjustment is indicated in combination with bacterial and/or viral cultures from the lesions, in order to determine whether an infection co-exists with the condition (Fisher et al., 2013). Oral

anti-pruritus drugs and oral corticosteroids like prednisolone (0.5-1 mg/kg), are suggested for a five-day administration while if steroid treatment proves unsuccessful, oral gabapentin and pregabalin can be effective as alternative treatments (Fisher et al., 2013, Lacouture et al., 2010). Two weeks into treatment and new assessment of pruritus symptoms is required; if the symptoms exist at the same volume or worse, then a cancer-treatment dose modification is required or even discontinuation of it (Fisher et al., 2013).

Other treatment approaches recorder in literature are the orally administered drug aprepitant (Wu and Lacouture, 2018), while in cases of elevated Immunoglobulin E (IgE) levels in the blood, the drug omalizumab was provided for management (Barrios et al., 2021). According to the study of Lacouture et al., (2010) aprepitant, an NK-1 receptor antagonist, which is typically used to prevent nausea and vomiting in cancer patients undergoing chemotherapy (Vincenzi et al., 2020), can act as an effective antipruritic medication. As per Santini et al., (2012) the dosage of aprepitant for severe pruritus induced by biological anticancer drugs is 125 mg on day one reduced to 80 mg on day three and 80 mg on day five of treatment. Figure 10, from the study of Qin et al., (2019), shows the benefits of using oral aprepitant therapy for patients with rash and pruritus due to the drug gefitinib. In Figure 5, the image (A) refers to baseline while image (B) shows results from one week after treatment. Figure 6 from the study by Fisher et al., (2013) shows a skin pruritus treatment algorithm.

Many topical creams and ointments, such as moisturizers, antihistamines and local anaesthetics, in combination with skin coolants and low-PH cleansing agents, were also recorded to be used in clinical practice to reduce pruritic symptoms (Song et al., 2018). The study of Lacuture et al., (2010) also mentions that antihistamines such as loratadine (second-generation antihistamine) and hydroxyzine (first-generation antihistamine) are utilized for pain relief due to pruritus. The same data show that patients treated with loratadine and hydroxyzine had significantly reduction in mouth dryness and sedation than patients treated with hydroxyzine ($p<0.01$) (Lacouture et al., 2010).

In general, is important to notice that the administration of corticosteroids for pruritus management should only last for a short period of time, as prolonged use could cause further adverse reactions such as skin atrophy and dry skin (Song et al., 2018). Additionally, even regular measures such as avoiding irritating factors, preventing skin

dryness and keeping skin moist can also prove appropriate for the treatment and management of skin pruritus (Song et al., 2018).

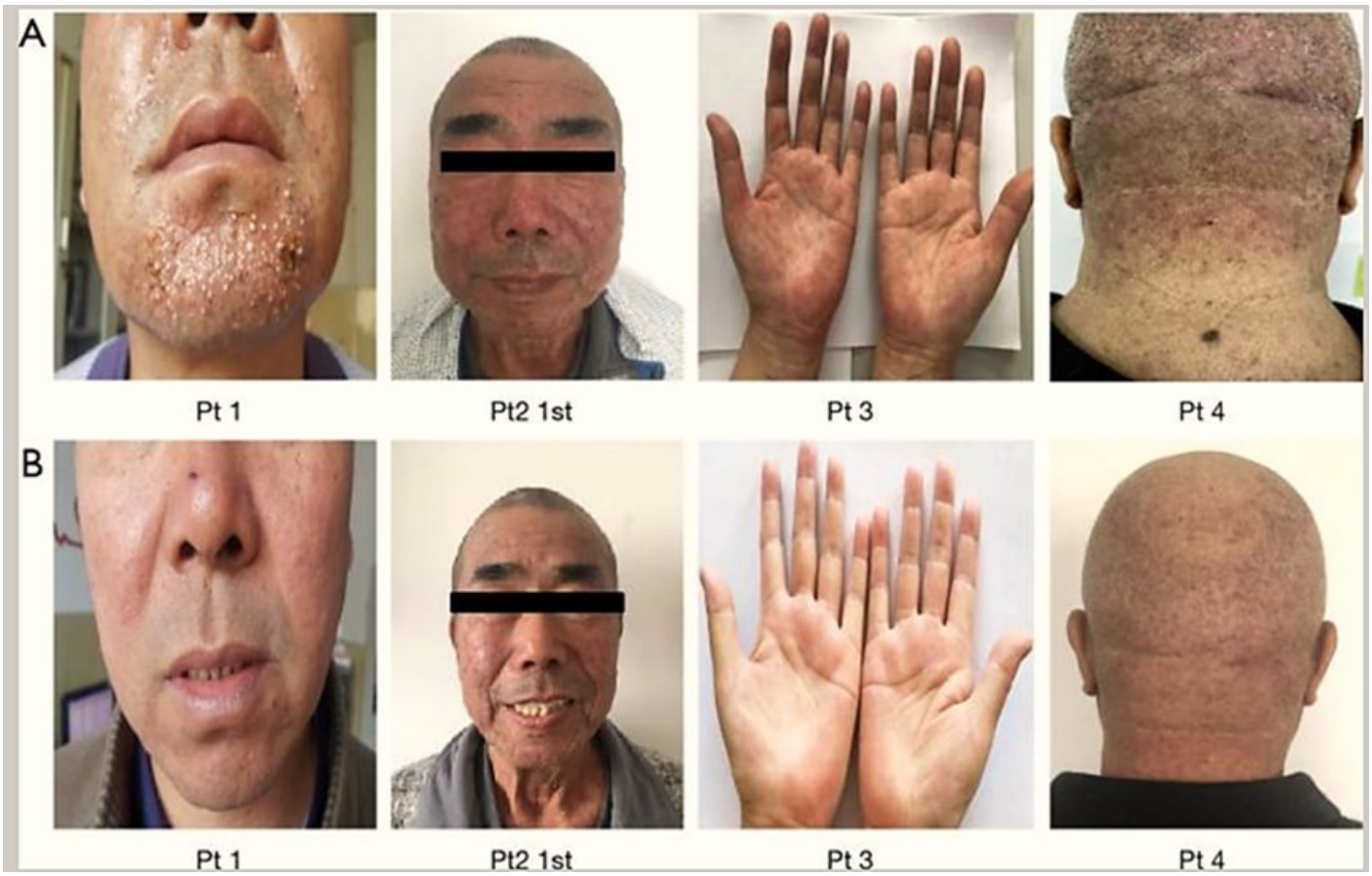


Figure 5 Benefits of aprepitant in gefitinib-induced rash and pruritus. (A) Baseline; (B) after one week of treatment.

Source: Qin et al., (2019)

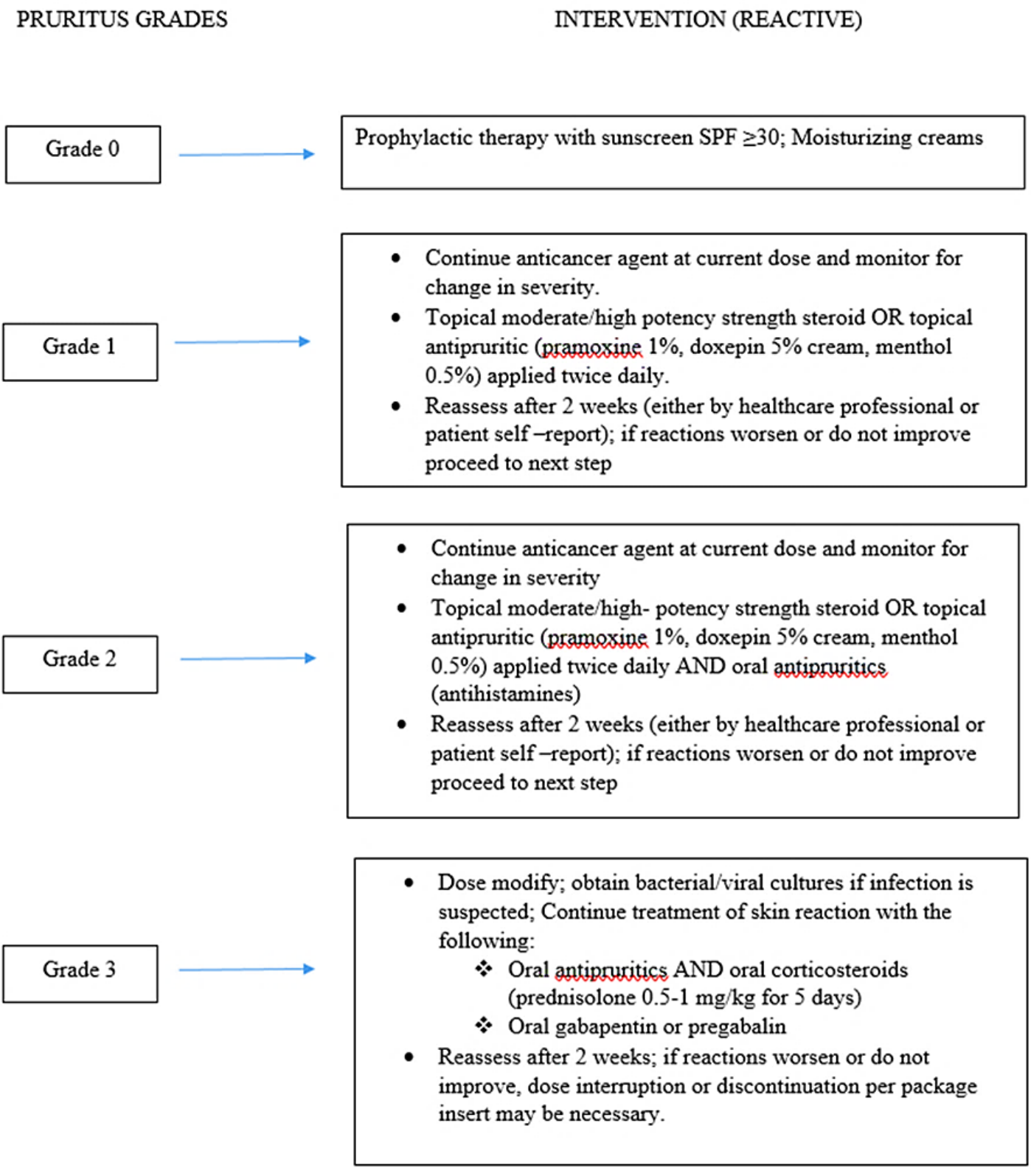


Figure 6 Pruritus intervention algorithm

Source: Fisher et al., (2013)

Finally, the study of Lacouture et al., (2010) noticed that skin pruritus can be a consequence of dry skin, so it is important to ensure measures to prevent dry skin. Preventative measures for dry skin include bathing in lukewarm water and using moisturizing bath oils and soaps that are fragrance and alcohol-free (Lacouture et al., 2010). Also, using heparinoid creams or lotions for 2 weeks, herbal moisturizers, and moisturizers containing ingredients like urea and propylene glycol, can help reduce pruritic symptoms due to dry skin (Satoh et al., 2021). Finally, patients should avoid exposure to extreme temperatures, such as those in very cold or very hot days (Lacouture et al., 2010).

4.5 New aspects on pruritus treatment according to bibliography

Recent evidence has suggested that, apart from corticosteroids, various therapeutic options for pruritus have been developed (Song, 2018). Below, we present some of the new therapeutic strategies for pruritus, excluding corticosteroids and antibiotics.

Among the newest approaches of pruritus treatment are topical calcineurin inhibitors called tacrolimus and pimecrolimus (Patel and Yosipovitch, 2010). Tacrolimus ointment and pimecrolimus cream are non-corticosteroid topical anti-inflammatory agents used to treat dermatitis (Patel and Yosipovitch, 2010), prevent skin atrophy and treat unpleasant skin reactions in sensitive skin areas. (Luger et al., 2013).

Orvepitant is another recent, oral drug that belongs to the class of NK1 antagonists, as aprepitant, and it is characterized by antipruritic effects in patients who develop itching following an EGFRI treatment (Vincenzi et al., 2020). The study of Vincenzi et al., (2020) evaluated the efficacy of 10 and 30 mg of orvepitant treatment, compared to placebo, over a 4-week period, and showed that it is a safe and well tolerated management option for pruritus experiencing-patients. Although, due to technological limitations and the small number of patients recruited for the study, the findings were not validated (Vincenzi et al., 2020).

The use of colloidal oatmeal lotion is presented in bibliography as another new treatment option for pruritus (Ke and Kuo, 2017). The colloidal oatmeal lotion is made from oats and has been used to treat adverse skin reactions since 1945, while it was

approved by the FDA as a skin protectant in 2003 (Ke and Kuo, 2017). Colloidal oatmeal contains proteins, starches, polysaccharides, essential fatty acids, phospholipids and A-glucan and is characterized by many favourable properties such as cleansing, moisturizing, anti-irritant, antipruritic, antioxidant, anti-inflammatory, and skin-repairing properties (Ke and Kuo, 2017). The study of Ke and Kuo, (2017) showed that pruritus was significantly reduced in the first week (p=.008) of use of the colloidal oatmeal lotion and declined over the next 4 weeks (p<.001). The generalized estimating equation model analysis of the pruritis scale for patients treated with colloidal oatmeal lotion is shown in Figure 7 (Ke and Kuo, 2017).

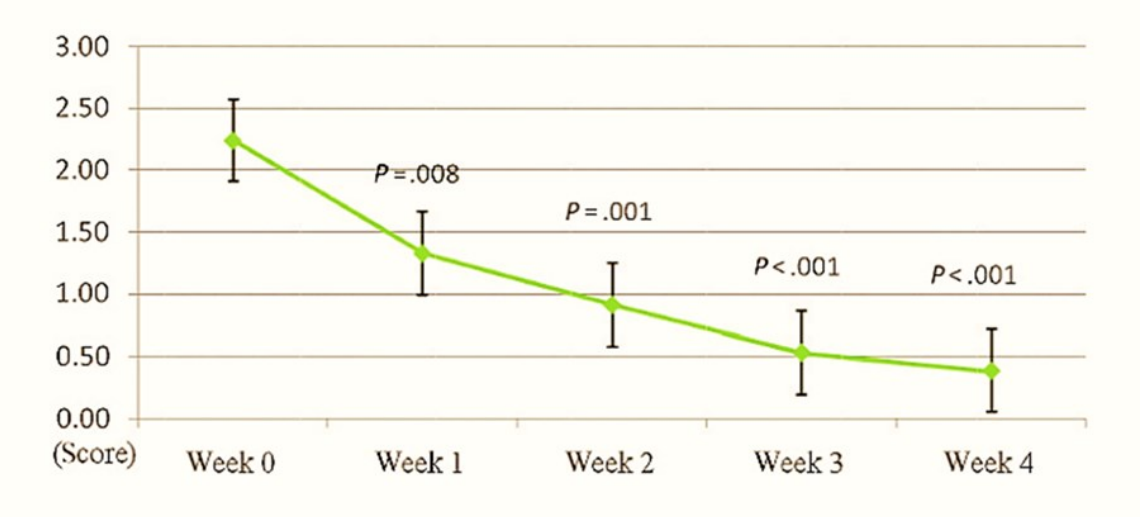


Figure 7 Generalized estimating equation (GEE) model analysis of pruritus scale for patients treated with the Colloidal oatmeal lotion

Source: Ke and Kuo, (2017)

Finally, selective serotonin reuptake inhibitors (SSRIs) Paroxetine and Fluvoxamine, drugs used to treat depression, were also found to be effective in treating chronic and generalized itch (Satoh et al., 2021). Oral paroxetine (20 mg/day) significantly reduces the symptoms of pruritus due to drug-induced itching (Satoh et al., 2021). These selective serotonin reuptake inhibitors (SSRIs) was proved that they can be used when other antipruritic treatments have failed (Satoh et al., 2021).

5 RASH

Rash is a skin condition characterized by the appearance of papules and pustules on the face, scalp, upper chest, and back (Fabbrocini et al., 2015). It is a common skin adverse event associated with EGFRI treatments (Zhang, Ran and Wang, 2016) and is classified into five stages according to its severity (Fabbrocini et al., 2015). Skin rash can lead to dose reduction of appropriate cancer treatment or discontinuation of it and can also impair patients QoL (Zhang, Ran and Wang, 2016).

The following sub-chapters describe the pathophysiology of skin rash (sub-chapter 5.1), the assessment for the skin rash grades according to the NCI- CTCAE v. 5.0 (sub-chapter 5.2), the management of skin rash according to bibliographic references (sub-chapter 5.3) and finally the new aspects of rash treatment according to bibliography (sub-chapter 5.4).

5.1 Pathophysiology of rash

Skin rash is the most common side effect of EGFRI treatments. EGFR, that stands for epidermal growth factor receptor, belongs to a family of tyrosine kinase receptors called ErbB that regulate tumor cell differentiation, survival, and proliferation (Lacouture, 2007, Fabbrocini et al., 2015). The EGFR family consists of EGFR (or ErbB1), ErbB2, ErbB3, and ErbB4 (Lacouture, 2007). EGFR is a 170-kd transmembrane glycoprotein receptor of the cell surface that plays an essential role in epidermal development and maintenance (Lacouture, 2007) and it is expressed in many different cell types in normal tissues, such as skin and hair follicles (Fabbrocini et al., 2015). The skin of a normal adult is composed of three layers: the epidermis, dermis, and hypodermis (Fabbrocini et al., 2015), with the highest EGFR expression found in the EGFR-expressing keratinocytes of the basal and suprabasal layers of the epidermis and the outer root sheath of hair follicles (Lacouture, 2007, Fabbrocini et al., 2015). As outer root sheath of the hair follicle is adjacent to the basal layer it shares common biochemical properties with it and one of those is the high EGFR expression.

Over 10 ligands can interact with one or more members of the ErbB family, including EGF, transforming growth factor alpha (TGF-"), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AR), epiregulin (ER), betacellulin (BTC), and the

neuregulins (Lacouture, 2007). For the purposes of cancer treatment, EGFR can be inhibited by monoclonal antibodies such as cetuximab and panitumumab, and small-molecule tyrosine kinase inhibitors such as erlotinib and gefitinib (Lacouture, 2007). Monoclonal antibodies target EGFR by preventing ligand binding and receptor dimerization, while the small-molecule tyrosine kinase inhibitors competitively inhibit ATP binding to the receptor, thus impeding autophosphorylation and kinase activation (Lacouture, 2007).

The inhibition of EGFR in keratinocytes due to EGFRI treatment induces apoptosis, arrests cell growth, reduces cell migration and increases cell adhesivity and cell differentiation (Fabbrocini et al., 2015). All these processes induce the release of inflammatory chemokines [chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-C motif) ligand 5 (CCL5), and C-X-C motif chemokine 10 (CXCL10)/interferon-inducible protein 10 (IP-10)] from keratinocytes (Fabbrocini et al., 2015). While all the above aim to fight cancer cells, the arrest of cell growth, the reduction in migration of keratinocytes and the inducement od inflammation, can eventually lead to a skin rash (Fabbrocini et al., 2015). Figure 8 shows the pathogenesis of inflammatory cell infiltration that occurs in an EGFRI-induced rash.

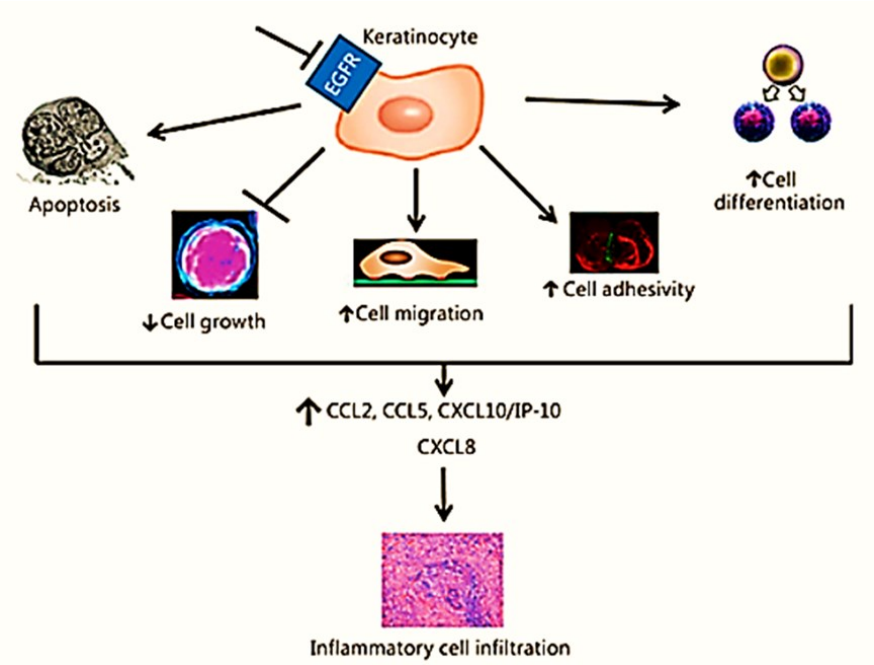


Figure 8 Pathogenesis of inflammatory cell occurring in the EGFRI-induced skin rash.

Source: Fabbrocini et al., (2015)

5.2 Grades of skin rash according to the NCI- CTCAE v. 5.0

A grade one rash manifests via papules and/or pustules that cover less than 10% of the BSA and may or may not be associated with signs of pruritus or sensitivity (CTCAE v. 5.0, 2017). Grade two rash is classified into two categories: a. with papules and/or pustules covering 10 to 30% of the BSA and b. with more than 30% of the BSA covered by papules and/or pustules with mild symptoms or no symptoms (CTCAE v. 5.0, 2017). A grade three rash is characterized by papules and/or pustules covering more than 30% of the BSA with moderate to severe symptoms (i.e., limiting self-care ADL) or is associated with a topical infection that requires oral antibiotics (CTCAE v. 5.0, 2017). Grade four rashes have life-threatening consequences or are characterized by papules and/or pustules covering any percentage of the BSA, may or may not be associated with symptoms of pruritus or sensitivity and are associated with widespread infection, requiring intravenous antibiotics. Finally, grade five rashes are lethal. Table 2 illustrates the degrees of skin rash according to CTCAE v. 5.0, 2017.

Table 2 Rash definition and grades

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash	Papules and/or pustules covering <10% BSA, may or may not be related	Papules and/or pustules covering 10 - 30% BSA, may or may not be related with signs of pruritus or	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; related with local	Life-threatening; papules and/or pustules covering any % BSA, which may or may not be related with symptoms of	Death

	with signs of pruritus or tenderness.	tenderness; associated with psychosocial impact; limiting instrumental ADL. Papules and/or pustules covering > 30% BSA with or without mild Symptoms.	superinfection, oral antibiotics indicated	pruritus or tenderness and are associated with extensive superinfection; IV antibiotics indicated	
Definition: A disorder characterized by an eruption of papules and pustules.					

Source: CTCAE v5.0 – November 27, (2017)

The following figure shows the percentage of body surface area (BSA) associated with adverse skin reactions regarding the degree of rash (Figure 9).

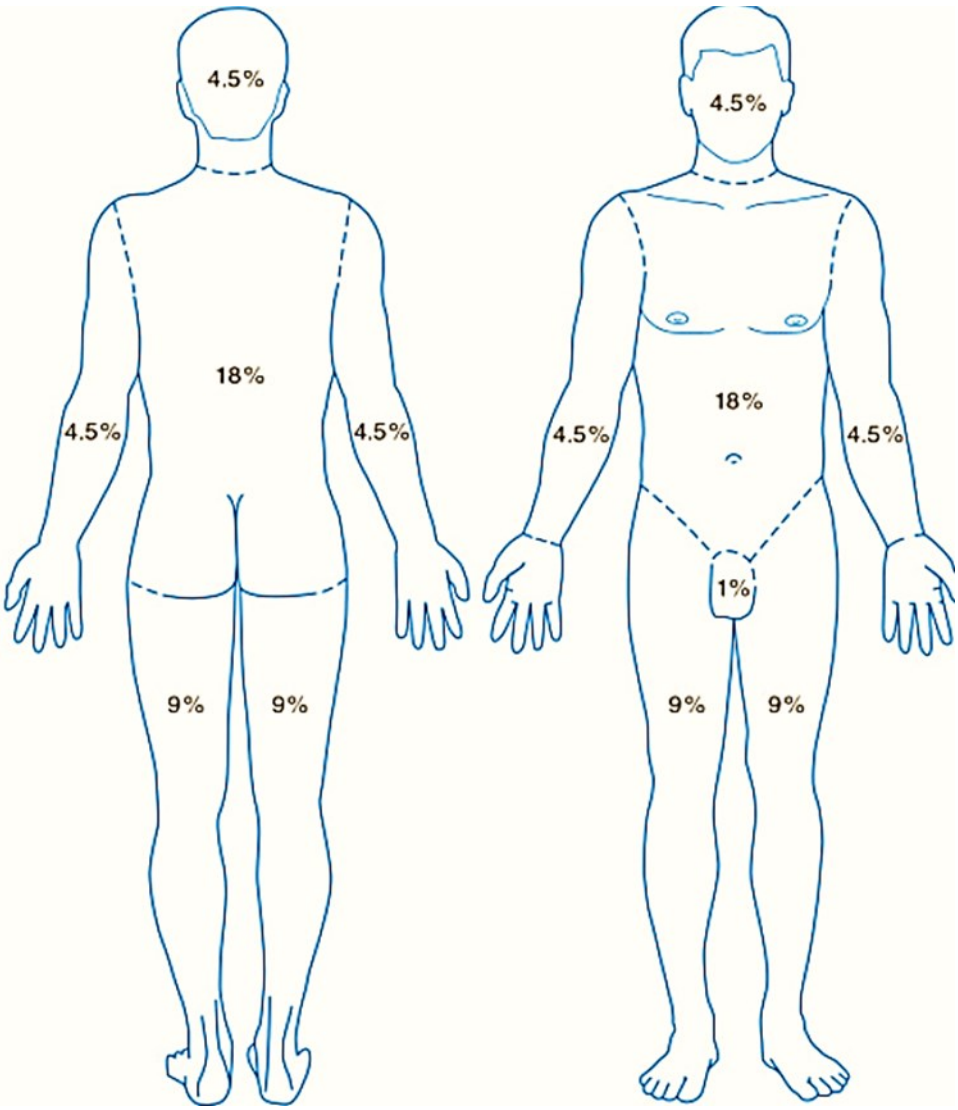


Figure 9 Schematic of body surface area (BSA)

Source: Haanen et al., (2017)

Furthermore, Figure 10 from the study by Melosky et al. (2015), illustrates the grades of rash, from grade one to grade four, to patients who received EGRI therapy. More precisely, image (A) shows a woman with grade one rash resulting from treatment with gefitinib; image (B) shows a patient with a grade two rash caused by erlotinib treatment. Images (C) and (D) refer to two different patients with grades three and four, respectively, caused by EGFRI treatment with erlotinib (Melosky et al., 2015).

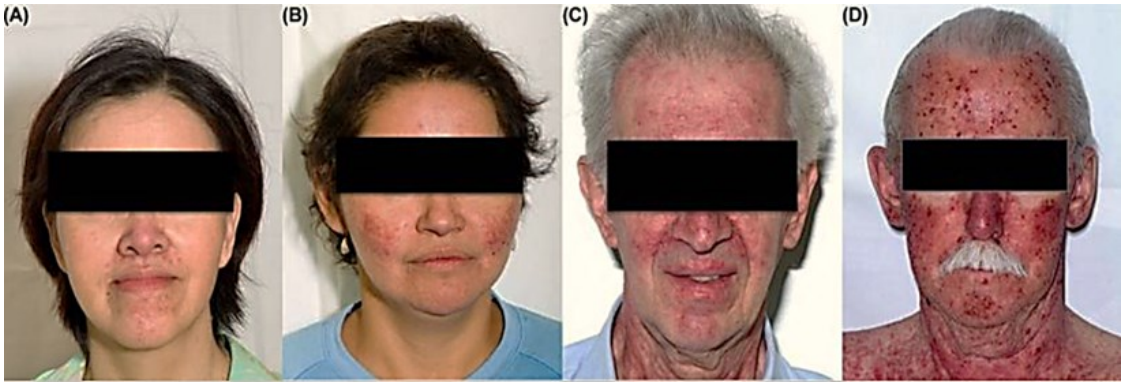


Figure 10 Skin rash due to EGFRI treatment

Source: Melosky et al., (2015)

5.3 Rash management through bibliographical references

The bibliographic references available indicated that the typical treatment for a rash of any degree includes antihistamines, topical corticosteroids and oral and topical antibiotics (Brown et al., 2016). Lacouture et al. (2011) recommend hydrocortisone 1% in combination with doxycycline tablets (100 mg twice daily) and moisturizers with sun protection for the first six weeks when initiating an EGFRI treatment. The same study also notes that minocycline tablet at a dose of 100 mg per day, is also an effective method of reducing the degree of rash during the first eight weeks of EGFRI treatments (Lacouture et al., 2011). The risk of developing skin photosensitivity is also lower with minocycline, while the doxycycline tablet presents a good safety record for treating rashes, especially in patients with co-current renal insufficiency (Lacouture et al., 2011).

According to the study by Fabroccini et al., (2015) for the management of rash grade one and rash grade two, topical hydrocortisone cream 1% or 2.5% or clindamycin 1% gel are indicated. For grade three rash the treatment should involve hydrocortisone cream 2.5%, clindamycin gel 1%, or pimecrolimus 1% cream with a combination of doxycycline tablets at 100 mg twice a day or minocycline tablets at 100 mg also twice a day. With the addition of methylprednisolone (Fabbrocini et al., 2015), dexamethasone, or prednisolone, the same intervention treatment could be utilised for rash grade four management (Kozuki, 2016).

The efficacy of oral minocycline over EGFRI treatment-induced rash was first tested in 2007 in a clinical trial by Scope et al. (2007). The study was conducted with a total of 48 patients and aimed to evaluate whether oral minocycline 100 mg could prevent rashes associated with EGFRI treatment (Scope et al., 2007). The study's data indicated that the number of facial skin lesions was significantly lower in patients who received the antibiotic tablet during week one, week two, and week four compared to those who received the placebo tablet. Specifically, rash lesions in the experimental group (minocycline group) versus the control group (placebo) were 17.1 and 47.9 respectively in week one ($p = 0.05$), 34.3 in the minocycline group and 132.5 in the placebo group at week two ($p = 0.025$) and 61 in the minocycline versus 110.2 the placebo group at week four ($p = 0.008$) (Scope et al., 2007).

Another randomized clinical trial from 2010 by Lacouture et al., with a recruit of 95 patients with metastatic colorectal cancer under panitumumab treatment (STEPP trial-Skin Toxicity Evaluation Protocol with Panitumumab), tested the efficacy of topical steroids, moisturizers, sunscreen and doxycycline as prophylaxis or as treatment against rash, depending on the severity of the skin reaction. Results were better in the prophylaxis group compared to treatment group as the rate of grade two rash or higher was 29% and 62% respectively in the groups. (Lacouture et al., 2010). A study by the same group from 2011, suggested also the application of a steroid cream or gel in combination with oral corticosteroids of 0.5 to 1 mg/kg/day for the management of rash (Lacouture et al., 2011).

Another study, from Fabroccini et al. from 2015, created a protocol for the treatment of EGFRI-induced rash which recommends the application of a combination of gentamicin 0.1% ointment and clindamycin 1% gel on a skin rash area and, in severe cases, prednisone 12.5–25 mg/day (Fabbrocini et al., 2015). According to their results, gentamicin ointment and clindamycin gel healed the rash within two weeks of application (Fabbrocini et al., 2015).

Unfortunately, though, if the rash is severe and cannot be managed by all the above, hospitalization may be required and cancer treatment should be suspended until further notice. Table 3 summarizes strategies for the management of EGFRI-induced rash.

Table 3 Strategy for the management of EGFRI-associated skin rash

	Systemic	Topical
Prevention	Minocycline 100 mg twice a day Tetracycline 250 mg twice a day Doxycycline 100 mg twice a day	Hydrocortisone 1% cream Steroid cream/ointment
Treatment	Minocycline 100 mg twice a day Tetracycline 500 mg twice a day Doxycycline 100 mg twice a day Prednisolone 10 mg/day (need to re-evaluate after 2 weeks of use)	Topical antibiotics Nadifloxacin cream and clindamycin gel

Source: Kozuki, (2016)

5.4 New aspects for the treatment of skin rash

To this sup-chapter we present some of the new therapeutic strategies for rash found in more recent bibliographic sources.

The study of Annunziata et al. from 2019, suggests that a cream with the brand name Fucimix Beta can be used by patients who develop skin rashes following treatment with panitumumab or cetuximab. This cream is a lipid cream for topical use and its main ingredients are fusidic acid in combination with betamethasone (Annunziata et al., 2019). Fucimix Beta cream has antibiotic and corticosteroid properties and is therefore used as an effective treatment for various types of skin diseases (Annunziata et al., 2019). In the aforementioned study, five patients with an EGFRI therapy-induced rash showed significant improvement following two weeks of treatment with the Fucimix Beta cream. Figure 11 illustrates five cases of patients with EGFRI treatment-induced rash through images a, c, e, g, i. The same cases appear in images b, d, f, h, and j

significantly improved following treatment with fusidic acid plus betamethasone lipid cream (Annunziata et al., 2019).

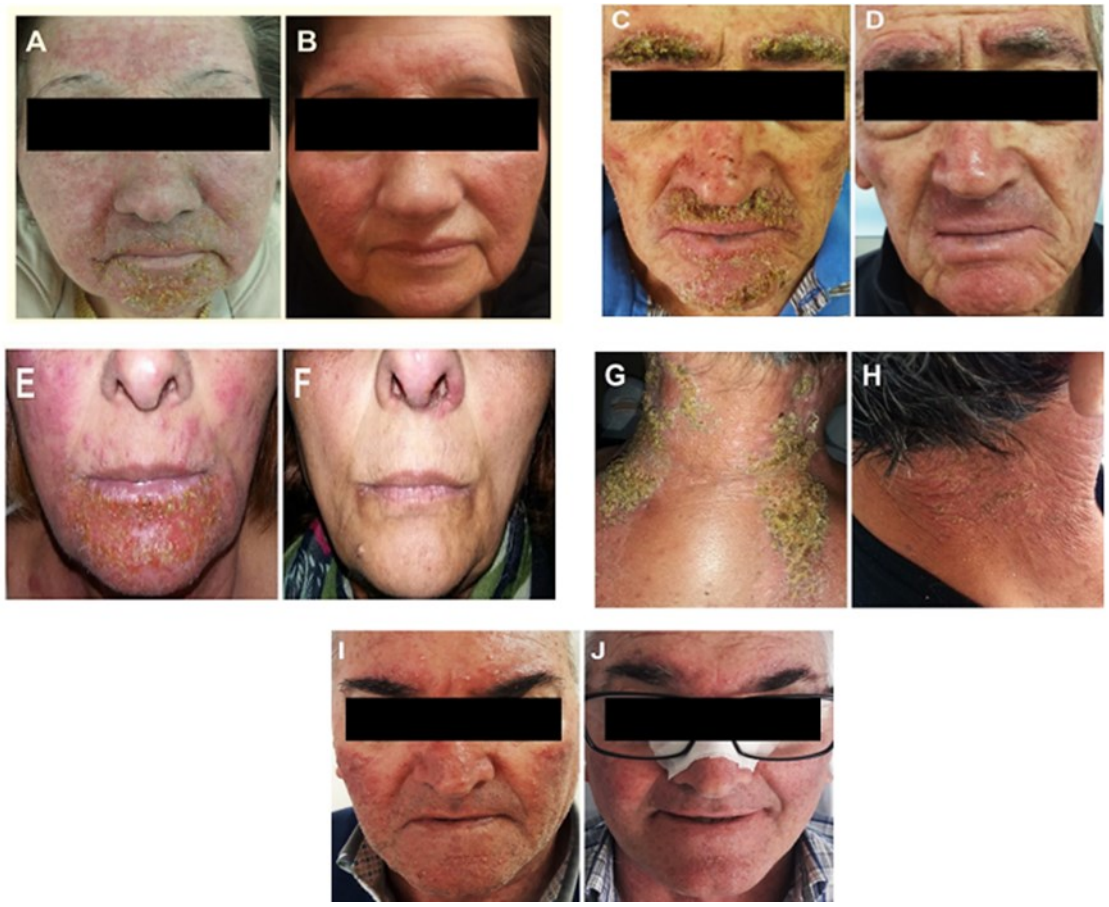


Figure 11 Improvement of the rash due to EGRFI treatment using fusidic acid plus betamethasone lipid cream

Source: Annunziata et al., (2019)

Topical application of vitamin K creams has also been suggested as an effective treatment for managing rashes (Lobo et al., 2020; Kozuki, 2016). Vitamin K1 (also called phylloquinone, phytomenadione) is an EGFR activator which can reduce rashes caused by EGFRI treatment (Li et al., 2015). More specifically, 0.1% vitamin K1 cream was used for the prevention of rash in cancer patients treated with EGFRI at the study of Lobo et al. (2020), while Kozuki's (2016) study recommends a twice daily application of 0.1% vitamin K1 cream in order to reduce the severity of these adverse skin reactions and decrease the duration of a rash.

Furthermore, a study by Andrews, Garg and Patel from 2020 concluded that oral retinoids may also be an effective treatment for rashes resulting from EGFRI treatment. Acitretin (10-25 mg/day) or isotretinoin (30-40 mg/day) can also reduce the severity of skin rashes (Andrews, Garg and Patel, 2020). A case study of a 70-year-old cancer patient who experienced rash grade two as a result of erlotinib treatment, saw a mild improvement after taking isotretinoin 20 mg daily for seven to eight months, something that enabled him to continue his treatment protocol without the use of antibiotics (Costello et al., 2021).

Applying aloe vera to the affected skin is another treatment suggestion for rash (Gürbüz, Akkuş, and Utkan, 2020). The case study by Gürbüz, Akkuş, and Utkan from 2020, refers to a 60-year-old male cancer patient who developed rash after receiving cetuximab treatment. The rash appeared on the patient's face one week after beginning cetuximab and progressed to grade three eventually (Gürbüz, Akkuş, and Utkan 2020). To treat rash, the patient applied gel from the aloe vera plant to the affected skin areas three times daily for two weeks (Gürbüz, Akkuş, and Utkan, 2020). The rash improved significantly and grade classification changed to grade one, while the aloe vera application was continued until the rash resolved completely resolved. (Gürbüz, Akkuş, and Utkan, 2020). Figure 12 depicts the abovementioned patient's rash following the initiation of cetuximab treatment and Figure 13 shows the patient's improvement following the application of aloe vera.

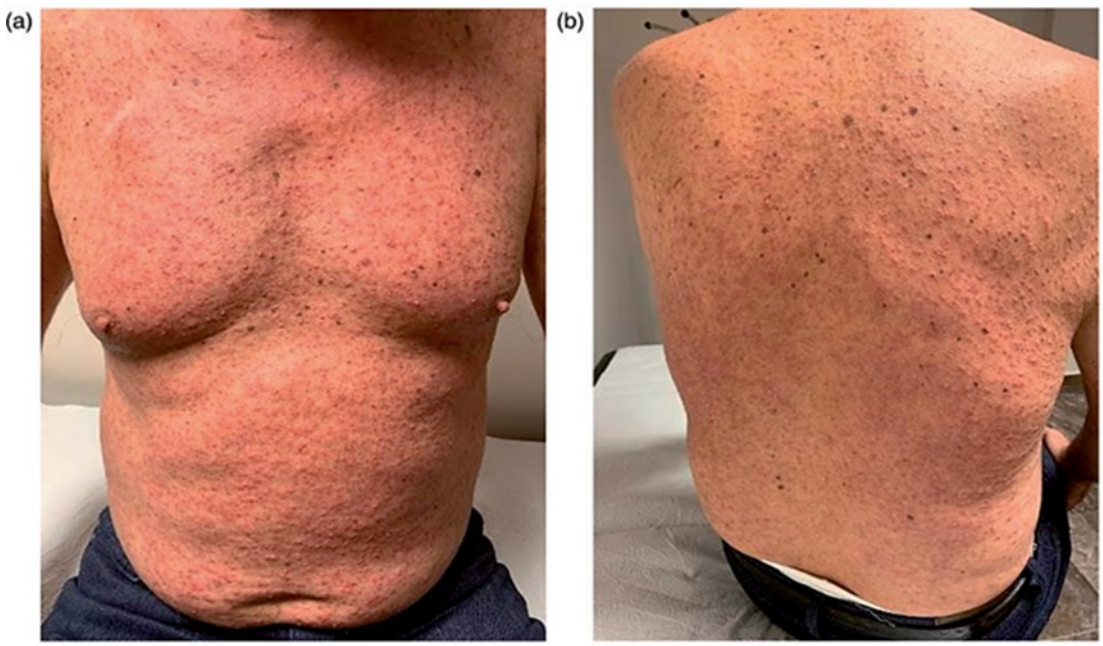


Figure 12 Skin rash after initiation of cetuximab treatment

Source: Gürbüz, Akkuş and Utkan, (2020)

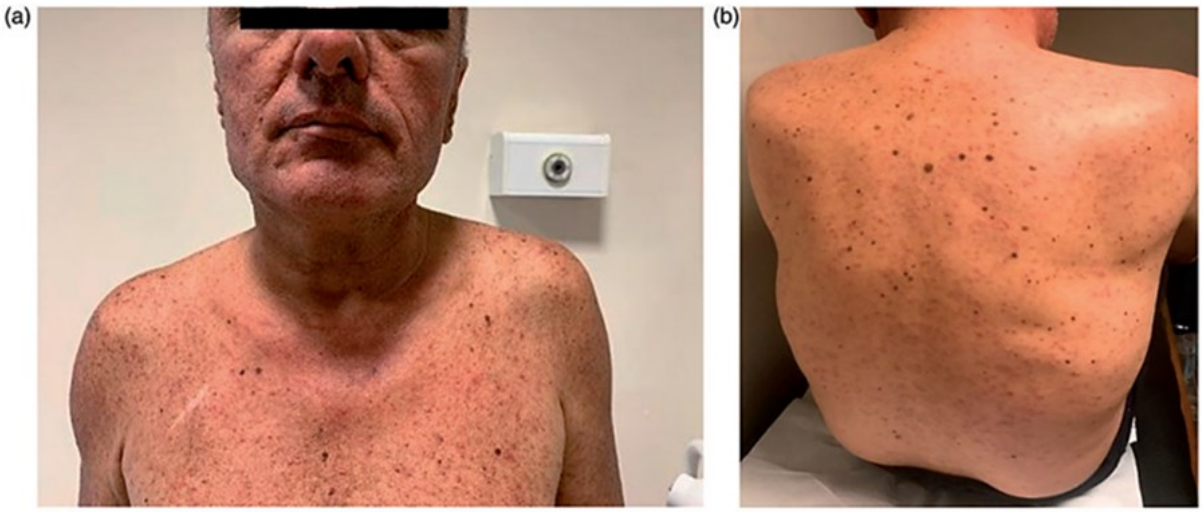


Figure 13 The patient's skin after using aloe vera

Source: Gürbüz, Akkuş and Utkan, (2020)

The use of honeysuckle (chrysanthemum tea), a traditional East Asian herb characterized by antioxidant and anti-inflammatory properties, is another recorded method used to manage skin rash resulting from EGFRI treatment (Liu et al., 2022). In 2022, Liu et al., conducted a randomized controlled trial to investigate the effect of honeysuckle as prophylaxis and treatment against rash, in colorectal and lung cancer patients treated with EGFRI therapy. For the purposes of the study, the participants were divided into three arms "A", "B" and "C". Patients in group "A" were given 10 g of honeysuckle twice daily in 200 ml of soup as a precaution, while in the appearance of rash, patients used 1 gauze soaked in 1,000 ml of water containing 50 g of honeysuckle for topical application to the affected skin area (Liu et al., 2022). Patients with a rash greater than or equal to grade 1 (arm "B" participants) received honeysuckle orally, twice daily in combination with the soaked topical gauze for topical application. Finally, patients in arm "C" received 100 mg minocycline daily in combination with 2% clindamycin and 1% hydrocortisone twice daily (Liu et al., 2022). According to the results of the study, patients in category "A" had lower rate of skin rashes compared to the other two categories, so the use of honeysuckle as prophylaxis was shown to be more effective (Liu et al. (2022). The results between the three groups, regarding the

incidence of rash, showed no statistical significance (p = 0.280). Figure 14 shows the effect of honeysuckle on cancer patients after 7, 14 and 21 days of use.

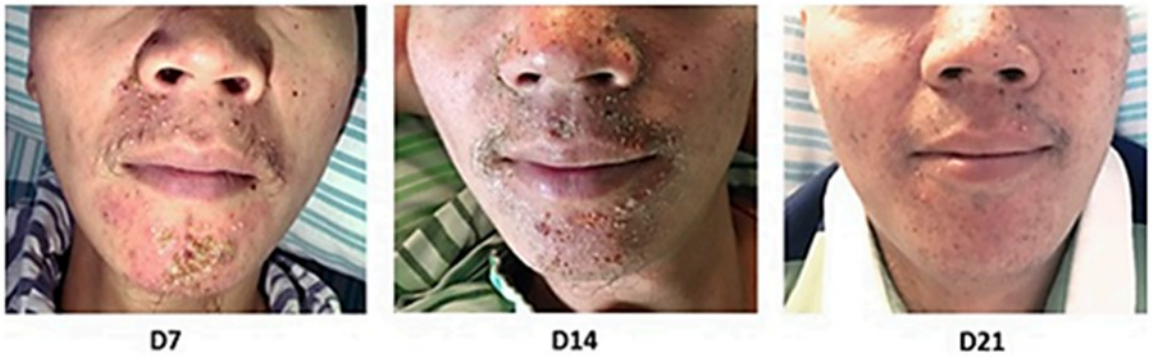


Figure 14 The effect of honeysuckle on rashes in group B patients recovering from grade 2 rash (days 7-21)

Source: Liu et al., (2022)

6 PHOTOSENSITIVITY

Photosensitivity is defined as the disorder where the skin presents high sensitivity due to exposure to light sources (Lembo et al., 2020). Clinically, photosensitivity is recognized as sunlight-induced dermatitis appearing after topical or systemic use of a photosensitizing drug, characterized by skin rashes that typically occur on sun-exposed areas, including the cheeks, nose, forehead, posterior neck, V region of the neck, dorsum of the hands, extensor side of the forearms, and lower legs (Lugović-Mihić et al., 2017, Lembo et al., 2020). According to symptoms severity, the condition has five grade classifications (Lembo et al., 2020). Therapies with BRAF kinase inhibitors (BRAFi) such as vemurafenib and dabrafenib, treatments with fluoroquinolones (5-FU) and EGFR inhibitors have been reported as the main cause of photosensitive skin reactions (Lugović-Mihić et al., 2017, Lembo et al., 2020). Chemotherapeutic drugs such as paclitaxel, nab-paclitaxel (Abraxane), and docetaxel have also been associated with skin photosensitivity (Beutler and Cohen, 2015). An example is demonstrated in the research study by Beutler and Cohen (2015) where a cancer patient, treated with a combination of anticancer drugs (carboplatin, pemetrexed, gemcitabine, vinorelbine and nab-paclitaxel), presented a photosensitivity skin reaction associated with nab-paclitaxel administration (Beutler and Cohen, 2015).

6.1 Pathophysiology of photosensitivity

Photosensitivity is divided into two subcategories, the phototoxic and the photoallergic skin reaction, according to the pathophysiological mechanism (Lugović-Mihić et al., 2017).

Drug-induced phototoxicity is mainly characterized by an exaggerated sunburn following sun exposure (Kowalska et al., 2021). The onset of phototoxicity occurs rapidly, within minutes from exposure, and the type and severity of symptoms depend on the provided photosensitizing drug or the therapeutic dose (Kowalska et al., 2021).

Phototoxicity is a non-immunological inflammatory mechanism resulting from direct cytotoxic damage caused mainly by radical oxygen species (ROS) and occurs following interaction of ultraviolet sunlight A (UVA) or ultraviolet B sunlight (UVB) with a phototoxic medicine (Hofmann and Weber, 2021). Phototoxic reactions necessitate the

endogenous or exogenous chromophore to engage with incoming photon radiation, thereby changing its structure from a stable to a motivating form (Hofmann and Weber, 2021). A photoproduct is produced when the structure becomes stable again, and this in turn triggers a complex photochemical process responsible for phototoxic reactions (Lugović-Mihić et al., 2017).

A drug-induced photoallergic reaction is characterized by eczema, which usually occurs 24 to 72 hours after the combination of a photosensitizing drug and exposure to UVA or sometimes UVB sunlight (Lembo et al., 2020). This response is a cell-mediated immune response in which the antigen is a photo-activated drug (Lembo et al., 2020).

Distinguishing between drug-induced phototoxicity and drug-induced photoallergy in patients can be difficult, although the treatment and management of these types of skin reactions usually do not differ (Blakely, Drucker and Rosen, 2019). The research by Kowalska et al. (2021) illustrates in a figure the pathophysiology of drug-induced photosensitivity dermatitis as well as the variations between phototoxicity and photoallergic pathology (Figure 15).

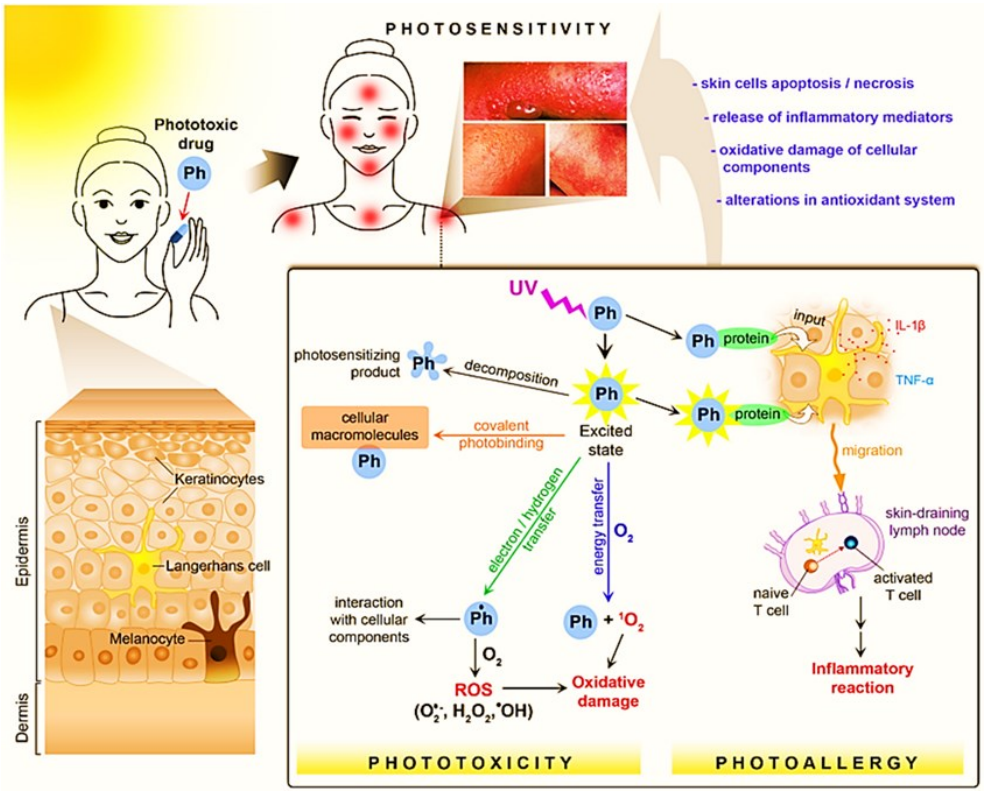


Figure 15 Mechanisms of drug-induced photosensitivity dermatitis

Source: Kowalska et al., (2021)

6.2 Grades of photosensitivity according to the NCI- CTCAE v. 5.0

Grade one photosensitivity manifests as painless erythema covering less than 10% of patient's BSA, while grade two is characterized as tender erythema covering 10 to 30% of BSA (CTCAE v. 5.0, 2017). Photosensitivity grade three is defined as erythema covering more than 30% of the BSA, requiring treatment with oral corticosteroid or pain control medication (CTCAE v. 5.0, 2017). In grade four photosensitivity, urgent intervention is required to manage life-threatening symptoms, while grade five photosensitivity is fatal (CTCAE v. 5.0, 2017). Table 4 shows the photosensitivity grades according to CTCAE v5.0.

Table 4 Photosensitivity definition and grades

CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

Source: CTCAE v5.0 – November 27, (2017)

Figure 16, taken from the study of Boussemart et al., (2013), illustrates the case of a woman with photosensitive dermatitis after 40 days of treatment with a photosensitizing drug.

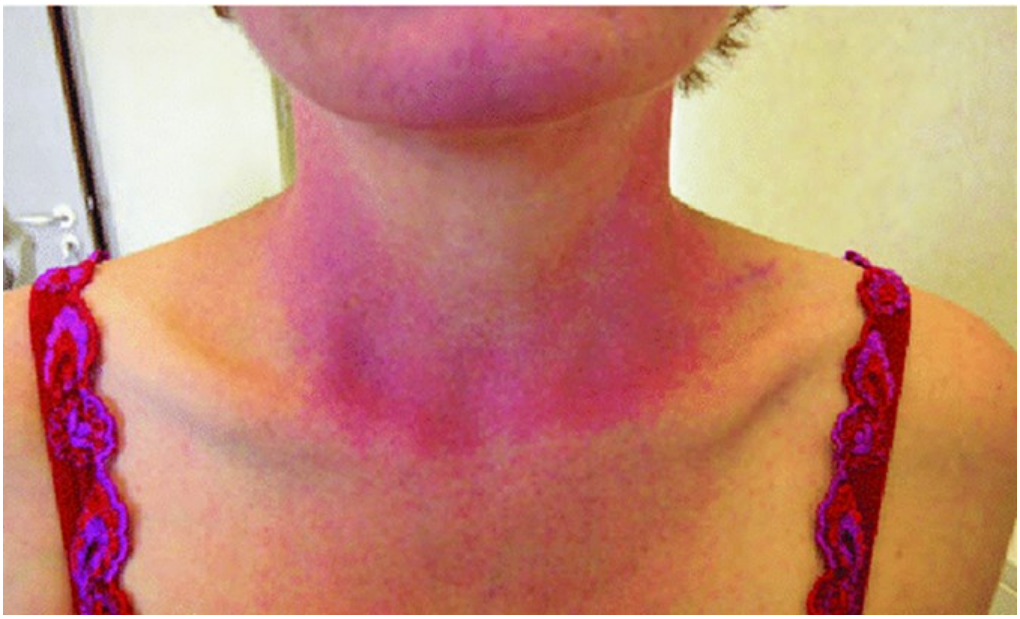


Figure 16 Photosensitivity after 40 days of treatment with a photosensitizing drug.

Source: Boussemart et al., (2013)

6.3 Management measures of photosensitivity from bibliographic references

The most effective treatment of photosensitivity is the discontinuation of the photosensitizing drug, with skin photosensitivity usually resolved shortly after discontinuation of the photosensitizer agent (Kowalska et al., 2021). For example, photosensitivity induced by fluoroquinolones usually disappears within a week, although it can last for several months in some cases (Kowalska et al., 2021). In the situation where patients are not able to stop taking the photosensitizing medicine, precautions should be taken in order to minimise the likelihood of developing photosensitivity (Kowalska et al., 2021).

Preventive measures for photosensitivity include wearing a wide-brimmed hat and sunglasses in addition to high UVA photoprotection sunscreen (Lembo et al., 2020).

Some useful tips extracted from the study of Moore et al., (2002) regarding the use of sunscreens, note that offer sunscreens should offer protection against UVB and UVA rays while their sun protection factor (SPF) should be 50 or higher. Sunscreens must also be water resistant and thoroughly cover all exposed skin areas when applied (Moore, 2002). Additionally, sunscreen should be applied generously about 15 minutes before sunlight exposure and reapplied every two hours while outdoors (Moore, 2002). On the other hand, sunscreen tanning products should be avoided as they contain dihydroxyacetone, also known as glycerone, that provides only medium to low photoprotection against UVA and even lower photoprotection against UVB (Moore, 2002).

Additional preventative measures against photosensitivity dermatitis include avoiding exposure to direct sunlight, staying indoors and away from windows and seeking shade when outdoors (Moore, 2002). According to the study of Moore (2002), another effective preventive measure is the turn to an antioxidant diet rich in vegetables, fruits and supplements of vitamins A, C and E, that offers antioxidant protection against UVA and UVB-induced photo-skin damage.

The study of Labadie et al., (2022) provides a figure of basic preventive measures for patients treated with rucabarib, an anti-cancer medicine, in order to reduce the risk of photosensitivity dermatitis in these patients (Figure 17).

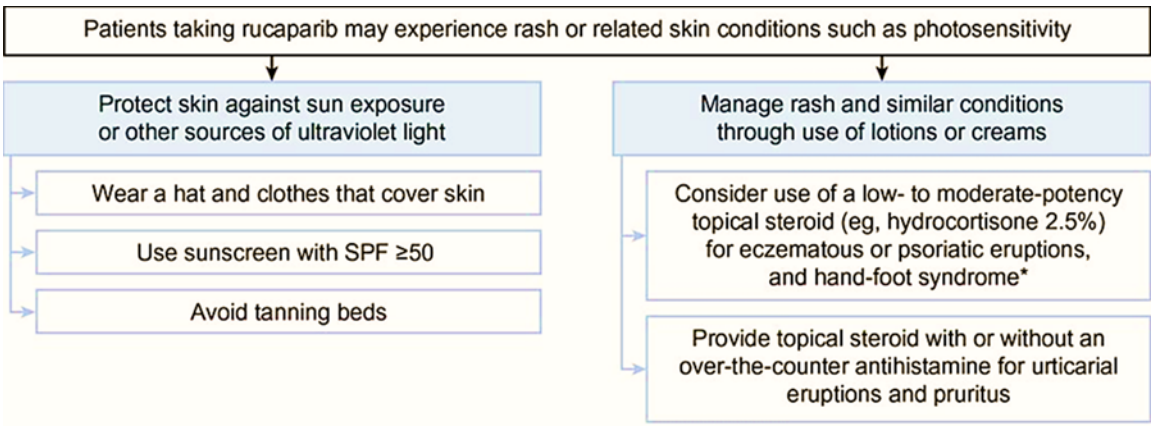


Figure 17 Measures to prevent sun exposure in patients treated with rucaparib (first column)

Source: Labadie et al., (2022)

Additionally, for patients who are symptomatic and the discontinuation of the photosensitizing drug is difficult, the use of corticosteroids may be helpful for the management of the drug-induced photosensitive dermatitis (Blakely, Drucker and Rosen, 2019). This option is also supported by the study of Kowalska et al., (2021) which states that topical corticosteroids, antihistamines and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for the treatment of photosensitive dermatitis as a primary treatment option. If blisters also appear on the skin due to photosensitivity, Moore et al. (2002) suggest the use of antibacterial ointments in order to prevent infection.

All in all, early management of the symptoms of any grade is highly recommended, as delayed response to the symptoms, may complicate the management of photosensitive dermatitis (Kowalska et al., 2021).

6.4 New aspects towards photosensitivity treatment

Protection from sunlight is considered necessary in order to protect the skin and prevent various skin diseases. (Passeron et al., 2021). As each person's skin type reacts differently to different wavelengths of sunlight, personalized sun protection recommendations are required for each person depending on their photo-type (Passeron et al., 2021).

Photo-types are classifications based on the sensitivity of the skin to sunburn and the ability of it to tan. The classification system was formed by Thoma B. Fitzpatrick in 1975 and consists of six photo-type categories, from Fitzpatrick photo-type I to Fitzpatrick photo-type VI (Figure 18) (Passeron et al., 2021). Fitzpatrick photo-type I describes a skin that always burns and never tans, Fitzpatrick photo-type II regards a skin that burns easily and occasionally tans, while Fitzpatrick photo-type III refers to skin that sometimes burns and always tans lightly (Passeron et al., 2021). Fitzpatrick photo-type IV regards a skin that burns rarely and tans easily, photo-type V describes an easily tanned skin, with moderate pigmentation that almost never burns and finally, Fitzpatrick photo-type VI describes skin that tans quickly and intensely due to high pigmentation and nearly ever burns (Passeron et al., 2021).

Another method for determining skin photo-type, more accurate than the Fitzpatrick classification, is the individual typology angle (ITA) method which is based on colorimetric measurements (Passeron et al., 2021). Skin tones with an ITA of 550 or higher are described as very light skin tones opposing to those with an ITA below -300 which are described as dark skin tones (Figure 18) (Passeron et al., 2021).

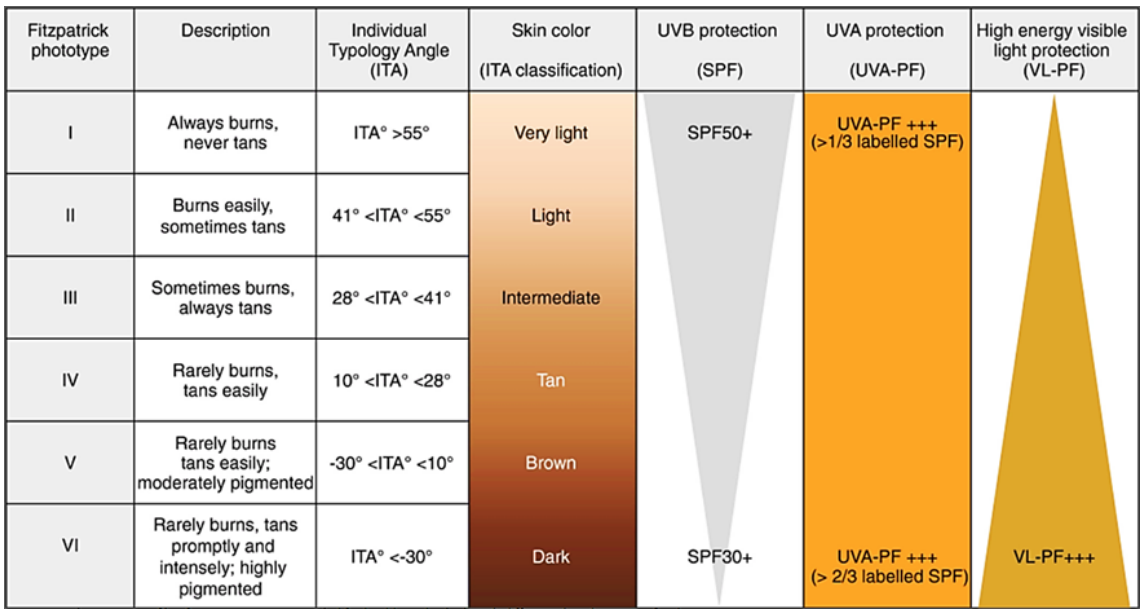


Figure 18 Spectral absorption profiles of sunscreens suitable for different skin photo-types.

Source: Passeron et al., (2021)

Sunscreens are the most accessible protection method against sun. They present properties related to the protection they offer for every photo-type, based on their protection against ultraviolet light A (UVA) and B (SPF) and visible light (VL) (Passeron et al., 2021). Details on the spectral absorption profiles of sunscreens and their similar suitability for skin photo-types are illustrated in Figure 18 from the study of Passeron et al., (2021).

In 2012, the FDA made changes to sunscreen labelling to ensure that sunscreen labels provide consumers with adequate information so that they can choose a sunscreen according to their needs (Ahluwalia and Marsch, 2019). The "Broad Spectrum" label on sunscreen, meaning that the sunscreen protects against UVA and UVB rays, was set as mandatory, while water resistance should be also stated on the product packaging to

provide information on the duration of sun protection in water or while sweating (Ahluwalia and Marsch, 2019).

Nowadays, people can choose between natural and synthetic sunscreens (Bhattacharjee et al., 2020). Natural sunscreens are in fact natural products such Aloe Vera, Rambutan, Propolis, Curcumin, Red Clover, Pomegranate, Ginkgo, and Avocado. On the other hand, synthetic sunscreens are divided into two categories depending on their type of filters; organic or inorganic (Bhattacharjee et al., 2020). Organic sunscreens consist of sunscreens with UVB filters, UVA filters or Broad Spectrum (UVA + UVB) filters (Bhattacharjee et al., 2020). This type of sunscreens utilize Dibenzoylmethane derivatives, Benzophenone derivatives, Para-Aminobenzoic acid (PABA) and its derivatives, Salicylate derivatives, and Benzotriazoles as filters (Bhattacharjee et al., 2020). The subcategory of synthetic inorganic sunscreens utilizes inorganic filters such as zinc oxide and titanium dioxide (Bhattacharjee et al., 2020). In contrast to natural sunscreens, the synthetic sunscreens containing chemical elements may end up being harmful or irritant for the skin (Bhattacharjee et al., 2020).

According to the study by Bhattacharjee et al., (2020), new technologies for the production of sunscreens are expected in the near future. Skin patches detecting exposure to ultraviolet radiation, sunscreens that are swallowed and even sunscreens that change colour when exposed to ultraviolet rays (Bhattacharjee et al., 2020, El Khoury et al., 2021). The latter was examined by El Khoury et al., (2021) when they tested for the first time the EBT3 Gafchromic film: when ultraviolet radiation reached the film, the colour became darker to the film part without sunscreen compared to the film covered with sunscreen where the colour change was less visible. This difference in the film colour indicates that the absorption is significantly lower when using a sunscreen (El Khoury et al., 2021). This type of research is an important step for the future of photo-protection because it can provide information about UV radiation and its effects on patients with skin diseases (El Khoury et al., 2021).

7 EDUCATION IS KEY

Education of cancer patients includes provision of information regarding treatment goals, disease process, diagnostic procedures, information about treatment options and psychosocial counseling, to enable patients to participate in the decision-making process (Jahraus et al., 2002). As defined by Fereidouni et al., (2019) patient education is the process by which health professionals provide patients, their families, and caregivers with appropriate clinical information in order to improve their health and encourage them towards informed decisions related to ongoing treatment. According to Friedman et al., (2011) patient education could be achieved through educational activities, counseling and behavior modification aimed at improving patients' health behaviors and knowledge. Well-educated patients can better understand early side effects and use their knowledge to manage these complications, while those patients were associated with improved health outcomes, treatment adherence, adequate self-management skills, satisfaction with treatment and reduced negative emotions in hospital patients, such as pain and anxiety (Fereidouni et al., 2019).

In 1989, the National Cancer Institute (NCI), recognizing the importance of patient education, created the Cancer Patient Education Network (CPEN) which consist of a healthcare professionals team groups who share evidence-based educational knowledge on all aspects of cancer patients' care, so as to achieve better results for patients (Ness and Kokal, 2014).

The studies by Li et al., (2015) and Perez-Soler et al., (2009) agree that cancer patients should be informed in advance by health workers about skin toxicities and advised to pay attention to any skin changes. Such education should be a priority for all multidisciplinary teams, including physicians, radiation oncologists, nurses, and dermatologists (Lacouture et al., 2011). As oncology nurses are in a unique position to spend a lot of time with cancer patients and understand their needs and concerns, they can play an essential role in educating those patients about these conditions (Jahraus et al., 2002).

This PhD dissertation focuses on the creation of a training program for patients who develop pruritus, rash and photosensitivity as a result of chemotherapy, EGFRI treatment, and immunotherapy. Additionally, evaluating the effectiveness of the aforementioned educational program is also provided in the research part section in this doctoral dissertation.

7.1 Patient education and therapeutic patient education

Patient education is crucial in the field of health care (Demir, Ozsaker and Ilce, 2007). It is a systematic experience where via the provision of information, advice and behavior modification techniques, the patient is taught how it can improve or maintain or learn to cope with a condition, especially a chronic one such as cancer (Engers et al., 2008). Patient education has long been a crucial component of therapeutic practice and it is increasingly recognized as a crucial intervention (Engers et al., 2008). Patients who get education are known to feel less anxious, be more prepared for discussions with medical professionals, participate actively in decision-making and have better outcomes (Demir, Ozsaker and Ilce, 2007). Patient education can increase patients' emotions of control and confidence, establish a collaborative relationship between patients and healthcare providers and allow patients to actively engage in their care (Demir, Ozsaker and Ilce, 2007).

A definition by WHO (1998) describes ‘therapeutic patient education’ (TPE) as an approach to support patients and their families in order to better understand the illness and therapeutic options (Rizzo et al., 2007). TPE is a patient-centered process that involves the transfer of skills (self-management, treatment adjustment) by a trained healthcare (Barbarot and Stalder, 2014). In France, TPE was incorporated as a public health priority in the HPST law (Hospital Health Patient and Territory) enacted in 2009 (Guerrero and Calmette, 2020). Nowadays, dermatological therapeutic patient education programs can be found providing better information to patients and make them more independent in dealing with disease in daily life (Guerrero and Calmette, 2020). On the other hand, TPE for skin adverse events management remains poor (Guerrero and Calmette, 2020).

Informal patient education and TPE differ between them as shown by the pedagogical criteria and methods: the former refers to the physician-patient relation, where the first

prescribes information, suggestions, advice, recommendations and instructions; the latter regards the empowerment of patients via training programs so as to enable them to practice themselves, rather than only rely on their doctor (Rizzo et al., 2007). Despite the fact that in 1998 the WHO included cancer into the published list of diseases to be benefited by applying TPE practices, their use in the oncology field still remains rare even though they could decrease the negative impact of diagnosis to the patients (Rizzo et al., 2007). This is because the TPE does not only provide an explanatory approach to the patients but also takes into account the psychological impact of the disease and helps patients to manage the stress related to the disease (Guerrero and Calmette, 2020) and improve their QoL (Barbarot and Stalder, 2014).

The TPE program consists of a four-steps process (Guerrero and Calmette, 2020). In order to identify the patient's challenges and resources, the first phase involves exploring the patient's current knowledge, beliefs, fears and desires (Guerrero and Calmette, 2020). As per Rizzo et al., 2007 this step could be defined as 'educational diagnosis'. During the second phase, the 'educational-therapeutic contract' (Rizzo et al., 2007), considering the patient's age, educational goals are set such as the development of necessary abilities (Guerrero and Calmette, 2020). At this point, it's crucial to determine the skills the patient requires based on their challenges and available resources in order to manage their illness more effectively (Guerrero and Calmette, 2020). The focus of the third step is the patient's acquisition of abilities (Guerrero and Calmette, 2020). During this step, healthcare professionals can make use of a variety of instructional resources during this phase (e.g., patient-centred communication techniques, practical demonstrations and educational tools) in order to train the patient (Guerrero and Calmette, 2020). The creation of a personal written action plan can help the patient, serve as a reminder of the therapeutic goals and encourage better adherence to the treatment (Guerrero and Calmette, 2020). A short-term appointment or follow-up plan, which can be handled by a hotline, mail, or an assistant nurse, could also be included in the written action plan. This process can be carried out alone or in groups (Guerrero and Calmette, 2020). The evaluation of TPE is a crucial component of the fourth step, which deals with the instructional process. To measure TPE effectiveness, a significant number of criteria are required and its assessment should include biological

outcomes, acceptable psychological scores and QoL scores (Guerrero and Calmette, 2020).

To conclude, a TPE program in order to be considered as high quality, must be evidence-based, tailored to a patient's individual educational and cultural background (rather than being standardized in form and content) and have well-defined content and activities (Guerrero and Calmette, 2020).

7.2 Teaching strategies and methods

Teaching strategies found to be used for TPE in literature include conventional lectures, health professional-patient discussions, use of computer technology, provision of written educational material, verbal recall, audio and video material (Friedman et al., 2011). Computer technology, demonstrations and recorded and written materials were mentioned as to be the most successful teaching strategies to increase knowledge and satisfaction and decrease anxiety among patients (Friedman et al., 2011). Combination of more than one teaching strategies was found similarly successful (Friedman et al., 2011). Moreover, structured-, culturally appropriate- and patient specific teachings were found to be better than occasional or generalized teaching (Friedman et al., 2011).

Conventional lectures compared to routine care were found to have a moderate effect size as educational tool, whereas health professional-patient discussions were found to have a small to moderate effect size (Friedman et al., 2011). Lectures or small workshops are examples of collective group sessions also used for TPE (Guerrero and Calmette, 2020). Following lectures, which are addressed to larger audiences, individual sessions can be planned based on each patient’s need and with feedback from the caregiver (Guerrero and Calmette, 2020). Smaller workshops are frequently led by a two-person team, such as an expert and a group facilitator: doctors, nurses and psychologists all participate in these sessions (Guerrero and Calmette, 2020). Workshop sessions typically run for two hours, regard patients comparable in age and aim to create a dialogue between patient and caregiver based on a certain subject (Guerrero and Calmette, 2020).

Computer Technology is found to be more effective compared to other standard educational methods (Friedman et al., 2011). Patients receiving personalized

information by computer were more satisfied than those receiving general information (Friedman et al., 2011).

Written materials, such as information booklets were also recorded as an efficient patient education method in terms of patient satisfaction and memory retention (Friedman et al., 2011). Written information included in booklets or new patient information packets increased patient understanding and lessened confusion, especially if information was given to the patient ahead of time rather than at the first session at the clinic (Friedman et al., 2011). As this type of method is popular, further written content needs to be created at a reading level appropriate for the general public (Friedman et al., 2011). When written materials and vocal health information were combined, knowledge dramatically increased compared to verbal information alone as reported by Friedman et al., in 2011. This is because verbal education could have drawbacks, as the true meaning of what is said might not become understood and might be quickly forgotten (Friedman et al., 2011). It is well- known that patient anxiety, the severity of nausea and vomiting, surgical complications, medication use and length of hospital stay are all reduced when education is provided via written materials to the patients (Demir, Ozsaker and Ilce, 2007). Giving patients written educational materials with the goal of transmitting lasting and recallable information after vocal communication and education, is preferred compared to employing only educational resources (Friedman et al., 2011). Audiotape as a teaching strategy provides controversial results (Friedman et al., 2011). Specifically, some studies notice that audiotape increased patient knowledge and reduced the anxiety whereas other studies noticed that audiotape provided patients with an excessive amount of information that led to further anxiety (Friedman et al., 2011). Furthermore, videotape can improve patient knowledge although the results are also controversial (Friedman et al., 2011).

Compared to training strategies, patient-education delivery methods did not include as much information available (Friedman et al., 2011). Patient education has frequently focused more on the disease than the patient despite the fact that it has been demonstrated that patient-centered methods enhance patient satisfaction, treatment adherence, health outcomes and all patient education objectives (Lamiani and Furey, 2009). Patient-specific information (targeted interventions) rather than general

information has higher patient satisfaction, less anxiety, and increased patients' knowledge (Friedman et al., 2011). For example, patients receiving chemotherapy remembered more information about the medications provided and their potential negative effects after an "instructional session" as noted in the study of Friedman et al., (2011). Additionally, they reported that orientation programs improved cancer patients' knowledge and reduced their stress. An example of individual education involves a study with type 2 diabetes patients in which, compared to conventional care, those getting personalized instruction had considerably better results at 6 months' post-intervention (Friedman et al., 2011).

The Agency for Healthcare Research and Quality (AHRQ) and the Institute for Healthcare Improvement (IHI) have advocated the teach-back method as a method for confirming patients' comprehension of their medical knowledge (Yen and Leasure, 2019). The main idea behind the teach-back method is that patients explain health information they received in their own words in order to test their comprehension (Yen and Leasure, 2019). Healthcare professionals (HCPs) should use caring and plain language in a shame-free environment so as to pass the educational information to the patients. At their turn, patients are asked to repeat the instructions they received by the HCPs in their own words. This way, the patient's obtained knowledge is assessed and if understanding is not demonstrated, HCPs reteach and/or modify teaching. Via this method, patients play an important role in the progress of their own health, while their ability to incorporate health advices in daily routine has a significant impact on their outcomes (Yen and Leasure, 2019). The teach-back method is recorded used along QOL improvement programs and interventions, employed in inpatient, outpatient, emergency department and community programs (Yen and Leasure, 2019). An example is a study performed among women with breast cancer that recorded their QoL found that with the use of teach-back method the mean happiness score increased from 37.2 to 62.9 ($P < .001$) in the intervention group (Yen and Leasure, 2019).

In order to personalize the TPE program, individual sessions can help healthcare professionals create a comprehensive patient profile. Individual sessions are often done by two professionals, a doctor and a nurse, although they can be provided only by a nurse (Guerrero and Calmette, 2020) and aim to form/provide individualized health

information so as to increase each individual's understanding of their health requirements, improved their health literacy, support self-management and promote improved health results for chronic patients (Yen and Leasure, 2019).

7.3 Writing materials and booklets

According to studies, the majority of patients discharged from the hospital are uncertain about their health care options while a sizable part of medical information given to them is forgotten upon discharge (Yen and Leasure, 2019). Thus, today there is an increasing demand for written materials during patient education due to people wanting more information about their health and treatment options (Demir, Ozsaker and Ilce, 2007).

Written educational material for patients is used to raise awareness, provide knowledge, modify behaviors and beliefs, support people's healthy living habits and assure compliance with new health conditions (Demir, Ozsaker and Ilce, 2007). As a result, the data presented in patient education materials has to be understandable to readers, supported by science and practical so as to beat any comprehensive deficits presented (Demir, Ozsaker and Ilce, 2007).

Written resources enable patients to learn at their own pace and absorb information gradually (Demir, Ozsaker and Ilce, 2007). Written teaching materials could convey important health messages but the only way for patients to benefit from these resources is if they can read, understand and recall them (Demir, Ozsaker and Ilce, 2007). Features of written materials, such as sentence structure, idea organization, design and presentation, can also have an impact on the reader's understanding of the topic (Demir, Ozsaker and Ilce, 2007). Therefore, when developing written educational materials, health practitioners should consider the suggestions offered by the literature to enhance the efficacy of the provided content (Demir, Ozsaker and Ilce, 2007).

Additionally, the language used in written materials must be understandable even to persons with limited reading skills (Cheung et al., 2007). According to the most recent Canadian Adult Literacy and Life Skills Survey, 15% of the population has extremely limited reading comprehension and is unable to figure out how much medication to give

a child based on the information stated on the container (Cheung et al., 2007). A further 27% of people are functionally illiterate, which means that they can read but have limited comprehension abilities (Cheung et al., 2007). Adding appropriate visuals to written content though, improves considerably the comprehension compared to text alone (Cheung et al., 2007).

Even though for a variety of patients, an educational booklet could prove a successful patient education tool (Cheung et al., 2007), the majority of the written materials used to teach patients are determined to be inappropriate in terms of their content, structure, design, composition and language, when assessed (Demir, Ozsaker and Ilce, 2007). For example, in the study of Demir, Ozsaker and Ilce from 2007, which included 138 surgical clinics in 22 hospitals and examined 59 written educational materials (18 booklets, 25 leaflets, 16 single-page A4/A2 documents), the mean score of the information quality and reliability of assessed educational material was low, with its overall appropriateness scores being average due to significant flaws in the instructional material.

More analytically, the above-mentioned study, which also evaluated the suitability of prostate cancer educational materials among others, found that the examined booklets were at an inadequate level, with 90% of the material being unsuitable from the aspect of readability while over half of the clinics included in the study did not even have written educational material, while most of them that had educational materials did not use them, with exception the university hospitals (Demir, Ozsaker and Ilce, 2007). In the UK, the Audit Commission, also stated that the assessed writing educational material received low points for design, information order, writing, language and font size, while publication year was not stated in approximately half of the examined booklets (Demir, Ozsaker and Ilce, 2007). The same study concludes that the lack of sufficient written patient education materials could be corrected by employing health professionals to create them in line with guidebooks and keeping the target audience in mind (Demir, Ozsaker and Ilce, 2007). Finally, the study suggests that as patient education plays a crucial role in nursing, the development of written educational materials must also become a routine aspect of nursing activities rather than a separate duty (Demir, Ozsaker and Ilce, 2007).

The 2016 study of Keinki et al., assessed the readability and understandability of information booklets for cancer patients available at German Web sites. Fifty-two different patient booklets were downloaded and evaluated in total in their study: one booklet for bladder cancer, seven booklets related to colorectal cancer, five booklets for lung cancer, fourteen booklets related to breast cancer, five booklets for melanoma, four booklets for oropharyngeal cancer, four booklets regarding pancreatic cancer, eight booklets for prostate cancer and four for endometrial cancer (Keinki et al., 2016). After evaluating all the booklets it was determined that in overall, greater medical background knowledge was required in order to comprehend them (Keinki et al., 2016). This comes in conflict with the fact that printed health information for cancer patients needs to be easy to read and comprehend, with simple language, in order to reduce worry and stress (Keinki et al., 2016). The same study suggested some key-factor improvements to contribute to better readability and, by extension, understandability: (a) the use of straightforward or well-known vocabulary; (b) avoiding the use of technical or medical terms; and (c) the use of a simpler sentence or phrase structure (Keinki et al., 2016).

In the field of oncology, writing educational materials are well received by cancer patients with varying literacy levels and can be effective tools for increasing patients' knowledge of cancer (Schleimer et al., 2020). Written material for cancer patients is supplied partly by the American Cancer Society (ACSO) and the European Society for Medical Oncology (ESMO). The American Cancer Society is a voluntary health organization dedicated to promoting healthy lifestyles and research into the prevention and treatment of cancer (American Cancer Society, 2020). One of its actions is to promote patient education through educational materials on various cancer-related topics (American Cancer Society, 2020). The image below shows an example of an American Cancer Society educational resource regarding skin changes related to cancer treatment (Figure 19).

Figure 19 Education material on skin changes in patients

Source: American Cancer Society, 2020, available at: https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/skin-problems/skin-rash.html, Last Revised: December 10, 2020, Assessed 20/09/2022

The aforementioned educational material includes information on skin changes and details on rashes, dry skin and itching. It also provides patients with precautions regarding skin reactions and ways to control them (American Cancer Society, 2020). The patient can find information such as: using an alcohol-free soap, shampoo or lotion, washing with lukewarm water rather than hot, moisturizing the skin throughout the day, shaving with an electric razor and avoiding the sun (American Cancer Society, 2020).

Furthermore, the European Society of Medical Oncology (ESMO) is a medical oncology organization with over 25,000 members in over 160 countries that aims in educating and informing both healthcare professionals and patients (European Society for Medical Oncology, 2022). ESMO publishes topics with up-to-date information in oncology with the primary goal of providing high-quality care to cancer patients and provides guidance on many topics (European Society for Medical Oncology, 2022). Figure 20, shows a patient guide by ESMO regarding the side effects of immunotherapy. ESMO has also created the ESMO Pocket Guide to provide practical access to guidance and the ESMO Interactive Guides app, which is compatible with

Android and iOS devices and includes content from ESMO Pocket Guides (European Society for Medical Oncology, 2022).

An interesting educational material for cancer patients, that is freely available online, is the educational booklet by Schleimer et al., (2020) called “Cancer and You” (last updated in September 2018). This booklet answers frequently asked questions about chemotherapy, explains side effects of anticancer treatment and discusses various management ways. It also includes tips (questions to ask, topics to discuss) for meeting with your doctor or nurse, as well as a list of places to get more information about chemotherapy and other cancer related topics (Schleimer et al., 2020).

Figure 20 ESMO patient guide regarding the side effects of immunotherapy

Source: European Society for Medical Oncology, 2022, https://www.esmo.org/for-patients/patient-guides/immunotherapy-side-effects, assessed on 20/09/2022

7.4 Theoretical Framework in education

Behaviorism, one of the Theories of Learning, supports that given the right environmental influences, all students can learn and all learners can acquire identical understanding (Weegar, M.A. and Pacis, D., 2012). The behaviorism school, which was rooted in the 1880s and continues to evolve through the twentieth-first century, was developed by Skinner and Watson who concluded that behavior could be predicted and controlled (Weegar, M.A. and Pacis, D., 2012). Behaviorists also support that "only observable, measurable, outward behavior is worthy of scientific inquiry" and thus their focus is on learning that is affected by changes in behavior (Weegar, M.A. and Pacis, D., 2012).

The Behavioral Learning Theory published in 1913 by Watson, focused on the relationship between organisms and their environment. This study was responsible for the movement towards behaviorism and its basis was Pavlov's findings on animal responses to stimuli (Weegar, M.A. and Pacis, D., 2012). As with Pavlov, Watson also believed that humans could be conditioned to respond to similar stimuli, like animals did. Thus, Watson mirrored Pavlov's famous experiment with the dog and the bell (Pavlov rang a bell at his dog's feeding time, and the ringing of the bell caused the dog to salivate, because the dog had been conditioned to eat at that time) by conditioning a young child to fear a white rabbit, due to the fact that he always pared the rabbit's presence with the loud clang of a metal bar (Weegar, M.A. and Pacis, D., 2012).

Based on Watson, Skinner also did extensive research with animals, especially rats and pigeons, to prove his theories on behaviorism. His most famous experiment involved the Skinner box, where a rat was taught that every time it was pressing a lever it obtained food, something that consequently reinforced the behavior (Weegar, M.A. and Pacis, D., 2012). However, Skinner realized that human learning abilities expand beyond the simple relation between sensory stimuli and unique corresponding response. He also noted that humans react to their environment based on previous experiences, but unfortunately failed to conceive that the "mind" (not the brain but thoughts, feelings, intentions, mental processes and so forth) do actually have a bearing on how people behave (Weegar, M.A. and Pacis, D., 2012).

About education, behaviorists also supported that all educational objectives are framed in specific, behavioral and observable terms (Weegar, M.A. and Pacis, D., 2012). As per this approach, the instructor is the focal point of the presentation and interaction and that individual students, that require extra assistance, could receive it when teachers work with them. The expected role of the student is to absorb the provided information and use them to create performances which indicate accomplishments as per the of correct mental models of behaviorism (Weegar, M.A. and Pacis, D., 2012).

Another famous learning theory found in bibliography is that of Piaget's cognitive theory (Wilson, 1995). Piaget investigated how humans acquire knowledge and create cognitive structures and according to his theory, it is by the interaction between the thinking ego and its environment (Wilson, 1995). This interaction adapts both the environment and the cognitive structures that come closer over time. Piaget described cognitive development via four stages in which humans use increasingly complex methods of organizing and processing information (Wilson, 1995). The first two stages refer to infants and toddlers and support that infants and young children learn through interacting with their surroundings (Wilson, 1995). The infants rely on sensory input and bodily motion to learn about the world during the sensorimotor stage, while children learn about the world primarily through their own actions during the preoperational stage (Wilson, 1995).

The two final stages of cognitive development are of importance for adulthood, when logical thinking develops (Wilson, 1995). The terms Concrete Operations (COs) and Formal Operations (FOs), who characterize these stages, refer to the ability (Operation) of adults to perform actions mentally. The word "Concrete" refers to the ability of thinking logically about objects and their properties, while collectively Concrete Operations include the ability to develop logical thoughts, distinguish relationships and define spatial relationships and the order of events. (Wilson, 1995).

Formal Operations, include the ability to consider possible consequences/results of future actions, poise elements in order to achieve the desired outcome and finally understand the logical relationship that exists between suggested actions (Wilson, 1995). When people reach the developmental stage of Formal Operations, this means they have already mastered all aspects of Cognitive Operations as well as achieved a qualitative change in reasoning methods (Wilson, 1995).

Piaget's theory that declares that humans develop their cognitive abilities via self-motivated action in the world lays between two opposing approaches in cognitive science: the empirical in which a human cannot form new realities due to a predefined environment that should only embrace it, and the a priori in which human cognition is enabled through a predefined set of structures (Wang and Rubart, 2006).

As with Piaget's theory, over time, further behavioral theories began to incorporate cognitive factors (Center for Substance Abuse Treatment, 2015). This expanded, mediational model has been described as cognitive social learning or cognitive-behavioral theory (Center for Substance Abuse Treatment, 2015). In the 1960s, Aaron Beck developed the cognitive behavior theory which eventually led to the formation of Cognitive Behavior Therapy (CBT). Beck's theory postulates that cognitive factors mediate all interactions between the individual, situational demands and the person's attempts to cope effectively (Chand, Kuckel and Huecker, 2022, Center for Substance Abuse Treatment, 2015). The theory is reinforced by the principles stating that peoples' perceptions of a situation influence their behavior and beliefs about their ability to control it; humans can change their perceptions of a situation (i.e., cognitive reframing); and peoples' ability to control a situation effectively can be improved by changing their perspective (Sherwood et al., 2005). Based on all that, the formation of Cognitive Behavioral Therapy provides the basis for a more inclusive and comprehensive approach to treating disorders as it represents the integration of principles derived from both behavioral and cognitive theories (Center for Substance Abuse Treatment, 2015).

In the field of oncology, cognitive-behavioral theorists have offered several accounts of potential etiological factors involved in depression, anxiety, chronic pain and eating disorders (Chand, Kuckel and Huecker, 2022). In a similar way with CBT, Cognitive Behavioral Interventions (CBIs) are currently utilized as a multimodal approach to symptom management, with recorded effectiveness in reducing symptom severity in cancer patients (Sherwood et al., 2005).

Educational interventions could prove more effective if guided by a theoretical model (Kroustalli, E et al., 2019). A known example of a study that applied the above, is the study of Masterson Creber R et al., which incorporated the principles of "The Situation Specific Theory of Heart Failure Self-Care" for patients' education, in order to provide suitable patient-centered advice to people with heart failure based on their cognitive and

social behavior. (Kroustalli, E et al., 2019). Such studies could present significant links among educational intervention and knowledge enhancement, self-care, life quality and reduction of readmissions, mortality and depression because of the use of a theory model (Kroustalli, E et al., 2019).

The review by Bashirian et al., from 2019 aimed to investigate whether the use of a health education model and theory-based behavioral interventions could be effective in women's breast cancer screening behavior. The review included twenty-six studies focusing on how health education could influence and change an individual's behavior (Bashirian et al., 2019). The Bashirian study confirmed that behavioral theory-based interventions increased breast cancer screening behaviors via identifying key concepts for behavior change of the target group (Bashirian et al., 2019).

In 2016, Lopez-Vargas et al., conducted a similar systematic review for theory-based educational interventions for patients with chronic kidney disease (CKD). All twenty-six included studies were focusing on educational interventions for the prevention and management of CKD but only five of them had used educational interventions based on theoretical frameworks despite the fact that theory-based interventions significantly improve patient education as it is more likely to produce larger and longer-lasting effects than those lacking an explicit theoretical background (Lopez-Vargas et al., 2016, Zhao et al., 2016, Simonsmeier et al.2022).

All in all, patient education is a planned, systematic, sequential and logical process of teaching and learning provided for patients via interventions based on each individual's assessment, evaluation, diagnosis, prognosis, needs and medical treatment requirements (Simonsmeier et al.2022). As educational interventions are aiming to empower patients to actively engage in their care, when developing and implementing these programs an organized and standardized approach is required, with a connection between theory and practice (Simonsmeier et al. 2022). Learning theories that have been proven to work could act as scaffolding for planning and implementing interventions (Simonsmeier et al. 2022). Future investigation could therefore close this knowledge gap and produce theory-driven interventions that serve as best practice guidelines (Simonsmeier et al. 2022).

8 QUESTIONNAIRES

8.1 Quality of life questionnaires and Health-related Quality of life questionnaires

This chapter explores the spectrum of available questionnaires used to assess the Quality of Life (QoL) and Health-Related Quality of Life (HR-QoL) of patients with chronic illnesses (the definitions for QoL and HR-QoL are presented in subchapter 3.4 and 3.5)

The study and assessment of patients' QoL is not a current trend, but it has rather interested researchers for decades now, something that it is obvious by the large number of questionnaires existing (Gill and Feinstein, 1994). Below we present some of the available QoL assessment questionnaires and demonstrate the parameters each one is examining.

The Quality-of-Life Scale (QoLS) questionnaire was first developed in 1970's, by American psychologist John Flanagan and has been adapted for use in patient groups with chronic illnesses such as diabetes, osteoarthritis, rheumatoid arthritis and post-ostomy surgery (Burckhardt and Anderson, 2003). The QoLS is a valid instrument for measuring quality of life across patient groups with different cultures and was originally a 15-item survey measuring five conceptual domains of quality of life: material and physical well-being, relationships with other people, social, community and civic activities, personal development and fulfillment, and recreation (Burckhardt and Anderson, 2003). The questionnaire was expanded by the addition of another domain for investigation, the "independence, the ability to do for yourself" following the feedback from persons with chronic illness regarding their perceptions of quality of life (Burckhardt and Anderson, 2003). Hence, the QoLS in its present format contains 16 items and in terms of reliability and validity, is considered to be reliable and internally consistent as confirmed by several studies (Burckhardt and Anderson, 2003).

Published in 1996, the McGill Quality of Life Questionnaire (MQoL) was designed to assess the QoL of patients facing life-threatening illnesses. Nowadays, the questionnaire is used extensively in palliative care research because of its perceived high content

validity and acceptability for terminally ill people (Cohen et al., 2019). While the original questionnaire scale comprised of four dimensions, Cohen and colleagues' (2019) expanded the latest version to an eight-parameter questionnaire to better assess the domains that terminal patients report as important for their QoL (Cohen et al., 2019).

Another questionnaire found in bibliography, is the WHOQOL-BREF questionnaire, a generic health-related questionnaire assessing 24 factors (incl. organism, tasks and environment) and providing a profile of scores on four dimensions of the QoL: physical health, psychological health, social relationships and the environment (Parthasarathi et al., 2008, Castro, Driusso and Oishi, 2014). The WHOQOL-BREF questionnaire is available in 19 different languages and is widely used for comparing indicators of QOL across cultures (Parthasarathi et al., 2008). Due to the fact that it is a multidimensional scale survey, it could be utilized for a wide range of psychological and physical disorders (Abbasi-Ghahramanloo et al., 2020).

Short-Form (SF-36) Health Survey is one of the most commonly used generic HRQoL questionnaires worldwide as it is widely validated in different languages and address to multiple cultures (Abbasi-Ghahramanloo et al., 2020; Lins and Carvalho, 2016). It consists of 36 questions categorized into an eight-domain profile of scores: physical functioning, general health, mental health, emotional role, physical role, bodily pain, social functioning and vitality, (Abbasi-Ghahramanloo et al., 2020). The SF-36 is also the most frequently used generic HRQoL assessment tool for patients with cancer as its adequate psychometric properties were documented both in cancer patients and in cancer survivors (Bunevicius, 2017). Due to extensive use and experience across patients and general population, the generic SF-36 questionnaire also allows to compare patient perceived health status not only across a variety of disorders but with the general population as well (Bunevicius, 2017).

Another known Health Related Quality of Life assessment tool is the Generic Measures Affect Balance Scale (ABS), that has been used in a variety of settings and populations, including cancer survivors (Victorson et al., 2017). This questionnaire investigates the psychological wellbeing of patients through ten study factors; five that deal with positive effects and five that deal with negative effects (Victorson et al., 2017).

Brief Symptom Inventory-53 (BSI) is a 53-item scale reflecting nine symptom dimensions, including somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism (Victorson et al., 2017). This questionnaire is useful in oncology settings as it helps clinicians to separate psychological effects from disease- or treatment-related effects (Victorson et al., 2017). It has been used extensively with cancer patient samples, including survivors of breast cancer and pediatric sarcoma (Victorson et al., 2017).

The Center for Epidemiological Studies-Depression Scale (CES-D) is a 20-item self-report inventory, designed to assess depression in the general population. The scale is comprised of four subscales: somatic and retarded activity, depressed affect, positive affect and interpersonal functioning. The CES-D has been used with a variety of medically ill populations, including survivors from bone marrow transplant and breast and lung cancer (Victorson et al., 2017).

Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report assessment tool that measures anxiety and depression, which is been used extensively in oncology settings for screening and clinical research purposes (Victorson et al., 2017). Although several studies have found the HADS to have sound psychometric properties in cancer studies, it has also been reported that it may be insensitive to differentiate anxiety and depression among cancer patients (Victorson et al., 2017).

Another assessment questionnaire used in studies is the Impact of Event Scale (IES), a 15-item self-report scale designed to measure two major psychological responses to stressful life events: the avoidance and the intrusion seven days post the stressful event (Victorson et al., 2017). The IES has been used extensively in studies with both cancer patients and cancer survivors (Victorson et al., 2017).

Benefit Finding Scale (BFS, 17 item version) is a 17-factors scale that measures the perceived positive contributions among people diagnosed and treated for cancer (Victorson et al., 2017).

The Functional Assessment of Cancer Therapy-General (FACT-G) is a 27-item self-report questionnaire with general questions concerning four primary HRQoL domains: physical well-being, social/family well-being, emotional well-being and functional well-

being (Victorson et al., 2017). The validation of this core tool in cancer and other chronic diseases has launched the evolution and development of multiple disease, treatment, condition and non-cancer-specific subscales (Victorson et al., 2017).

Further questionnaires/assessment tools found in scientific literature are also: the Lerman Cancer Worry Scale (LCWS), a 4-item scale used with cancer survivors and measuring risk-related worry towards developing cancer and the effect of this worry on daily functioning, the Long Term Quality of Life Scale (LTQL), a 46-item self-report questionnaire designed to assess long-term QoL in female cancer survivors through four subscales (somatic concerns, philosophical/spiritual view of life, health habits and social/emotional support) and the Memorial Symptom Assessment Scale (MSAS), a 32-item self-report survey with adequate internal consistency comprised of three subscales (Global Distress Index, Psychological Symptoms, and Physical Symptoms) and evaluating common cancer-related symptoms through rating the severity, frequency and extent of symptom-related distress (Victorson et al., 2017).

The Mental Adjustment to Cancer Scale (MAC) is a 40-item self-report tool used with long-term cancer survivors to assess a patient's ability to cope with cancer and treatment (Victorson et al., 2017). It contains four main subscales (fighting spirit, anxious preoccupation, hopeless/helplessness, and fatalism) and an additional item that deals with denial/avoidance (Victorson et al., 2017).

Two further questionnaire used for HRQoL assessment specifically in cancer patients, is the Quality of Life Index-Cancer Version III (QLI-CV III) and the Rotterdam Symptom Checklist (RSC) (Victorson et al., 2017). The first is a 66-item self-report scale that measures satisfaction and importance of different aspects of patients' life via four subscale scores, health and functioning, psychological/spiritual, social/economic and family, while the latter is a 30-item self-report tool designed to assess physical and psychological distress via testing three primary domains, physical symptoms, psychological symptoms, activities of daily living (Victorson et al., 2017).The RSC scores are rated on a 4-point scale (not at all to very much) while good subscale internal consistency evidence has also been reported (Victorson et al., 2017).

Finally, the 30-item European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) is a generic questionnaire used to assess HRQoL via examining cancer patients' physical, psychological and social

functions (Husson et al., 2019, Kaasa et al., 1995). The EORTC QLQ-C30 contains five functional scales of assessment (physical, role, cognitive, emotional, and social functioning), a global QoL scale, three symptom scales (fatigue, nausea, vomiting, pain) and six single items (appetite loss, diarrhea, dyspnea, constipation, insomnia, financial impact) (Husson et al., 2019). It has a 1-week time frame and uses a four-point response format ("not at all," "a little," "quite a bit," and "very much"), with the exception of the global QoL scale, which has a seven-point response format, while the scores are linearly transformed to a score between 0 and 100 (Husson et al., 2019). For the functioning and the global QoL scales, a higher score indicates better health (Husson et al., 2019).

8.2 Questionnaires for the Impact of Skin Problems on the Quality of Life

There are several questionnaires that are used to assess the impact of skin diseases on the patients' QoL. Such questionnaires are the Dermatology Life Quality Index (DLQI), the Dermatology Specific Quality of Life (DSQL) and the Skindex-29. More disease-specific questionnaires are the Psoriasis Disability Index (PDI), the Psoriasis Life Stress Inventory (PLSI), and the Acne Disability Index (ADI) (Finlay, 1998). In this subchapter we will describe the DLQI, the DSQL and Skindex but not the disease-specific questionnaires due to irrelevance with our study subject.

The Dermatology Life Quality Index (DLQI) was the first questionnaire of its kind to be assembled and therefore the most widely used and the one with which investigators have the most experience (Finlay, 1998). DLQI consists of 10 questions, each one answered by one of the provided four scoring choices from 0 to 3. The total maximum score is 30, indicating maximum disability caused by the dermatological disease (Finlay, 1998). DLQI is a useful dermatology-specific health-related QoL as its score can be analyzed according to various clinical factors, including demographics, anti-cancer therapy and specific skin problems induced by anticancer agents (Lee et al., 2018).

The Dermatology-Specific Quality of Life (DSQL) questionnaire is an instrument through which the effects of a skin disease are quantified based on the impact on physical discomfort and experiencing symptoms, psychological well-being, social functioning, self-care activities, performance at work or school and self-perceptions.

The DSQL instrument was developed to meet clinical investigators' need for a comprehensive yet relatively brief instrument for general use in dermatology for clinical trials and observational research. The DSQL contains five scales and eight global rating items and is intended as a self-administered QOL profile, which can be completed in 15 minutes or less (Anderson and Rajagopalan, 1997). As a disease-targeted measure, the DSQL is designed to focus on adverse effects of dermatological diseases without contamination by other diseases (Anderson and Rajagopalan, 1998). The DSQL asks the patients to report only the effects which they believe are caused by the dermatological problem, something which is necessary to control the confounding effects of extraneous medical and non-medical factors that may impact on HRQoL (Anderson and Rajagopalan, 1998). The development of the DSQL along with its reliability and validity have been described and documented by several reports (Anderson and Rajagopalan, 1998).

The third questionnaire, the Skindex-29, is a disease-specific self-administered questionnaire that measures the complex effects of skin disease on patients' QoL through three multi-item scales: physical symptoms (7 items), emotional state (10 items), and social function (12 items) (Andreis et al., 2010). Answers on Skindex-29 are given on a 5-point scale, from 'never' to 'all time', and for each scale the score is calculated as the mean of responses to the items included in the scale, while at the end the scale scores are standardized to 100 (Andreis et al., 2010) Skindex-29's validity and reliability is also well documented (Andreis et al., 2010).

8.3 How to select a questionnaire for a study

In this subchapter we will discuss the importance of questionnaires in order to define upon which measures are best suited for the purposes of the present study, as we are seeking for tools that focus on investigating the impact of skin disease both broadly and specifically.

Quality of life (QOL) questionnaires investigate the conceptions of the quality of life through notions the encompass satisfaction about housing, employment, standard of living, marriage, interpersonal relationships, religion and environment (Lin, Lin and Fan, 2013). It is a concept that broadly covers all aspects of human experience about the necessities of life and is characterized as the individuals' subjective well-being with

general measures of how happy and/or satisfied they are with their life as a whole (Lin, Lin and Fan, 2013). However, the health care system and its providers do not take responsibility for all these global human concerns, and therefore a distinction was mandatory in order to separate the notion of health-related quality of life (HRQoL) (Lin, Lin and Fan, 2013). Nowadays, health-related quality of life (HRQOL) has become an important index in medical treatment and clinical care, as this patient-reported outcome measure is enabling health professionals to assess an individual's wellbeing and their potential treatment and recovery outcomes and focus on improving the quality of life and health influenced by illness (Lin, Lin and Fan, 2013, Davies et al., 2020).

Good health is not only the absence of disease or infirmity but also a state of complete physical, mental and social well-being (Lin, Lin and Fan, 2013). Hence, the concept of HRQoL is encompassing all the important aspects of QOL related to health and is influenced by an individual's experiences, beliefs, expectations and perceptions (Lin, Lin and Fan, 2013). HRQoL reflects the way individuals perceive and react to their health status and the nonmedical aspects of their lives, which include health-related factors, such as physical, functional, emotional and mental well-being as well as non-health-related elements, such as job, family, friends etc. (Lin, Lin and Fan, 2013).

In bibliography, two types of measures can be found assessing HRQoL: general and specific. Generic HRQoL measures (tools, questionnaires), referred also as broad outcome indicators, examine physical, mental/emotional and social health as well as global perceptions of health and well-being (Lin, Lin and Fan, 2013). Generic measures enable comparison across different types and severities of disease, treatments or interventions and their variations across demographic and cultural subgroups, but they may not properly describe condition-specific outcomes (Lin, Lin and Fan, 2013, Davies et al., 2020).

On the other hand, HRQoL specific measures are used to assess only disease- or condition-related attributes, not allowing this way measurement and comparison of QoL across different conditions or populations (Lin, Lin and Fan, 2013, Davies et al., 2020). They enable a detailed investigation of particular outcomes on a specific area of primary interest, such as the disease type (e.g., cancer or heart disease), a population of patients (e.g., children or elderly), a certain function (e.g., sleeping or eating) or to a disease-

derived problem (e.g., pain) with primary goal to measure responsiveness or clinically important changes (Davies et al., 2020, Lin, Lin and Fan, 2013).

Although a variety of different tools for measuring HRQoL exists, none of them is considered as the best in an absolute sense, but there are only tools best suited to a particular condition (Lin, Lin and Fan, 2013). In addition, both types of measures have benefits and weaknesses, so researchers must determine their specific research question and desired outcome data before deciding which to use (Davies et al., 2020). It is also a general recommendation though, that generic tools should be supplemented by specific tools in order to address clinically important positive and negative changes, while the criteria for selecting and judging each measure's appropriateness should include: (a) appropriateness: measure should match the specific research purpose; (b) reliability; (c) validity; (d) responsiveness: adaptability to changes in the research's aspects; (e) precision: the number and accuracy of the distinction made by the measure; (f) interpretability: the results' interpretation; (g) acceptability: how easily participants accept to complete the questionnaire; and (h) feasibility: how much effort the staff put, how much they were burdened and disrupted while using the tool (Lin, Lin and Fan, 2013).

In the field of oncology, patient-reported outcomes (PROs) are currently used as a prognostic tool for patients, who self-report directly how they feel and function, without the interpretation of their health care professional" (Husson et al., 2019). This way "any patients with cancer can provide a unique perspective on their own symptom burden, functioning and health-related quality of life (HRQoL) (Husson et al., 2019). The PROs assessment tool has focused primarily on the improvement of the HRQoL by examining the effects of disease and treatment on physical, psychological and social functioning through the patients' perception (Husson et al., 2019). Such an example can be found in the study of Quinten et al. (2009) where data from thirty clinical trials, studying eleven different cancer types, indicated that for each cancer site, at least one examined HRQoL domain provided prognostic information beyond the provided information by clinical and sociodemographic characteristics (Husson et al., 2019).

Despite the growing interest and attention on anticancer therapy-induced skin problems, their impact on QoL distraction was not much considered. In particular, clinical factors that cause more distraction in dermatology-related QoL have not been studied, although

this information can help clinicians to counsel patients and manage their skin problems during anticancer therapy (Lee et al., 2018). To this study, with the use of questionnaires, we aim to examine the Health-Related Quality of Life (HRQoL) of cancer patients experiencing a treatment related skin disease. More specifically, as this study's setting is making it feasible, we will administer both a specific and a generic questionnaire and test the HRQoL of patients by investigating the impact of skin disease both generally and specifically.

As per subchapter 8.1, the available options for general HRQoL measures include the WHOQoL-BREF questionnaire, the SF-36 questionnaire and the EORTC QLQ-C30 questionnaire. The SF-36 questionnaire is considered one of the most prevalently used measures of HRQoL assessment while it contains a variety of domains under examination: physical functioning, role limitations, social functioning, pain, mental health and vitality (Karimi and Brazier, 2016). As one of the General Health Questionnaires, the SF-36 is a more objective measure, as its questions regard capability and disability, opposingly to the WHOQoL-BREF that focuses on individual opinions about the quality of life (Castro, Driusso and Oishi, 2014). The SF-36 tool provides better discrimination between health-related known-groups whereas the WHOQoL-BREF seems to be the better choice for an overall assessment of quality of life in a population of young individuals (Castro, Driusso and Oishi, 2014). In the oncology setting, the EORTC QLQ-C30 and the SF36 are considered two of the few self-completed questionnaires that can be deemed valid, reliable, and sufficiently brief in order to be of practical use in the clinical research setting, while both are used in European patient populations often (Lins and Carvalho, 2016). The SF-36 has been increasingly reported in the scientific literature in the last years as a global measure of health-related quality of life while it was also used in many studies published in highly prestigious journals (Lins and Carvalho, 2016). Thus, our choice for a general HRQoL measure is the SF-36 as it seems to score higher in popularity and usefulness among the other candidate questionnaires. The Dermatology Life Quality Index (DLQI) was our primary choice to be utilized as a condition-specific Health-Related QoL questionnaire. This questionnaire is considered appropriate in order to meet the purposes of our study (see subchapter 6.2) as it is the first developed skin-specific health-related QoL questionnaire and its validity and reliability and responsiveness to change have been

tested by more than a 100 independent studies, for over 25 years and in various skin diseases (Rencz, Szabó and Brodszky, 2021, Lee et al., 2018). It is simple, practical and patient-assessed and is able to evaluate the impact of many skin diseases and their treatments, over patients' QoL (Lee et al., 2018). Since its publication, it has become by far the most frequently used instrument to measure HRQoL in dermatology, while it has been translated to over than 110 languages and is now used in over 40 skin conditions worldwide (Rencz, Szabó and Brodszky, 2021). This tool is also widely used in both clinical practice and research setting, including randomized controlled trials, patient registries and national treatment and reimbursement guidelines (Rencz, Szabó and Brodszky, 2021).

9 SYSTEMATIC REVIEW OF THE LITERATURE

Systematic review of the literature: the extent to which the last decade has yielded additional treatment options for EGFR-associated rash besides classic treatment with antibiotics and corticosteroids - a systematic review

This chapter outlines the method used to conduct the systematic literature review, highlights studies that have been conducted on the effects of EGFRI treatment on rashes in cancer patients, and summarizes the study findings.

9.1 Introduction

There are many studies on the management and treatment of the skin rash associated with EGFRI treatment. Most of these studies are based on expert opinion or expert panels. For example, Pinto et al. (2011), a group of Italian experts voted to determine the final version regarding the measurement of adverse skin events in cancer patients (Pinto et al., 2011). Another illustration is Chu et al 2017 study, which determined rash prevention outcomes by voting in accordance with the judgments of a Taiwan Dermatological Association (TDA) consensus committee (Chu et al., 2017).

Despite the use of multiple medications, primarily antibiotics, and corticosteroids, the rash is still one of the most serious side effects for cancer patients treated with EGFRIs. The severity of the issue and its effects have been covered in detail in earlier chapters of this work.

To date, effective measures need to be found to address this serious problem affecting cancer patients due to the high frequency of rashes and the consequences of side effects on the skin. Numerous studies have been done on the treatment and prevention of rashes caused by EGFRI therapies using oral, intravenous, and topical antibiotics as well as corticosteroids.

There is a lack of information in the literature addressing the treatment and prevention of EGFRI-induced rashes without the use of steroids and antibiotics. Therefore, based on the above data, it was deemed necessary to conduct a study to investigate different methods other than antibiotics and cortisone products for the prevention and treatment of EGFRI treatment-induced skin rash.

9.2 Aim

This systematic review aims to investigate the effectiveness of different interventions apart from antibiotics and cortisone products, for the prevention and treatment of EGFRI treatment-induced rash that has appeared in the last decade.

9.3 Method

9.3.1 Data sources and search

An extensive search of the electronic databases was carried out between January 1st and March 30th of 2019, while the search was repeated in September of 2020 with expanded inclusion criteria in order to include newly published articles. The articles extracted collectively from both search periods, included published studies regarding the past decade, from January 1st 2009 until September 30th of 2020.

Search strategies were limited to studies published in the last decade in the Medline database, available through the Pubmed databases and Cochrane. The following keywords were used: 'Acneiform Eruptions', 'EGFRI', 'epidermal growth factor receptor', 'exanthema', 'skin rash', 'skin toxicity', 'rash', 'erlotinib', 'gefitinib', 'cetuximab', 'panitumumab', 'afatinib', 'management', and 'patient education' using keywords combined with appropriate operators (AND, OR).

9.3.2 Inclusion and exclusion criteria

The inclusion criteria for this systematic review were predefined. Eligible published studies were studies that met the following inclusion criteria:

a) published studies in English language,

b) studies that focused on the prevention and/or treatment of skin rash due to EGFRI treatments or combinational treatments with EGFRI therapy, for example EGFRI plus other chemotherapy medicines or EGFRI treatment plus radiotherapy,

c) all tumor types and all cancer stages were included in the study.

The exclusion criteria for the systematic review were:

a) article types such as letters, guidelines, clinical recommendations, reviews, and meta-analyses,

b) studies that investigate the treatment and /or management of the skin rash due to EGFRI therapy with antibiotics and steroids, as these methods of treatment have received extensive attention in the literature and their effectiveness is well established and documented,

c) studies that examined the Objective Response (OR) of EGFRI treatments, Progression-Free Survival (PFS), the Disease Control Rate (DCR),

d) studies that examined the cost of the EGFRI treatments or the cost deriving from the management of the side effects due to EGFRI treatments,

d) studies that focused on the comparison of other chemotherapies and/or radiotherapy with EGFRI treatments were also excluded.

For the second update research, the search criteria were extended due to the small number of studies in order to include article types such as case series and case report studies.

9.3.3 Screening

The initial search was performed on PubMed. Firstly, the authors screened the titles and abstracts based on the above-mentioned criteria. The total number of articles resulting from the search strategy was 811 studies. No additional articles were found in Cochrane.

During this phase, 344 studies were removed due to irrelevant titles, 345 studies were excluded due to the fact that the content of the summary did not meet the specified criteria, and 97 studies were excluded due to parallel posting in different databases.

Taking into account the above, 25 studies were fully read after meeting the title and abstract criteria, of which 13 studies were excluded due to lack of relevance to the research topic, and, finally, an additional article was handwritten from the study reports. Finally, a total of thirteen studies were selected following this process to be included in this systematic review for further analysis.

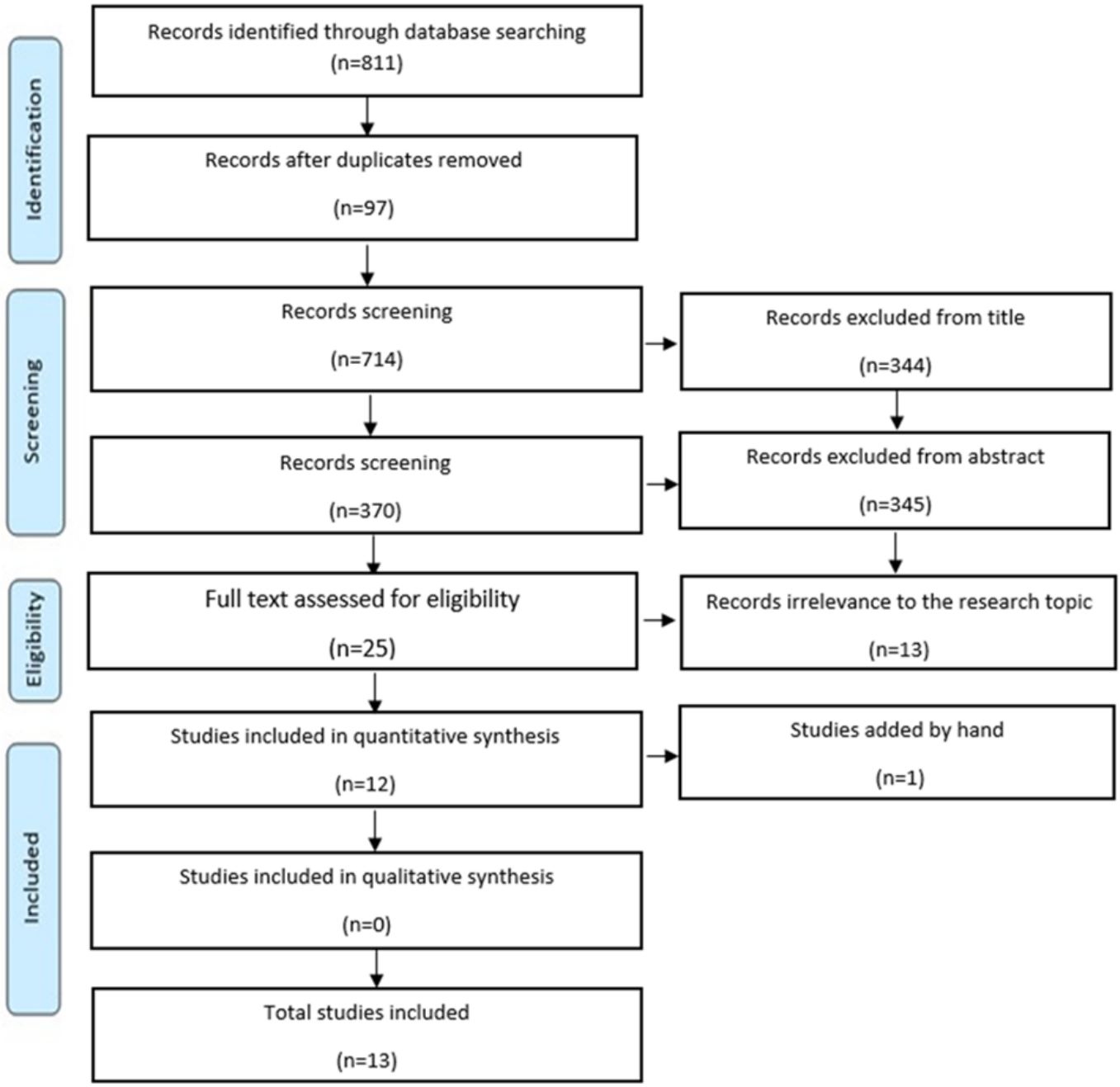


Figure 21 Prisma Flow Diagram

9.3.4 Quality appraisal

Each study was evaluated for its methodological quality based on the Jadad (Jadad et al., 1996) and CASP tools (CASP, 2017) for the clinical trials and case-control studies, respectively, the NIH Quality Assessment Tool for the case series studies, and the CARE checklist was used (Gagnier et al., 2013) for the case report studies.

Randomization, blinding, and withdrawals are the three main parameters of the Jadad scoring system. The Jadad tool can take a score between zero and five. A zero score means a very poor study, and a five score means that a study is rigorous. Details of the scoring system of the Jadad tool are provided in the table below (Table 5).

Table 5 Jadad tool scoring system

Item	**Maximum Points**	**Description**
Randomization	2	• 1 point: if randomization is mentioned (this includes the use of words such as randomly, random, and randomization) • 1 additional point: the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.) • Deduct 1 point: the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

Blinding	2	• 1 point: if study described as double blind • 1 additional point: the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.) • Deduct 1 point: the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)
Withdrawals	1	• 1 point: if there is a description of withdrawals and dropouts

Source: Hempel et al., (2011)

In our systematic review, the included studies of Eriksen et al. (2017), Jatoi et al. (2010) and Kim et al. (2020) had score 5/5, the score for the study by Chayahara et al. (2019) and Lacouture et al. (2010) was 3/5 whereas three studies (Pinta et al., 2014; Hwang et al., 2016; Fuggetta et al., 2019) did not correspond to any of the Jadad criteria.

The CASP tool, used for case control studies, does not suggest a scoring system but provides questions as key criteria. The CASP tool includes 11 questions divided into three sections; “Section A” examines if the results of the study are valid, “Section B” examines how the results are analyzed; and “Section C” examines whether the results will help locally. The table 6 shows the 11 questions of the CASP tool checklist.

Table 6 Questions of CASP tool checklist

Sections	Questions
Section A: Are the results of the trial valid?	1. Did the study address a clearly focused issue?

	2. Did the authors use an appropriate method to answer their question? 3. Were the cases recruited in an acceptable way? 4. Were the controls selected in an acceptable way? 5. Was the exposure accurately measured to minimize bias? 6. (a) Aside from the experimental intervention, were the groups treated equally? (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?
Section B: What are the results?	7. How large was the treatment effect? 8. How precise was the estimate of the treatment effect? 9. Do you believe the results?
Section C: Will the results help locally?	10. Can the results be applied to the local population? 11. Do the results of the study fit with other available evidence?

Source: CASP, (2017)

Moreover, case series studies evaluated with the NIH Quality Assessment Tool. This tool includes nine questions: Was the study question or objective clearly stated; Was the study population clearly and fully described, including a case definition; Were the cases consecutive; Were the subjects comparable; Was the intervention clearly described; Were the outcome measures clearly defined, valid, reliable and implemented

consistently across all study participants; Was the length of follow-up adequate; Were the statistical methods well described; Were the results well described. Based on the answers of the above questions, the quality rating can be good, fair or poor. The studies of Tomková et al. (2013) and Gobbo et al. (2012) lag behind the statistical method so the quality rating is fair.

The studies of Gürbüz et al. (2020) and Ferrari et al. (2016) are case reports studies and evaluated with CARE checklist. The CARE checklist includes thirteen questions about the title, the keywords, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic intervention, follow up and outcomes, discussion, patient perspective and informed consent (Gagnier et al., 2013). For example, the checklist for the title is 'The diagnosis or intervention of primary focus followed by the words "case report", and the question checklist for the key words is: '2 to 5 key words that identify diagnoses or interventions in this case report, including "case report" (Gagnier et al., 2013).

The case reports studies which included in these systematic review in the patient information question family and psycho-social history they omitted to mention and overlook in the keywords section the phrase 'case report'. Information about the collection of informed consent from the patients was absent. Finally, the study of Ferrari et al. (2016) did not include the type of study in the title. Finally, both studies corresponded clearly to the criteria of the CARE checklist.

Overall, the above procedure was performed in order to limit any potential biases and exclude unreliable results from our literature review. The major strengths identified in the studies reviewed regard the methodology: all studies described the inclusion and exclusion criteria and methods of participant selection. A major weakness identified in some of the studies was the statistical method used: the failure to describe the efforts to address potential bias sources and the variable criteria, together with the fact that the majority of the studies did not report how potential confounders were addressed.

9.4 Analysis of the findings

Retrieved data were combined and clustered into categories. The purpose of sorting the data in such a way was to investigate how the research question and important concepts were previously approached in the scientific literature.

Since the used studies in this review were outputs from a variety of fields (clinical, academic/research), structured synthesis methods were used during clustering of the findings. Subsequently, this systematic review mainly categorizes rather than expounds its retrieved data. Categories resulted following quality rating and classification based on the similarity of study conclusions.

In this systematic review, the authors extracted and congregated findings in the following two categories based on the intervention method used: four studies used “Category A” creams and nine studies focused on different intervention methods such as laser treatment, Polydatin (PD) cream treatment, treatment with sunscreen, Adapalene gel treatment, topical aloe vera treatment, topical hydration treatment, the impact of a pre-emptive skin treatment, and finally epidermal growth factor ointment treatment (“Category B”). The table 7 illustrates the characteristics of the studies reviewed.

Table 7 Characteristics of the studies reviewed

CATEGORY A - VITAMIN K1 / VITAMIN K3						
AUTHORS, YEAR	**AIM**	**DESIGN**	**INSTRUMENTS**	**SAMPLE SIZE/ INCLUSION CRITERIA**	**ANALYSIS METHOD**	**OUTCOMES**
(Eriksen et al., 2017)	To investigate the effect of a vitamin K3 cream on cetuximab - rash. Secondary aim: to investigate any possible side effects of vitamin K3 cream.	A randomized, double-blinded placebo-controlled trial.	CTCAE v. 4.0	n = 30 (n=18 for final analysis) Patients with metastatic cancer (rectum, colon, pancreas, esophagus, head & neck, unknown primary) receiving cetuximab 500 mg/m2 every second week plus chemotherapy. At least 18 years old. No other diseases (including chronic skin disease)	Bland-Altman plots and linear regression, Descriptive statistics, Changes in the number of follicular eruptions- t test after testing for normal distribution Using QQ-plots.	The mean number of elements: At baseline: 4.9 (placebo) versus 5.1 (vitamin K3) (p =0.9). Week 2: 11.1(placebo) versus 14.1 (vitamin K3) at (p=0.5). Week 6: 8.9 (placebo) versus 7.3 (vitaminK3) (p=0.7).

				No concomitant treatment with vitamin K. No hypersensitivity to vitamin K3.		Week 4: 6.1 (placebo) versus 6.3 (vitamin K3).
(Tomková et al., 2013)	To assess the possible effect of topical Vitamin K1 pre-treatment in diminishing the extent and severity of acne-like follicular rash	Case series	CTCAE v.4.0	n=20 Patients with colorectal cancer or head and neck cancer. Treated with panitumumab or cetuximab	/	75%: grade I 25%: grade II

	associated with epidermal growth factor receptor inhibitor therapy					
(Li et al., 2015)	To investigate the impact of 0.1% vitamin K1 cream on cetuximab-skin toxicity	Case-control study.	NCT-CTC v 3.0	n= 60 Patients with colorectal cancer. Patients taking cetuximab plus F0LF0X 4/14 days and cetuximab plus FOLFIRI/ 14 days. Exclusion criteria: Patients with skin disease and diabetes.	Wilcoxon rank-sum test	No grade 4 in both groups. There was no statistically significant difference between the two groups for the rash (P= 0. 642).
(Pinta et al., 2014)	Evaluate the prophylactic use of Vitamin K1	Pilot Clinical Trial.	CTCAE v 3.0	n= 41 Patients with Metastatic Colorectal Cancer received	/	No grade 4 was reported. Grade 0 – 15% Grade 1 – 45%,

	cream (Vigorskin) in patients taking Cetuximab.			cetuximab with or without other chemotherapy.		Grade 2 – 25% Grade 3- 15%

CATEGORY B - STUDIES WITH DIFFERENT INTERVENTION METHOD						
AUTHORS, YEAR	**AIM**	**DESIGN**	**INSTRUMENTS**	**SAMPLE SIZE/ INCLUSION CRITERIA**	**ANALYSIS METHOD**	**OUTCOMES**
(Gobbo et al., 2012)	Evaluate the effectiveness of high-level laser therapy in reducing the severity of facial acneiform rash induced by	Case series	Visual analogue scale (VAS) and Cetuximab-Related Toxicity scale (CTR)	n=6 Patients with metastatic colorectal cancer, head and neck cancer showing cetuximab- Induced rash.	/	All the patients start with grade II rash, after the second laser application two patients had grade I rash and after the end of the laser application all the patients had grade I rash.

	cetuximab, an epidermal growth factor receptor inhibitors.					
(Fuggetta et al., 2019)	Evaluate the effect of topical application of a moisturizer containing PD (Polydatin) to prevent skin rash due to EFGR therapy.	Pilot clinical trial.	CICTCAE v 3.0	N=34 patients. Patients with mutated non-small cell lung cancer (NSCLC) stage IV treated with afatinib 40mg/die. Patients (age≥18years). ECOG performance status of 0 to 2. Exclusion criteria: Poor patient compliance, allergic/sensitive to PD, concomitant skin diseases.	/	The incidence of skin rash (all grades) was 41.2% and grade 2 rash was 20.6%, and grade 3 rash was not observed. None of the patients discontinued therapy due to rash.

(Jatoi et al., 2010)	Determine whether sunscreen prevents or mitigates rashes.	Placebo-controlled, double-blinded Trial.	CTCAE v 3.0 Skindex-16	n=110 (54 patients received sunscreen, and 56 received placebo) Patients >18 years, a cancer diagnosis, an EGFR inhibitor started or about to be started by the patient within 3 days of randomization, patient appearing capable of applying sunscreen as instructed and of completing questionnaires independently or with help.	Fisher exact test, logistic regression.	During the 4-week intervention rash for any grade occurred in 78% and 80% for the sunscreen and the placebo respectively (p=0.36). No significant difference in rash between the two groups

(Chayahara et al., 2019)	To evaluate the prophylactic efficacy of adapalene. Primary endpoint: The difference in total facial lesion count of acne-like rash at 4 weeks. Secondary endpoints: 1. Complete control rate (CCR) of acne-like rash (≤5 facial lesions)	Randomized, placebo-controlled, evaluator-blinded, left-right comparative trial.	CTCAE v 4.0, IGA scale, Multinational Association For Supportive Care in Cancer scale (MASSC)	n=36 patients were enrolled (of whom 26 were evaluable) Patients with head and neck cancers, non-small cell lung cancer, and colorectal cancer, ≥20 years of age, ECOG performance status of 0–2, Adequate organ function, Receive treatment with cetuximab, panitumumab, gefitinib, erlotinib, or afatinib.	Investigator's Analysis: Inactive because results did not meet primary endpoint	No statistically significant differences in any of the efficacy endpoints between adapalene treated and placebo-treated sides. On the IGA scale, 15 of 26 patients scored equally between the placebo and adapalene sides, and 8 of the remaining 11 patients had a higher score on the adapalene side VS placebo side. On the MASSC scale, 16 of 26 patients had the same score for both sides, 8 of the remaining 10 patients had a greater score

	2. Global skin assessment (Investigator's Global Assessment [IGA] scale, grade 0–4) at 4 weeks.					on the adapalene side VS placebo side. The overall incidence for 4 weeks of therapy was: 51% (Adapalene) VS 48% (placebo)
(Gürbüz et al., 2020)	Presented a metastatic colon cancer case which developed acneiform rash under cetuximab treatment and	Case Report	NCCTCAE v 4.0	A 60-year-old male patient with malignant polypoid lesions in the sigmoid colon, and pathological examination revealed colonic adenocarcinoma. The patient had peritonitis carcinomatosa, liver,	/	Cetuximab-related severe acneiform rash was effectively treated by topical aloe vera.

	was managed by aloe vera extract.			lung and bone metastases.		
(Ferrari et al., 2016)	To tested a compound of a mixture of paraffin, silicone and macrogol in a patient with rash treated with cetuximab.	Case Report	/	A 50-year-old woman with metastatic colorectal cancer.	/	The rash disappeared in about 2 weeks. Not observe any reactivation of the skin rash in the following weeks with cetuximab

(Kim et al., 2020)	To evaluate the efficacy of EGF ointment for EGFR inhibitor-related skin adverse events (ERSEs) Primary endpoint: response rate (RR) of EGF ointment: (a) reduction of ERSEs from grade ≥2 to grade ≤ 1 or	Placebo-controlled, double-blind, multicenter, pilot phase III trial	NCI-CTCAE v 4.0 Skindex-16 questionnaire	N=90 (n=80 for the final analysis) Between June 2015 and October 2017 Inclusion criteria: Patients with non-small cell lung cancer, pancreatic cancer, or colorectal cancer who are treated with gefitinib, erlotinib, afatinib, or cetuximab 11 institutions in South Korea, age ≥20 years, ECOG ≤2, an estimated life expectancy of at least 3 months.	Pearson's chi-square test Cochran Armitage trend test Chi-squared test. Fisher's exact test Kruskal-Wallis test or Mann-Whitney U test SAS statistical software For continuous variables, summary statistics included number, mean, SD, median, and range	Acneiform rash and pruritus were the main ERSEs Grade 3 ERSEs were observed in 10% patients. There were no significant differences in baseline NCI-CTCAE ratings of ERSEs among the three arms. RR was 44.4% (arm 1), 61.5% (arm 2), and 77.8% (arm 3) (p = .042). RRs were significantly different between arm 1 and the combination of arms 2 and 3 (p = .028). There was a significant linear correlation between EGF concentration

	(b) grade ≥3 ERSEs downgrading to grade 2 and lasting for at least 2 weeks. Secondary endpoints: QoL and safety			Exclusion Criteria: Dermatologic treatment for skin lesions within 4 weeks, prior organ transplantation, history of hypersensitivity to EGF ointment or chemotherapeutic agents patients receiving immunosuppressive agents.		and response (p = .012). The RR was significantly higher in arm 3 than that in arm 1 (p = .049). In patients treated with EGFR TKIs, RR was 50.0% in arm 1, 72.7% in arm 2, and 78.6% in arm 3 (p = .209) There were no significant concomitant medication differences among study arms (p = .662). There was no influence on response of EGF ointment by concomitant medication (p = .797) In patients not receiving concomitant oral medication

						for the management of ERSEs, RR in arm 2 (60.9%) or arm 3 (77.3%) was higher than that in arm 1 (42.9%, p = .070) although it was not significantly higher.
(Hwang et al., 2016)	Evaluated the effect of epidermal growth factor (EGF) ointment on erlotinib-related skin effects (ERSEs). The effectiveness	Open-label, non-comparative multicenter, phase II trial.	NCI-CTCAE v 3.0 Skindex-16	N=52 (n= 46 patients for final assessment) Patients from 7 institutes in Korea. Between October 2012 and November 2013 Inclusion criteria: Patients with NSCLC treated with erlotinib alone	$\chi 2$ tests or Fisher's exact tests. SPSS software v. 20.0	EGF ointment was effective in 69.2 % of the patients. No statistically significant differences in the effectiveness of the EGF ointment by gender (p = 0.465), age (p = 0.547), tumor type

	of the ointment was defined as follows: (1) grade 2, 3, or 4 ERSEs downgraded to ≤grade 1 or (2) grade 3 or 4 ERSEs downgraded to grade 2 and persisted for at least 2 weeks.			and PC treated with gemcitabine and erlotinib in combination with chemotherapy. Sufficient liver, kidney, and bone marrow functions to undergo treatment. All the patients had grade ≥2 ERSEs.		(p = 0.085), erlotinib dosage (p = 0.117), and number of prior chemotherapy sessions (p = 0.547) Rating of rash and itching improved from 2.02 ± 0.83 to 1.13 ± 0.89 and 1.52 ± 0.84 to 0.67 ± 0.90, respectively (p < 0.001)
(Lacouture et al., 2010)	Examine differences between pre-emptive and reactive	Phase II, multicenter, open-label, randomized clinical trial	Medical Dictionary for Regulatory Activities	N=95 patients Patients with metastatic adenocarcinoma of the colon or rectum,	A logistic regression model, Wald method, Kaplan-Meier (KM) plots,	In the pre-emptive group, the incidence of grade 2 skin toxicities were 29% vs 62% in the reactive group.

	skin treatment for specific skin toxicities in patients with mCRC for any EGFR inhibitor. Primary objective: 1.to estimate the difference in incidence of specific grade 2 skin toxicities between patients in the pre-emptive and reactive skin treatment		(MedDRA) version 9.0. NCICTCAE v3.0 Modified CTCAE v. 3.0. for panitumumab-related skin toxicities. Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) DLQI	disease progression or unacceptable toxicity with first-line treatment containing 5-FU and oxaliplatin, with or without bevacizumab, age> 18 years old, ECOG 0 or 1. Adequate hematologic, renal, metabolic, and hepatic function, no prior irinotecan treatment or anti-EGFR therapy or vaccine treatment for mCRC, no incidence of pulmonary embolism, deep vein thrombosis, or any other significant	Cox regression models	Grade 2 skin toxicities of interest were reported in 23% of patients in the pre-emptive group VS 40% of patients in the reactive group. Grade 3 skin toxicities of interest, with 6% and 21%of patients in the pre-emptive and reactive groups experiencing grade 3 events, respectively Median time to first occurrence of specific grade 2 skin toxicities of interest was not reached in the pre-emptive group and was 2.1 weeks in the reactive group

	groups during the 6-week skin treatment period. Secondary objectives: 1. incidence rates of skin toxicities of any type during the 6-week skin treatment period 2.efficacy and safety of panitumumab given concomitantly			thromboembolic event within 8 weeks before random assignment.		

	with second-line irinotecan.					

The following table briefly summarizes the therapeutic intervention method for each study in category 'A' (Table 8) and Table 1 provides brief details of the therapeutic intervention method for each study in category 'B'.

Table 8 Details about the treatment interventions method for each study (Category 'A')

Study reference	Treatment interventions
Eriksen et al. (2017)	vitamin K3 cream manufactured at Glostrup Pharmacy in Denmark. The cream contains purified water (78.5%), sorbitol (7%), cetylanum (5%), paraffin liquid (5%) and 85% glycerol (4%) and 56.5 mg purified vitamin K3. In general, cream with 0.05% of vitamin K3
Li et al. (2015)	vitamin K1 cream manufactured at the Institute of Materia Medica, Chinese Academy of Medical Science. The cream contains: glycerin monostearate, stearic acid, liquid paraffin, Vaseline, lanolin, sodium lauryl sulfate, nipagin, triethanolamine, distilled water
Pinta et al. (2014)	Vigorskin cream used: 0.1% vitamin K1 (phytomenadione), urea, Triticum volgare germ oil, hydrolysed wheat protein, ceramides-1, -3, and -6 II, and phytosphingosine
Tomková et al., 2013	vitamin K1 cream manufactured at Hoechst-Biotika Ltd, Martin, Slovak Republic. Cream containing 10 mg of phytomenadione (Hoechst-Biotika Ltd, Martin, Slovak Republic) in 1 mL, which was added to ambi-derman, a hydrophilic cream base, oil in water, to obtain the final concentration of 0.05% or 0.1%

Table 9 Details on the treatment intervention method for each study in category 'B'

Study reference	Intervention method
Gobbo et al. (2012)	High-Level Laser Therapy (HLLT): wavelength 970 nm, power 5.0 W, 10 J/cm2, duty cycle/ pulsed mode 50%, frequency 10-1,000 Hz, spot size diameter between 0.8 and 2.5 cm
Fuggetta et al.,(2019)	Moisturizer containing Polydatin (PD)
Jatoi et al. (2010)	Sunscreen: 7.5% titanium dioxide and 7.5% zinc oxide.
Chayahara et al. (2019)	Adapalene gel 0.1% (trade name: Differin Gel 0.1%) - a topical retinoid
Gürbüz et al. (2020)	Topical aloe vera
Ferrari et al. (2016)	hydrating and moisturizing cream consisted of a mixture of glycerol, white soft and liquid paraffin, stearic acid, siloxane, silicone oil, macrogol 600, trolamin, propyl-hydroxybenzoate, and purified water
Kim et al. (2020)	EGF ointment
Hwang et al. (2016)	EGF ointment

Lacouture et al. (2010)	pre-emptive skin treatment: moisturizer (face, hands, feet, neck, back, and chest) daily in the morning; sunscreen (SPF 15) applied to exposed skin areas before going outside; topical 1% hydrocortisone cream (steroid) to face, hands, feet, neck, back, and chest at bedtime; and doxycycline (antibiotic) 100 mg twice per day. reactive skin treatment: consisted of any treatments the investigator considered necessary.

9.5 Results

The results from the studies in the category 'A' are controversial. Specifically, the study of Eriksen et al., (2017) noticed that the use of vitamin K3 was no effective for the cancer patients who experienced skin rash due to cetuximab treatment (mean number of elements at week 4-primary endpoint, was 6.1 to control group and 6.3 in the experimental group). The same view is expressed by the study of Li et al., (2015) for the vitamin K1 (0.1%) cream because the study found no statistically significant difference between the control and experimental group ($p= 0.642$). On the other hand, the studies of Pinta et al., (2014) and Tomková et al., (2013) concluded that there was a possible benefit for skin rash using the vitamin K1 cream as prophylaxis from the EGFRI treatment.

The results from the studies in the category 'B' cannot be grouped for a single conclusion due to different intervention methods and for this reason the results of each study are presented alone.

The study of Gobbo et al., (2012) concluded there was a benefit from laser treatment for the patients who experienced skin rash due to cetuximab treatment. Additionally, the study of Fugetta et al. (2019) indicated that a moisturizer containing Polydatin (PD) can

reduce the incidence of skin rash grade more than two in patients treated with afatinib treatment, the study of Gürbüz, Akkuş and Utkan, (2020) indicated that the topical application of aloe vera may be used in the management of skin rash due to cetuximab treatment and finally the study of Ferrari et al., (2016) recommended that the use of a hydrating and moisturizing cream can use for a skin rash treatment due to cetuximab therapy. Moreover, the study of Kim et al., (2020) and the study of Hwang et al., (2016) concluded that EGF ointment was effective in treating EGFRI treatment related rash ($p = 0.042$ and $p < 0.001$ respectively). Sunscreen with an SPF 60 was not recommended as prophylaxis from the skin rash due to EGFRI treatment according to the study of Jatoi et al., (2010) ($p = 0.36$). The study of Chayahara et al., (2019) indicated that adapalene gel is not recommended as a prophylaxis for rash due to EGFRI treatment. Finally, the results in the study of Lacouture et al. (2010) illustrated that the results in the pre-emptive group were better compared to the results in the reactive treatment regarding to the skin rash grades.

The studies of Eriksen et al. (2017) and Gürbüz et al. (2020) used Cetuximab at a dose of 500mg/m2 every second week plus chemotherapy, while in the study of Fuggetta et al. (2019) the patients received afatinib at 40mg/die. In the case report of Ferrari et al. (2016), the patient was started with cetuximab at initial dose of 400mg/m2 infused over 2 hours and later was switched to 250 mg/m2 weekly over 1 hour followed by chemotherapy (Ferrari et al., 2016). In the study of Li et al. (2015), the patients were treated with either cetuximab plus FOLFOX or cetuximab plus FOLFIRI. The patients in the study of Pinta et al. (2014) were treated with one of the following therapeutic schemes containing cetuximab: cetuximab plus FOLFIRI/XERILI, cetuximab plus FOLFOX/XELOX, cetuximab plus irinotecan, cetuximab plus Fluoropyrimidine, or single-agent cetuximab (Pinta et al., 2014). In this study, each patient received the regimen either as first- or second-line therapy, or as single-agent therapy. In the study of Tomková et al. (2013), the patients received cetuximab or panitutumab with the dose ranging between 400mg to 800mg either alone or with irinotecan. In the study of Kim et al. (2020), the patients received gefitinib, erlotinib, afatinib, or cetuximab for the treatment of pancreatic cancer. The dose is provided only for the patients that received erlotinib, which was 100mg, whereas in the study of Hwang et al. (2016) the dose of erlotinib was 150 mg/100 mg. Finally, in the study of Lacouture et al. (2010) the

patients were treated with panitumumab 6.0 mg/kg plus FOLFIRI every 2 weeks and panitumumab with 9.0 mg/kg plus irinotecan every 3 weeks.

For the rash's evaluation, three studies used the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Eriksen et al., 2017; Gürbüz, Akkuş and Utkan, 2020; Kim et al., 2020). In addition, the study of Eriksen et al. (2017) used skin photos and skin biopsies were also obtained from ten patients one month before and after treatment, from each treatment area. Five studies used the CTCAE version 3.0 for the evaluation of the EGFRIr (Fuggetta et al., 2019; Jatoi et al., 2010; Li et al., 2015; Pinta et al., 2014, Hwang et al., 2016). Additionally, Jatoi et al. (2010) used the Skindex-16 questionnaire to evaluate the impact of rash on patients' quality of life, another brief rash incidence questionnaire and a questionnaire on patient compliance with the EGFRI treatment (Jatoi et al., 2010). Finally, the study of Tomková et al. (2013) used the CTCAE version 4.03, while the study of Gobbo et al. (2012) used the visual analogue scale (VAS) and the CTR (Cetuximab-Related Toxicity) scale to assess the rash grade. The study of Chayahara et al. (2019) used two of the global skin assessment tools – the Investigator's Global Assessment (IGA) scale and the Multinational Association for Supportive Care in Cancer scale (MASSC), whereas two blinded dermatologists independently evaluated the endpoints from photographs. Additionally, one study used the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) study schema for the evaluation of the EGFRIr (Lacouture et al., 2010). On the other hand, one study failed to mention the grading system clearly, thus we hypothesised that they used the US National Cancer Institute catalogue of common toxicity criteria (NCI-CTC, version 4.0) (Ferrari et al., 2016). The reason for this hypothesis is because in the introduction of the study it says: "Among the many proposed criteria to grade the severity of cutaneous toxicity from EGFR inhibitors, the most commonly used are the NCI-CTC, version 4.0."

9.6 Analysis of the findings

9.6.1 Category A - studies using vitamin K1 or vitamin K3 containing creams

Studies confirmed that Vitamin K is an EGFR activator which not only can rescue the skin reactions induced by cetuximab, but also enables direct action on skin for external use even with minimum absorption (Li et al., 2015).

Vitamin K3 (menadione) is a stable and lipophilic molecule with a small molecular size, a synthetic pro-drug of vitamin K, and is suggested to be able to re-phosphorylate EGFR (Eriksen et al., 2017). Vitamin K3 is a potent phosphatase inhibitor and a potent EGFR activator and protector against erlotinib and cetuximab (Pinta et al., 2014).

The study of Eriksen et al. (2017) was conducted, no commercial product with the exact required amount of vitamin K3 was available on the market, so the cream was manufactured at Glostrup Pharmacy in Denmark specifically for research purposes. The placebo cream consisted mainly of purified water (78.5%), sorbitol (7%), cetylanum (5%), paraffin liquid (5%) and 85% glycerol (4%). The vitamin K3 cream consisted of the ingredients of placebo cream along with 56.5 mg purified vitamin K3 per 100 mL placebo, corresponding to 1.5 mM/L. In this study the vitamin K3 concentration corresponds to 0.05% of menadione (Eriksen et al., 2017).

The study of Eriksen et al. included thirty patients (18 patients in the final analysis) who received cetuximab every second week plus chemotherapy. In each patient, vitamin K3 cream and placebo were applied twice daily on two separate areas either on the chest or back (application area set at 10x10cm). Each patient was their own control. The application of the vitamin-containing cream continued for up to 2 months. For some patients the cream was used in a prophylactic way from the start of the treatment while with other patients it was utilised as treatment when the rash appeared.

The mean number of rash spots that appeared was 4.9 for placebo cream area VS 5.1 for vitamin K3 cream area at baseline ($p = 0.9$), increased to 11.1 (placebo) VS 14.1 (vitamin K3) at 2 weeks ($p=0.5$) and 8.9 (placebo) VS 7.3(vitamin K3) at 6 weeks ($p=0.7$). At week 4, which was the primary endpoint, no difference at all was found, with results being 6.1 (placebo) VS 6.3 (vitamin K3) (Eriksen et al., 2017).

Vitamin K1 (also called phylloquinone, phytomenadione) is found in high amounts in green leafy vegetables. It is metabolized to vitamin K2 homologues (menaquinones), the active storage form in animals, via intermediate vitamin K3 (Hofheinz et al., 2018).

For the study of Li et al. (2015), vitamin K1 cream was manufactured at the Institute of Materia Medica, Chinese Academy of Medical Science. The main component was 0.1% Vitamin K1, with: (1) glycerin monostearate (ointment bases and stabilizer, making products smoothingly); (2) stearic acid (hydrophilic ointment bases); (3) liquid paraffin (adjusting the ointment consistency); (4) Vaseline (enhancing water absorption together with lanolin); (5) lanolin (with property close to the sebum, easy to penetrate the skin, suitable for drugs required to absorb); (6) sodium lauryl sulfate (anionic emulsifier); (7) nipagin (common bacteriostatic agent in soft stalk); (8) triethanolamine (emulsifier, pH regulator); (9) distilled water (oil-in-water ointment diluent)(Li et al., 2015).

For the study of Pinta et al. (2014), Vigorskin cream was used. The cream contained 0.1% vitamin K1 (phytomenadione), urea, Triticum volgare germ oil, hydrolysed wheat protein, ceramides-1, -3, and -6 II, and phytosphingosine (Pinta et al., 2014).

In the study of Tomková et al., 2013 the cream was again manufactured for the purposes of the case series from phytomenadione (vitamin K1) solution containing 10 mg of phytomenadione (Hoechst-Biotika Ltd, Martin, Slovak Republic) in 1 mL, which was added to ambi-derman, a hydrophilic cream base, oil in water, to obtain the final concentration of 0.05% or 0.1% (Tomková et al., 2013).

The study of Li et al. (2015) included 60 patients with colorectal cancer that were divided into two groups: the experimental and control group (30 patients in each group). Patients in the experimental group applied vitamin K1 (0.1%) cream on their face, neck, chest, back and nails three times a day. The study found no statistically significant difference between the control and experimental group ($p= 0.642$). Additionally, no grade 4 rash cases occurred in any of the groups. More specifically, the occurrence rates of EGFRIr for Grades 0-3 in the experimental group were: 0%, 40%, 36.7%, and 23.3% respectively, while in the control group the rash for Grades 0-3 was: 0%, 36.7%, 33.3%, and 30% respectively.

The occurrence rate of EGFRIr in Grade 2-3 for patients in the experimental group was smaller than in the control group (Li et al., 2015).

The study of Pinta et al. (2014) included 41 patients with metastatic colorectal cancer. The vitamin K1-containing cream was applied twice a day on the face and trunk on the first day of cetuximab provision. Data for the rash grade were recorded weekly by the investigators. The results regarding the occurrence rates of EGFRIr for this study were 15% for Grade 0, 45% for Grade 1, 25% for Grade 2, 15% for Grade 3, and 0% for Grade 4. The study concluded that there was a possible benefit of the vitamin K1 cream as prophylaxis from the cetuximab-induced rash in patients (Pinta et al., 2014).

The study of Tomková et al. (2013) included 20 patients with colorectal and head and neck cancer. The application of the cream on the face, chest and upper back was performed twice daily during the first month of cetuximab or panitumumab therapy. The initial application was performed in the morning before the first infusion of the treatment. During the second month the application frequency was changed to once daily.

The beginning concentration of phytomenadione 0.05% was increased after 7 months to 0.1% for all patients that followed. The percentage of the patients with Grade 1 EGFRIr was 75%, while 25% had Grade 2 rash. This study concluded that topical pre-treatment with Vitamin K1 cream might become useful in EGFRI treatment-induced rash (Tomková et al., 2013).

9.6.2 Category B - studies with different intervention methods

The study of Gobbo et al. (2012) used a diode laser K1200 by Eltech S.r.l. (Via Castagnole, 20/H– 31100 Treviso, number K-1200-00149) for the treatment of EGFRIr via the High-Level Laser Therapy (HLLT) method. The laser parameters used were: wavelength 970 nm, power 5.0 W, 10 J/cm2, duty cycle/ pulsed mode 50%, frequency 10-1,000 Hz, spot size diameter between 0.8 and 2.5 cm (Gobbo et al., 2012).

The study included four patients with metastatic colorectal cancer and two patients with head and neck cancer, all treated with cetuximab. For the purposes of the study, the patients were treated with two 8-minute consecutive sessions per day for 4 days of treatment. The two laser applications were provided with a 5-minute interval so the total duration of treatment was 21 minutes.

An evident decrease in the dimension of EGFRIr was recorded after the first two laser sessions for two patients, from Grade 2 to Grade 1, and after the third session for the remaining four individuals (again for Grade 2 to Grade 1). At the end of the treatment, all six patients showed complete healing of the EGFRIr and the study concluded there was a benefit from laser treatment.

Before HLLT treatment, four of the participating patients had been using topic compounds: (Aquacutis - emollient, vitamin K1, Hydracial™ Skin Vigor Cream and Fissan cream) on their skin lesions during the previous 10-12 months without clinical improvements. These compounds were prescribed to the patients by dermatologists, oncologists, and GPs without success, and all topical treatments were suspended before the beginning of HLLT in order not to interfere with the laser therapy itself (Gobbo et al., 2012).

Polydatin (PD) is a glycosylated polyphenol (3,4′,5-trihydroxystilbene- 3-β-mono-D-glucoside, also known as piceid) with anti-inflammatory activity in human epidermal keratinocytes. It is a polyphenol extracted from the root stem of a traditional Chinese herb named Polygonum cuspidatum (Fuggetta et al.,2019).

The study of Fuggetta et al. (2019) included 34 patients in order to evaluate the effect of topical application of a moisturizer containing PD. One day before commencing the afatinib (a potent second generation irreversible ErbB family blocker that inhibits tyrosine kinase activity of EGFR and all relevant ErbB family dimmers), all patients were initiated on topical administration of a 1.5% PD-based cream twice a day, every day, until the end of afatinib treatment. The patients were monitored every 7 days for the first month and subsequently every twenty days or as needed. According to the study, the incidence of rash regarding all grades was 41.2% in total. For Grade 2 EGFRIr the percentage was 20.6%, while Grade 3 rash was not observed. Moreover, none of the patients discontinued therapy due to rash. In conclusion, this study indicated that a PD cream can reduce the incidence of Grade ≥2 in patients treated with afatinib.

Despite the fact that the study of Fugetta et al. (2019) mentions the small sample size as a large limitation, their results following the use of PD cream are equivalent to those of studies documenting benefit from tetracycline as prophylaxis from EGFRIr, a well-recognized therapeutic strategy. According to the author’s knowledge of the present

systematic review, the study of Fuggeta et al. was the only study that examined the effect of the PD cream treatment in patients treated with EGFRI.

For the management of EGFRIr, the study of Jatoi et al. (2010) used sunscreen provided by Pharmaceutical Specialties Incorporated (Rochester, MN), which included 7.5% titanium dioxide and 7.5% zinc oxide.

The study included fifty-four patients who received sunscreen with an SPF 60 (sun protection factor) while fifty-six patients received a placebo (Jatoi et al., 2010). The placebo formulation was identical to the sunscreen but lacked titanium dioxide and zinc oxide. The sunscreen or placebo were applied to the face, trunk, and extremities twice a day. During the 4-week intervention, ranging grades of rash occurred in 78% and 80% of the patients using sunscreen and placebo, respectively (p=0.36). These results illustrated no significant difference in the EGFRIr between the two groups. However, Grade 2 rash recorded-percentage for the two study arms differed: 33% for patients using sunscreen and 52% for patients using a placebo (p=0.06). At eight weeks of intervention all grades rash percentages were 78% and 75% for the sunscreen arm and placebo arm, respectively (p=0.82). Here, Grade 2 EGFRIr percentage was recorded at 39% for sunscreen-using patients and at 52% for placebo-using patients (p=0.19). The above results were extracted from the physician-reported data and concluded that there was no benefit from the use of sunscreen to the prevention of EGFRI treatment-induced rash (Jatoi et al., 2010).

The study of Chayahara et al. (2019) evaluated the use of Adapalene gel versus a placebo as prophylaxis for EGFRIr. Adapalene gel 0.1% (trade name: Differin Gel 0.1%) is a topical retinoid and is used to treat acne vulgaris. In the study, the patients were randomly assigned to once-daily Adapalene gel 0.1% application on one side of the face and with a placebo on the other side. Additionally, all participants applied moisturizer to both sides of their face twice daily, and received oral antibiotic (minocycline 100mg) daily. The concurrent treatments with moisturizer and antibiotic were initiated on the day of the initiation of EGFR treatment. The results showed that areas treated with Adapalene gel had a greater lesion count than the placebo after twenty-eight days of use, although the difference was not statistically significant (mean, 12.6 vs. 9.8, p = .12). Also, no significant differences were observed in the complete control rate (CCR) of rash (54% vs. 50%) or the IGA scale (mean grade, 1.9 vs. 1.7).

All in all, this study indicated that Adapalene gel is not recommended as a prophylaxis for rash due to EGFRI treatment (Chayahara et al., 2019).

The report of Gürbüz et al. (2020) presented the case of a 60-year-old male with colon adenocarcinoma with peritoneal, liver, lung and bone metastases. The patient received cetuximab plus chemotherapy and developed Grade 3 rash, despite prophylactic vitamin K1 0.1% cream provision, topical corticosteroid and doxycycline 100mg orally. Due to persisting rash, the patient expressed the wish to stop rash-related treatment and use topical aloe vera instead. Thus, he used topical aloe vera extract three times daily for two weeks. Aloe vera is an extract from a tropical cactus called Aloe and its leaf extract has anti-inflammatory, antioxidant, anticancer and immunomodulatory effects. In the study, the patient used aloe vera for the treatment. The patient's lesions regressed significantly at the end of the second week to Grade 1, while after three weeks of use the lesions resolved completely. Skin toxicity did not relapse with the next doses of cetuximab. Based on this study, topical application of aloe vera may be used in the management of cetuximab-related EGFRIr without any side effects (Gürbüz, Akkuş and Utkan, 2020).

The research group of Ferrari et al. (2016) studied the case of a patient diagnosed with metastatic colorectal cancer who received chemotherapy plus cetuximab. The patient developed EGFRIr and was managed with hydrating and moisturizing cream after the second cycle of treatment. Prior to the use of this cream, the patient had used vitamin K cream topically and oral minocycline, but developed grade 2 dermatitis. The rash disappeared completely after a twice-daily application of the hydrating and moisturizing cream that contained paraffin, silicone compounds, and macrogol. More specifically, the cream consisted of a mixture of glycerol, white soft and liquid paraffin, stearic acid, siloxane, silicone oil, macrogol 600, trolamin, propyl-hydroxybenzoate, and purified water (Dexeryl; Pierre Fabre, Paris, France). After the second day of administration of the hydrating and moisturizing cream, the skin became more hydrated and soft, the density of the EGFRIr was reduced, and the rash disappeared in about 2 weeks. Based on its findings, this study recommends the use of this hydrating and moisturizing cream as possible treatment for cetuximab- related rash (Ferrari et al., 2016).

The study of Kim et al. (2020) evaluated the efficacy of EGF ointment towards EGFRIr. Participating patients were randomly separated into three arms based on provided

treatment: group 1 corresponded to the placebo arm, group 2 corresponded to use of 1 ppm of EGF ointment, and group 3 corresponded to use of 20 ppm of EGF ointment. Patients from all groups applied ointment to their skin lesions twice daily. Rash and pruritus were the main side effects of the participants in this study. There were no significant differences in baseline NCI-CTCAE ratings of ERSEs among the three arms. The response rates were measured 2 weeks after the treatment and every 4 weeks thereafter and indicated 44.4% response in group 1, 61.5% in group 2, and 77.8% in group 3($p = .042$). In arm 3 RRs were significantly different between arm 1 and the combination of arms 2 and 3 ($p = .028$). Fourteen of the participants (17.5%) received concomitant oral medication for the management of the rash and the pruritus, but this did not affect the results between the three study groups. The study concluded that EGF ointment was effective in treating EGFRI treatment related rash and pruritus and this compound had a better effect at a higher dose (Kim et al., 2020).

The study of Hwang et al. (2016) also examined the efficacy of EGF ointment (Daewoong Pharmaceuticals Co. Ltd.). The ointment utilised contained 1 ppm of nepidermin and was evenly applied to the skin lesions twice daily for patients with Grade 2 lesions or greater. The results of the study were divided into two categories: Category 1 were lesions greater or equal to Grade 2 downgraded to Grade 1 or less, and Category 2, Grade 3 or 4 lesions were downgraded to Grade 2 and sustained for at least two weeks. For cases where the lesions did not improve after eight weeks of EGF ointment, the treatment was stopped and classified as “no effect.” According to this study, the EGF ointment offered effective management up to a point for EGFR related lesions for 69.2 % of the participants, while ten participants showed no response to the ointment. Conclusively, this study showed that EGF ointment is effective for the adverse events due to EGFR treatment (Hwang et al., 2016).

In the study of Lacouture et al. (2010), the patients were divided into pre-emptive skin treatment and reactive skin treatment. Pre-emptive skin treatment started one day before the first dose of EGFRI treatment and continued for one to six weeks, whereas the reactive skin treatment was prescribed when skin reactions appeared. Pre-emptive skin treatment included skin moisturizer (face, hands, feet, neck, back, and chest) daily in the morning; sunscreen (SPF 15) applied to exposed skin areas before going outside; topical 1% hydrocortisone cream (steroid) to face, hands, feet, neck, back, and chest at bedtime;

and doxycycline (antibiotic) 100 mg twice per day. On the other hand, the reactive skin treatment regimen consisted of any treatments the investigator considered necessary for the management of the EGFRI treatment-induced skin reactions. The results in the study of Lacouture et al. (2010) illustrated that in the pre-emptive group, the incidence of grade 2 skin toxicities was 29% versus 62% in the reactive group. Grade 2 skin toxicities of interest were reported in 23% of patients in the pre-emptive group, whereas in the reactive group the percentage was 40%, and grade 3 skin toxicities of interest were 6% in the pre-emptive group, and 21% of patients in the reactive groups.

9.7 Discussion

The aforementioned systematic review investigates the effectiveness of different intervention methods for the prevention and treatment of skin rash due to EGFRI treatments, excluding the use of antibiotics and cortisone products.

9.7.1 Acceptance for studies

This systematic review systemically excluded studies which evaluated the impact of EGFRIr using antibiotics or steroid treatment. However, it is worth noting that two of the studies included in this systematic review used antibiotic or steroid treatment (Eriksen et al., 2017; Pinta et al., 2014). However, the results in Eriksen's study were independent from the use of systemic tetracycline and thus this study was not excluded from this systematic review. In addition, from the study of Pinta et al. 2014 we preserved solely the results for Grade 0 and Grade 1 rash because the study initiated patients on antibiotic or steroid treatment when they experienced Grade 2 and Grade 3 EGFRIr. The number of cases excluded from our review was small, as only 6 patients out of 41 advanced to Grade 3 rash and required minocycline and corticosteroids.

The study of Jatoi et al. (2010) examining the effectiveness of sunscreen use against EGFRIr made adjustments for sun intensity by gender, performance status score, geographical zone, season, photosensitivity medications and the treatment with corticosteroid products. This adjustment was a big asset for the study as the authors took into account the main factors that could affect the results in the two study arms. Despite the adjustments, no statistically significant difference in EGFRI treatment-induced rash development was noticed.

Despite the fact that the study of Kim et al. (2020) does not differentiate between the two EGFRI related adverse events, rash and pruritus, we have included it in our study as it describes an effective compound against the EGFRIr as a side effect.

The study of Hwang et al. (2016) was not excluded from this systematic review regardless of the fact that participants received antihistamines and antibiotics (6 patients: Ucerax, Azeptin antihistamine, 4 patients: minocycline oral antibiotic, 3 patients: both). This is due to the fact that there was no difference in the effectiveness of the EGF ointment in the patients who received the co-medication and those who did not.

In the study of Chayahara et al. (2019), all patients received an oral antibiotic and had topical moisturizer co-applied to both sides of the face, along with the use of a placebo and Adapalene gel. Thus, since all participants received the same intervention, the end result in regards to the effectiveness of the EGFRIr treatment was not differently affected.

Regarding the results from the clinical trial of Lacouture et al. (2010), the authors of this systematic review were initially reluctant to include them for two reasons: firstly, the Lacouture study was focused on comparing the importance of pre-emptive versus reactive treatments, while our work examines the universal effectiveness of treatment options against EGFRI-associated rash. Secondly, in the study of Lacouture et al. (2010) there were differences in the interventions used between the two groups; for patients undergoing reactive management the regimen consisted of any type of treatment that was considered necessary, while for patients undergoing preventive management all received moisturizer, sunscreen, steroids and antibiotics.

In the end, the study was included in our review for its results regarding solely the interventions used in the pre-emptive group (moisturizer, sunscreen).

9.7.2 Comparing the findings with other studies

Some of the studies in this systematic review can be compared with other studies that were not included in this systematic review.

A study that is comparable to the study of Eriksen et al. (2017) is an ongoing study with an identifier number: NCT01393821 (as found on ClinicalTrials.gov) of which the results have not yet been published (Active, not recruiting).

In addition, the results in the study of Tomková et al. (2013) were comparable with the results of the study of Ocvirk et al. (2008), which was the first study that demonstrated the effectiveness of Vitamin K1 cream in the treatment of rash due to EGFRI treatment (Ocvirk & Rebersek, 2008). Data from the study of Ocvirk et al. illustrated a reduction of rash with Vitamin K1, 0.1% cream from grade 3 to Grade 2 after 1.2 weeks and from Grade 2 to Grade 1 after 2.3 weeks. The study of Tomková et al. concluded that topical pre-treatment with Vitamin K1 cream is useful in EGFRI treatment-induced rash.

As in the study of Chayahara et al. (2019) that is described in our systematic review, a similar study (Scope et al., 2007) examined the effectiveness of another retinoid as prophylaxis for EGFRIr. This study utilized tazarotene 0.05% cream for the management of rash and its use was eventually interrupted as it caused local irritation to participants (Scope et al., 2007). Conclusively, retinoids have proven ineffective and rather harmful for the management of EGFRIr.

9.7.3 Comparison of results with other recently published studies

A recent study focusing on Polydatin products, published in 2021, suggested that Polydatin could be used as an effective agent to prevent rashes associated with EGFRI treatment (Bavetta et al., 2021). In our systematic review, a study by Fuggetta et al. (2019) investigated the effects of polydatin in cancer patients with EGFRI-induced skin rashes. Both studies agree that polydatin may be an effective treatment for skin rashes associated with targeted cancer therapies. Specifically, the study of Bavetta et al., (2021) concluded that Polydatin was effective in preventing skin rashes, and Fuggetta et al., (2019) suggested that Polydatin was effective for the treatment of rash grade more than 2. Main characteristics and results of the studies by Bavetta et al. (2021) and Fuggetta et al. (2019) are illustrated in Table 10.

Table 10 Main study characteristics and results from the study of Bavetta et al., (2021) and Fuggetta et al., (2019)

Study Reference	Study Characteristics	Main Results

Bavetta et al., (2021)	• n=40 patients • treated with cetuximab, panitumumab, afatinib, gefitinib, osimertinib • patients were suffering from metastatic colon cancer, metastatic lung cancer, metastatic laryngeal cancer and metastatic rectal cancer.	a statistical significance improvement ($p < 0.05$) of the skin rash at week 4.
Fuggetta et al.,(2019)	• n= 34 patients • treated with afatinib. • patients with mutated non-small cell lung cancer (NSCLC)	Polydatin can reduce the incidence of moderate to severe skin rash

Source: Bavetta et al., (2021) and Fuggetta et al., (2019)

No other recently published studies were found to compare category "A" and category "B" results. Most studies have focused on therapeutic interventions based on antibiotic or steroid methods. A recent example is the single-center, randomized, double-blind, placebo-controlled study published in 2020 investigating the prophylactic topical treatment of skin rashes due to EGFRI treatment (Amitay-Laish et al., 2020). The intervention method divided in three arms. The first arm was a topical application with chloramphenicol 3% (an antibacterial agent) in combination with prednisolone 0.5% ointment (a corticosteroid) otherwise called CHL-PRED, the second arm concerns the usage of chloramphenicol 3% ointment named as CHL and finally the third arm was the usage of aqua cream otherwise AQUA (Amitay-Laish et al., 2020). The study

concluded that the use of chloramphenicol 3% in combination with prednisolone 0.5% ointment was effective for patients treated with EGFRI therapy ($p < 0.05$) compared to the other two treatment arms (CHL and AQUA), the results of which were not statistically significant (Amitay-Laish et al., 2020).

According to the above data, there is a gap regarding the evaluation of the processing interventions, apart from antibiotics and steroids, used for prevention and/or treatment for rashes due to EGFRI treatment. For this, this study highlighted the need for studies conducted, such as clinical trials, to provide more consistent evidence in this area of research.

9.8 Limitations

This systematic review has both strengths and limitations. According to the authors' knowledge, there is a gap in relation to reviewing treatment interventions, except antibiotics and steroids, utilized for the prevention and/or treatment for EGFRIr.

This systematic review highlighted the necessity of conducted studies such as clinical trials, since the majority of the research studies based on the EGFRIr are expert opinions and reviews. The systematic review and meta-analysis study of Ocvirk et al. (2013) also expressed the above concern.

The studies included in this review show some heterogeneity: some studies use different grading systems in order to evaluate the severity of EGFRIr. For example, the study of Eriksen et al. (2017) assessed the EGFRIr using the CTCAE v. 4.0, whereas the study of Li et al. (2015) evaluated it with CTCAE v.3.0. Furthermore, this systematic review included studies with patients suffering from different primary cancers, as opposed to the recent systematic review of Lacouture et al. (2018) that included studies only with metastatic colorectal cancer patients. Moreover, the studies included in this review were published only in English, meaning that this might affect our findings.

Finally, the studies included in this review are studies with a different study design like clinical trials and case series, as opposed to the systematic review of Ocvirk et al. (2013), which included only clinical trials studies. The homogeneity in the studies of the review of Ocvirk et al. allowed the authors to proceed with a meta-analyisis in contrast to the present systematic review. In addition, this study did not proceed with a meta-

analysis, as the studies included were clinically diverse, there was a mix of comparisons of different treatments and the range of tools used to investigate the EGFRIr would probably have made the meta-analysis meaningless.

9.9 Conclusion

Skin rash due to EGFRI treatment is an important skin adverse event that plagues cancer patients treated with EGFRI.

The authors of this review concluded that the use of some of the proposed interventions can yield a positive effect on the management of EGFRIr, while others may prove ineffective and rather harmful for the patients. Specifically, the use of treatment with sunscreen alone and Adapalene gel is not encouraged by the studies reviewed, while the authors of this review cannot draw a conclusion regarding the use of vitamin K as the efficacy of the vitamin for the management of EGFRIr is controversial. On the other hand, the laser treatment, Polydatin-containing moisturizer, topical aloe vera, topical hydration, pre-emptive skin treatment routine with moisturizer and sunscreen, and the epidermal growth factor ointment compounds were found to produce a positive effect for EGFRIr management and can be listed as effective interventions.

A large gap exists regarding the management strategies for EGFRI reactions (Lowe et al., 2019). We chose to exclude the aforementioned as several studies have been conducted concerning the effectiveness of the treatment with antibiotics or steroids in EGFRIr, which contributed to an improved statistical significance.

SPECIFIC SECTION

10 RESEARCH PART

This chapter presents the aim of this study and analyses the secondary objectives and the methodology procedures used, along with the results and discussion emerging from this pilot study.

10.1 Aim

The aim of this randomized controlled pilot study was to evaluate the effectiveness of an educational program of non-pharmacological interventions for cancer patients with pruritus or rash or photosensitivity induced by chemotherapy, EGFRI treatments, or immunotherapies.

10.2 Primary objectives

a) Develop the educational program for cancer patients with pruritus or rash or photosensitivity induced by chemotherapy, EGFRI treatments, or immunotherapies.

b) Ensure that each patient enrolled in the study has an equal chance of being assigned to control group or intervention group (randomization).

c) To compare the grade of skin reactions (pruritus, rash and photosensitivity separately) between control and intervention group for week 0 (baseline) and week 3 (week 0 and week 3).

d) To compare the grade of skin reactions (pruritus, rash and photosensitivity separately) within the control group for week 0 (baseline) and week 3 (week 0 and week 3).

e) To compare the grade of skin reactions (pruritus, rash and photosensitivity separately) within the intervention group for week 0 (baseline) and week 3 (week 0 and week 3).

10.3 Secondary objectives

a) To evaluate the Health Related - Quality of Life (HR-QoL) for patients with pruritus, rash, or photosensitivity induced by chemotherapy, EGFRI treatments, or immunotherapies between control and intervention group for week 0 (baseline) and week 3 (week 0 and week 3).

b) To evaluate the Health Related - Quality of Life (HR-QoL) for patients with pruritus, rash, or photosensitivity induced by chemotherapy, EGFRI treatments, or immunotherapies within the control group for week 0 (baseline) and week 3 (week 0 and week 3).

c) To evaluate the Health Related - Quality of Life (HR-QoL) for patients with pruritus, rash, or photosensitivity induced by chemotherapy, EGFRI treatments, or immunotherapies within the intervention group for week 0 (baseline) and week 3 (week 0 and week 3).

d) To estimate the percentage of dose reduction of the appropriate treatment in the control and intervention group for week 0 (baseline) and week 3 (week 0 and week 3).

e) To estimate the percentage of emergency admissions in the control and intervention group for week 0 (baseline) and week 3 (week 0 and week 3).

10.4 Material and method

10.4.1Study design

This study is a pilot randomized controlled study and was register in the Clinical Trials Registry with the trial ID: NCT03992664.

10.4.2Study population and sampling

In the literature, the sample size for similar pilot studies ranged from 24 patients (12 per group) (Julious, 2005) to at least 50 patients (Sim and Lewis, 2012). The study of Kieser and Wassmer (1996) recommended 20-40 patients while the study of Browne (1995) recommended 30 patients.

A study carried out by Johanson and Brooks (2009) noticed that the confidence intervals from pilot study data may prove useful. According to the writers, parameter estimation and confidence intervals are considered high quality when the number of patients included in the study, stated as N, ranges from 30 to 50 and when the sampling procedure is truly random. Johanson and Brooks (2009) concluded that 30 participants are recognized as a reasonable, minimum sample size for pilot studies. Furthermore, the impact of increasing sample size on the length of the confidence interval for Pearson correlations was examined. The data indicated that a sample size between 24 to 36 patients may be a reasonable sample size for that (Johanson and Brooks, 2009).

According to our knowledge, the present study is the first that evaluated the effectiveness of an educational training program regarding skin reactions induced by chemotherapies, EGFRI treatments and immunotherapies without the use of any pharmaceutical factors such as antibiotics, steroids, topical creams or lotions. Therefore, there were no previously reported data on the expected effect size on this topic.

For the aforementioned reasons, this pilot trial included 40 patients who were randomly allocated in two groups the intervention and the control group each consisting of 20 participants. This trial included cancer patients who experienced pruritus or rash or photosensitive dermatitis and the onset of their symptoms was due to a provided chemotherapy treatment, an EGFRI treatment, or an immunotherapy.

Patients' demographic data (sex, age, occupational status, academic qualifications), type and initial date of cancer diagnosis, provided chemotherapy treatment name and date of initiation were required for the purposes of the study and were collected by one of the authors (E.P.).

Thereafter, patients in the experimental group were assigned to attend the educational program once a week, for a total of 4 weeks under the supervision of author E.P. The educational program initiated day each participant signed the consent form.

10.4.3Inclusion criteria

Prospective participants were assessed according to the following inclusion criteria:

a. Adult cancer patients (>18).

b. Patients who suffered with pruritus, or rash or photosensitive dermatitis, in the onset of the symptoms due to immunotherapies or EGFRI treatment or chemotherapy irrespective of the therapy dose.

c. Patients treated with immunotherapies including Ipilimumab, Pembrolizumab, Opdivo and Nivolumab or patients treated with EGFRI treatment including Panitumumab, Cetuximab, Erlotinib, Afatinib, Gefitinib or chemotherapy medicine including Avastin, Caproblatin, Docetaxel, Epirubicin, Cyclophoshamide, 5-FU, Vincristine, Doxorubicin, Gemcitabine, Abraxane, Cisplatin and Taxol

d. Willing to participate.

e. Ability to complete the questionnaires.

f. A performance status of two or less on the Eastern Cooperative Oncology Group (ECOG).

g. Patients with no pre-existing dermatological condition that may limit the interpretation of results.

10.5 Measures

10.5.1Primary and secondary endpoints

For the primary endpoint data about skin pruritus, rash and photosensitivity were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (National Cancer Institute U.S., 2010).

For the Secondary endpoints we: a) investigated the functional health and well-being of patients by utilizing the SF-36 questionnaire, b) evaluated how much the skin reaction affected the patient's life over each past week during the educational program with the use of the Dermatology Life Quality Index (DLQI) questionnaire, c) investigated the percentage of the patients who required reduction of the treatment dose through the treatment information form , d) investigated the percentage of the patients who need emergency admissions dose through the treatment information form.

In chapter 8.3 we described in detail the reasons for the selection of SF-36 and DLQI questionnaires, among other questionnaires, as tools for this study's secondary objectives. In the following paragraphs we will analyze the form, scores and validity of

the Greek version of the two questionnaires used in this study, for the assessment of this study's Greek speaking sample.

The RAND developed the 36-Item Short Form Health Survey (SF-36), which is a practical, reliable and valid measure of physical and mental health (Hays and Morales, 2001). We chose to utilize the SF-36 questionnaire for this study because it provides a comprehensive list of 36 patient-reported questions that assist researches in measuring the functional health and well-being of the patients from their point of view. The SF-36 measures eight parameters: physical functioning, physical health, emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health (Ware and Sherbourne, 1992). Each parameter is rated on a 0-100 scale where the lower the score, the greater the disability the patient presents (Hays and Morales, 2001).

Many healthcare professionals utilize the SF-36 questionnaire to evaluate the quality of life (QoL) of patients, for a wide range of disorders, as it is considered a valuable general assessment (Lithoxopoulou et al., 2014,). In the oncology setting, the SF-36 is utilized both in research studies as well as the clinical oncology field to assess trustworthily the quality of life of cancer patients (Clabbers et al., 2016, Ahmed et al., 2017, Chen, Liu and You, 2018, Georgakopoulos et al., 2013). Over 4,000 research studies have been reported to have used the SF-36 questionnaire worldwide, as it has been translated into more than 50 other languages (Lithoxopoulou et al., 2014). For the purpose of this study, the SF-36 questionnaire was provided in its Greek version, as all the study population was Greek speaking. The Greek format (Greek SF-36) of the Short Form 36 (SF-36) questionnaire has been validated and normed in 2005 by Pappa, Kontodimopoulos and Niakas and the absence of differences in mean scale scores between the Greek and versions in other languages was a strong evidence in favor of the successful translation of the SF-36 into the Greek language. The validated Greek version of the generic SF-36 was also used in 2013 in the study by Georgakopoulos et al., as a "gold standard" to assess two other questionnaires translated in Greek (EORTC QLQ-C30 and FACT-Lym).

The second questionnaire used to evaluate participants of the study, in both control and intervention groups, was the Dermatology Life Quality Index (DLQI). This questionnaire is widely used in studies with main objective to evaluate the impact of skin problems to the Quality of Life in patients treated with anti-cancer agents over each

of the previous weeks of the study (Panariello et al., 2020, Vaccaro et al., 2015, Lee et al., 2018, Barbu et al., 2018, Finlay and Khan, 1994). The Dermatology Life Quality Index (DLQI) was developed in 1994, initially to evaluate the quality of life of dermatology patients (Basra et al., 2015). Due to its reliability and validity though, it is currently the most commonly used questionnaire in clinical trials, has been translated and thoroughly validated into more than 110 languages (Greek language included) and its use has been covered in more than 3,000 publications (Basra et al., 2015, Lewis and Finlay, 2004).

Emergency admissions, dose reduction and treatment interruption were also evaluated in this trial through the treatment information form. The treatment information form (*see* appendix 3) has a section to fill with four questions:

a. reduction of dose? (yes/ no),

b. emergency admissions? (yes/no),

c. end of treatment? (yes/no)

This section was filled in by the E.P during the weekly assessment of each patient for a total of 3 weeks (week 1 – week 3).

10.6 Procedures and interventions

10.6.1 Procedures

The study was performed at two private hospitals specializing in cancer treatment in Nicosia and Limassol, Cyprus. The patients were selected and monitored within the clinic either during their treatment or during scheduled weekly appointments. All meetings were held at the two private hospitals mentioned earlier, and each eligible participant received an individual intervention. Patient recruitment was completed within 23 months (January 2019–December 2020).

Details and instructions regarding the educational program were provided in paper form to the participants of the intervention group on the first day of their recruitment, right after they had signed the consent form. One of the authors read and explained the details of the educational program to each patient separately and then proceeded to provide the paper with the information to him/her.

On the other hand, patients in the control group did not receive the specific information regarding the educational program. However, the usual information was provided to them, as with any cancer patient who initiates chemotherapy, immunotherapy or EGFRI treatment. The usual information was provided in the form of a 'treatment booklet' which included: explanation regarding the methods of drug administration (cannula, central venous access device, portable pump), forms of chemotherapy provision (oral chemotherapy, injections, cream, chemoembolization), tips on how to spend the time during chemotherapy (e.g. reading a book), safety precautions (e.g. what to notice while using the toilet, how to handle laundry carefully) and what to expect and how to prepare regarding side effects such as fatigue, nausea or emesis, diarrhea or constipation, hair loss, mouth sores, skin and nail changes, sexuality and fertility issues. Each time, the follow up appointments were also noted inside the treatment booklet while on the first page of it the emergency numbers of the oncology team were provided.

The grades of skin reaction were evaluated every week (since participant's selection day - week 0), for all participants in both groups. To determine the effectiveness of our intervention (the educational program for cancer patients experiencing pruritus, rash or photosensitivity induced by chemotherapy, EGFRI treatment, or immunotherapy) the patients' HR-QoL was assessed weekly via the use of the SF-36 and DLQI questionnaires, for each of the 40 patients participating in our research, along with the measurement of the grade of their skin reaction.

Induction day to the study for each participant was considered the day of symptoms onset and signing of the consent form, while this day marked the start of week zero (week 0 - baseline) to the program for each patient. The patients were assigned to attend the educational program individually once weekly, for a total of four consecutive weeks.

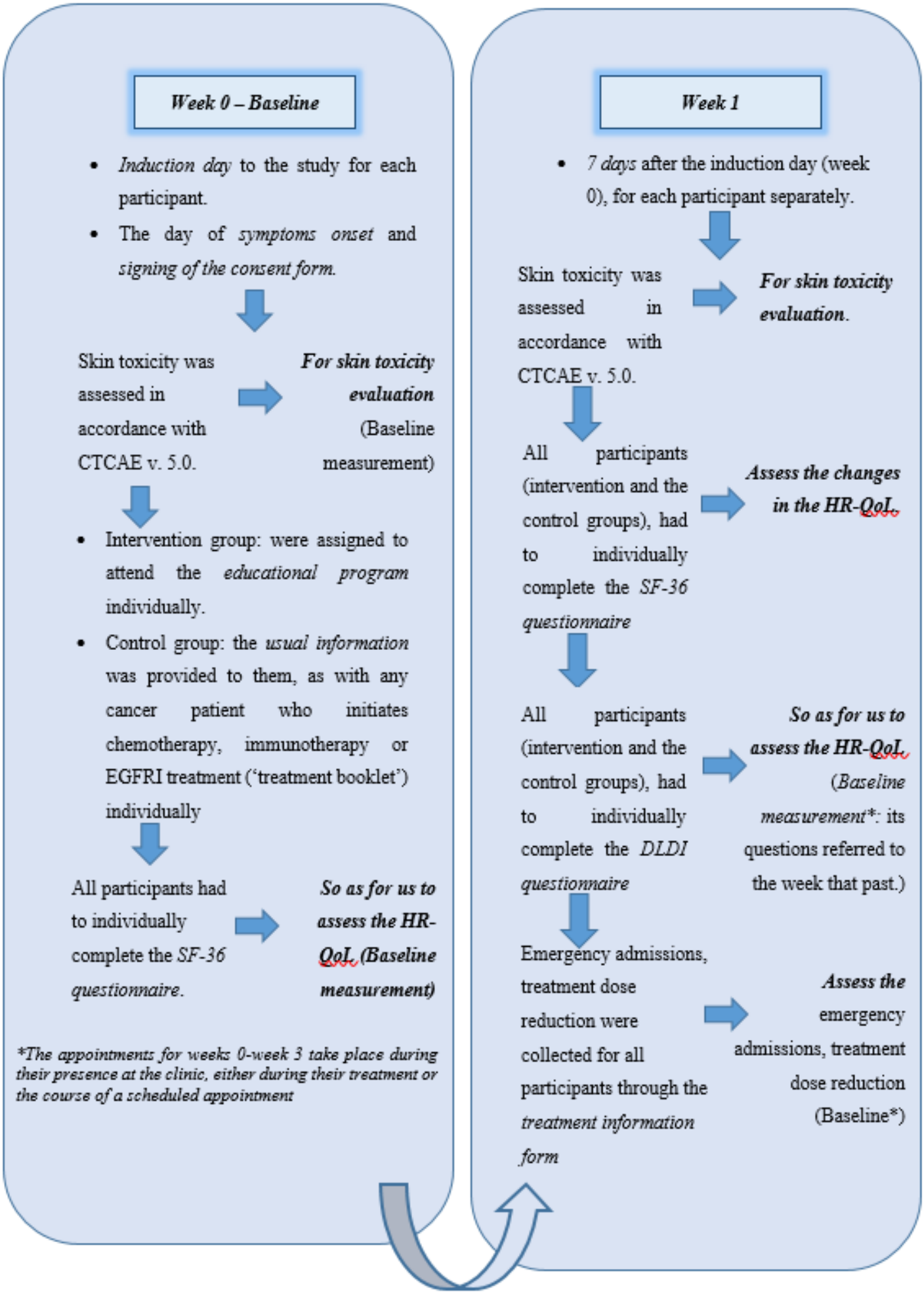
All participants, both from the intervention and the control groups, had to individually complete the paper formats of SF-36 and the DLQI questionnaires, every 7 days, during their presence at our clinic, either during their treatment or the course of a scheduled appointment, so as for us to assess the changes in the HR-QoL.

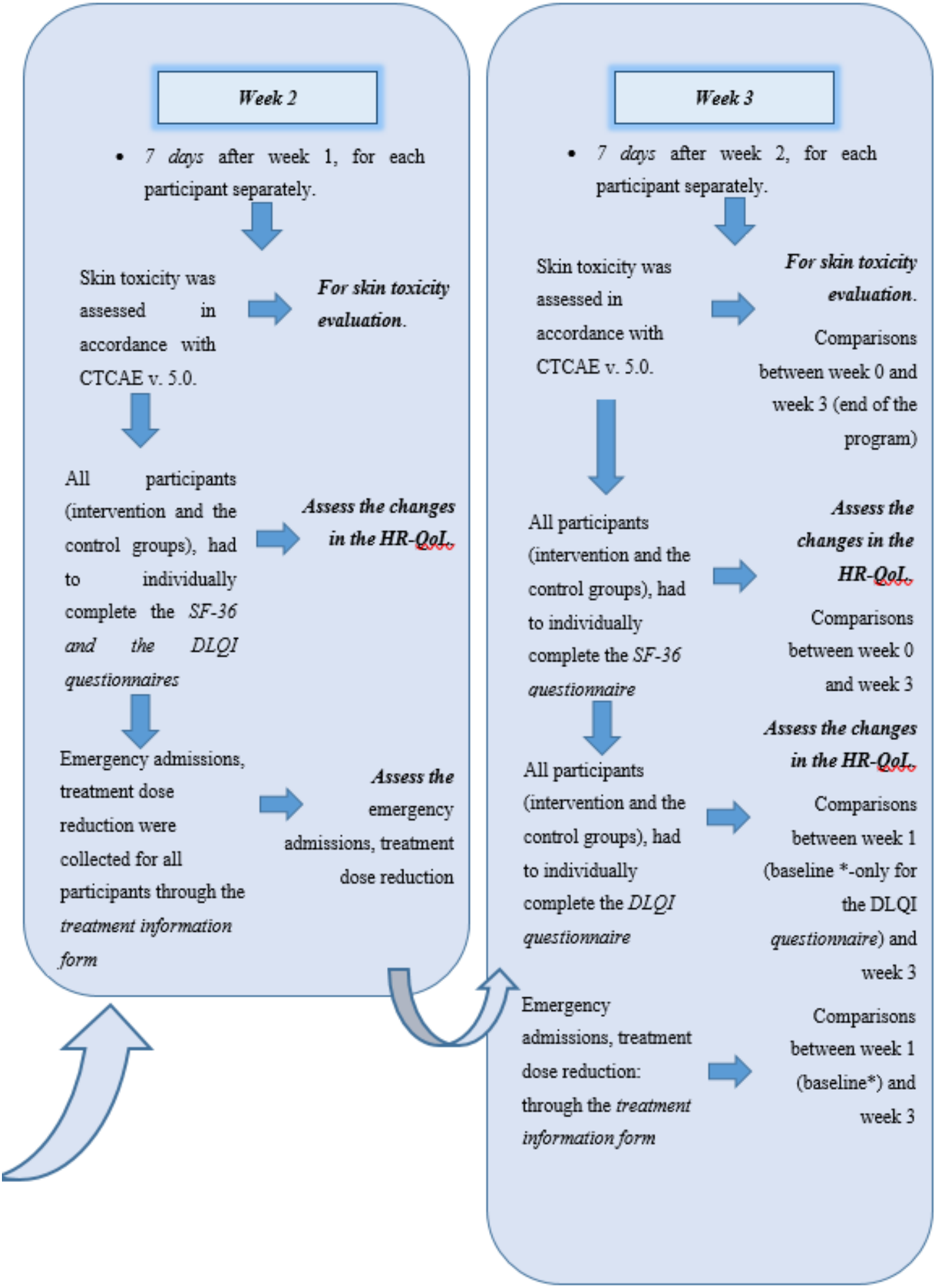
More specifically, the SF-36 questionnaire was filled by the participants at the initial meeting and following was completed weekly during all 4 weeks of the program; from week zero up to the end of week three. In this way, we have collected data for the HR-QoL from all participants' first day on the program (week 0) until their last day on

fourth week (week 3 - the end of follow up). These data allowed us to make comparison of the results between groups (intervention and control), as well as within participants of the same group, from day one of the program until its last day, in order to discover if our suggested intervention is effective.

The DLQI questionnaire was first distributed to patients (intervention and control group) at week 1, one week after the first meeting and their induction to the program, as its questions referred to the week that past. More precisely, the questionnaire given in week 1, was seeking the results produced at baseline week (week 0). Hence the results produced from the DLQI questionnaire represent the results from baseline (week 0) up until the third week of follow-up, opposingly to the results of the SF-36 questionnaire which cover a period from week 0 until the fourth week of follow-up (week 3).

Finally, information regarding the participating patients' emergency admissions, treatment dose reduction or treatment discontinuation, the secondary endpoints of the study, were collected weekly from week 1 and onward, by the research team of this study, through the treatment information form and each patient's chemotherapy protocol. The documentation of the measurement selection is presented in the scheme below.


Week 0 – Baseline
Induction day to the study for each participant.
The day of symptoms onset and signing of the consent form.
Skin toxicity was assessed in accordance with CTCAE v. 5.0.
For skin toxicity evaluation (Baseline measurement)
Intervention group: were assigned to attend the educational program individually.
Control group: the usual information was provided to them, as with any cancer patient who initiates chemotherapy, immunotherapy or EGFRI treatment ('treatment booklet') individually
All participants had to individually complete the SF-36 questionnaire.
So as for us to assess the HR-QoL (Baseline measurement)
*The appointments for weeks 0-week 3 take place during their presence at the clinic, either during their treatment or the course of a scheduled appointment
Week 1
7 days after the induction day (week 0), for each participant separately.
Skin toxicity was assessed in accordance with CTCAE v. 5.0.
For skin toxicity evaluation.
All participants (intervention and the control groups), had to individually complete the SF-36 questionnaire
Assess the changes in the HR-QoL
All participants (intervention and the control groups), had to individually complete the DLDI questionnaire
So as for us to assess the HR-QoL (Baseline measurement*: its questions referred to the week that past.)
Emergency admissions, treatment dose reduction were collected for all participants through the treatment information form
Assess the emergency admissions, treatment dose reduction (Baseline*)


Week 2
• 7 days after week 1, for each participant separately.
Skin toxicity was assessed in accordance with CTCAE v. 5.0.
For skin toxicity evaluation.
All participants (intervention and the control groups), had to individually complete the SF-36 and the DLQI questionnaires
Assess the changes in the HR-QoL.
Emergency admissions, treatment dose reduction were collected for all participants through the treatment information form
Assess the emergency admissions, treatment dose reduction
Week 3
• 7 days after week 2, for each participant separately.
Skin toxicity was assessed in accordance with CTCAE v. 5.0.
For skin toxicity evaluation.
Comparisons between week 0 and week 3 (end of the program)
All participants (intervention and the control groups), had to individually complete the SF-36 questionnaire
Assess the changes in the HR-QoL.
Comparisons between week 0 and week 3
All participants (intervention and the control groups), had to individually complete the DLQI questionnaire
Assess the changes in the HR-QoL.
Comparisons between week 1 (baseline *-only for the DLQI questionnaire) and week 3
Emergency admissions, treatment dose reduction: through the treatment information form
Comparisons between week 1 (baseline*) and week 3

**The baseline for the DLQI questionnaire is week 1 rather than week 0, as its questions refer to the previous week.*

** The baseline for the data on emergency admissions and treatment dose reduction concerns week 1 instead of week 0, as patients are collected on the day of symptom onset, making it impossible to need hospitalization or dose reduction.*

10.6.2 Educational program

The presented educational program was created by the research team who conducted this study and addressed to cancer patients who presented cancer treatment-induced pruritus, rash, or photosensitive dermatitis. The program was developed based on guidelines provided by the American Academy of Dermatology (American Academy of Dermatology, 2018) and the American Cancer Society (American Cancer Society, 2020) in conjunction with information from bibliographical references and the researchers' knowledge and experience (on a small scale).

During the development of the intervention (educational program) this researchers' team took into consideration the cognitive behavioral theories (see chapter 7.3) and designed the intervention in order to assist patients to understand the nature of their symptoms and improve their belief in their ability to control symptoms, additionally to teaching them problem-solving skills (Sherwood et al., 2005). Our method was based on the perception that cognitive-behavioral interventions may resolve patients' dysfunctional thought patterns (cognitive) or actions (behavioral) that damage the skin or interfere with dermatologic therapy (Sherwood et al., 2005).

Through the website of the American Cancer Society (ACS), we have retrieved valuable measures regarding the management of adverse skin reactions related to cancer treatment (pruritus, rash and photosensitivity) (American Cancer Society, 2020). More specifically, under the subsection 'Dealing with Side Effects' of the section 'Treatments and Side Effects', we found useful information and measures at the category 'Hair, skin and nails' (subcategories 'Itching' and 'Skin rash) that we included into our intervention (American Cancer Society, 2020).

From the subcategory 'Itching', which refers to pruritus, the data we adopted can be found below. In regard to the use of skin creams, these should be alcohol and fragrance free and applied two to three times daily, especially following bath, when the skin is still damp (American Cancer Society, 2020). The guidelines for bathing instruct patients to bathe gently in lukewarm warm with unscented soap and a soft washcloth, while following bath, drying off should be performed via gentle patting and all scented or alcohol-based products on the skin, such as powders, after-shaves, or perfumes, should be avoided (American Cancer Society, 2020). As to avoid cuts and irritations, shaving

should be performed by an electric razor rather than a blade. In case of an itch episode, keep nails clean and short, wear clean fabric gloves if possible and try rubbing, putting pressure or cool cloths, or vibration on the skin instead of scratching and breaking the skin (American Cancer Society, 2020). Distracting yourself via music, reading and conversation could also prove helpful (American Cancer Society, 2020). Other general suggestions to assist with itching mention wearing loose, soft-fabric clothes, stay out of the sun as much as possible and hydrating (American Cancer Society, 2020). If itching becomes severe, then the patient should contact his clinician and receive prescription drugs to help relieve the symptom (American Cancer Society, 2020).

If pruritus evolves, the American Cancer Society, (2020) suggests patients to 'Call their cancer care team'. Specifically if the itching does not go away after two days, if they notice yellowish skin or tea-color urine, if the scratched skin has open wounds, is bleeding or has blisters , if the skin appears to be bright red or develops crusts, if scars have foul-smelling drainage or pus coming out or if the patient itself becomes very anxious and restless (can't sleep through the night due to itching), develops hives, shortness of breath, swelling of the throat or face, or other signs of a severe allergic reaction (American Cancer Society, 2020). All these measures were also adopted and adjusted to our educational program.

The American Cancer Society, (2020) provides the same suggestions as above, and for cancer patients dealing with treatment-induced skin rash, hence we have also included them when forming our intervention.

The website of the American Cancer Society, (2020) does not have a dedicated section for the management of skin photosensitivity, but the 'Be safe in the sun' category includes a subcategory titled 'Take Steps to Protect Yourself', from where we retrieved measures such as the following: Avoid sun exposure between 10 am and 4 pm, as UV rays are stronger and more harmful mid-day, especially during spring and summer months. Even on a cloudy day, UV rays can get through to the ground, hence seek shade, protect your skin with clothing, use sunscreen, wear a hat, wear sunglasses that block UV rays and avoid tanning beds and sun lamps (American Cancer Society, 2020).

Through our search to the database of the American Academy of Dermatology, (2022) we discovered guidelines regarding sun protection. The category 'Shade, clothing and sunscreen' along with the subcategory 'Practice Safe Sun' (path: "Everyday care"/ "Sun

protection”/ “Shade, clothing, and sunscreen”/ “Practice Safe Sun”) provide recommendations on how to protect the skin from the sun’s harmful UV rays (American Academy of Dermatology, 2022). Some regard the types of clothing and accessories required to protect the skin and eyes from the sun (lightweight and long-sleeved shirts and pants, sunglasses with UV protection, wide-brimmed hats), seeking shade when appropriate and especially between 10 a.m. and 2 pm when the sun’s rays are stronger and applying sunscreen (American Academy of Dermatology, 2022). In respect to the use of sunscreen, the American Academy of Dermatology, recommends the use of sunscreens that offer broad-spectrum protection (protects against UVA and UVB rays), have SPF 30 or higher and are water and sweat resistant (American Academy of Dermatology, 2022). The use of sunscreen is also recommended throughout the year while re-applying is mandatory every two hours or immediately after swimming or sweating (American Academy of Dermatology, 2022).

Beyond the American Cancer Society and the American Academic of Dermatology, information was also acquired through scientific publications. The search database used was PubMed and the search, performed in May of 2018, included the key criteria: “treatment”, “prevention”, “measures” “pruritus”, “rash” and “photosensitivity”. The search focused on articles published in the last decade so as for the data and guidelines included in this study to be the most recent.

The study of Jatoi et al., (2010), a placebo-controlled trial performed to evaluate whether sunscreen prevents rash in patients treated with EGFR inhibitors, provided us with useful details regarding the effectiveness of sunscreens, while the study of Kiyohara et al., (2013), a review presenting a practical approach for treating erlotinib-related cutaneous side effects in Japanese patients with advanced non-small cell lung cancer, provided us with important insights on the efficacy of daily practices (i.e., bathing). Finally, the study by Potthoff et al., (2011) was an expertise guide for us since it provided recommendations, based on peer-reviewed publications, regarding the treatment of skin reactions in patients under EGFRI therapy, from an expert’s panel in medical oncology, dermatology and clinical pharmacology.

The data we get form the studies and from the American Cancer Society, (2020), the American academic of dermatology, (2022) and a small portion from the researcher knowledge we categorized the data and we create the educational program with the

purpose to make an easy to read, understandable, small and practical educational program.

Specifically, the educational program consisted of five categories: "clean – hydrate', "protection from the sun", "protection from other external stimulations', "observe – inform' and "cosmetic products". The educational program included measures and actions that patients should take to manage the skin reaction but did not include any oral or topical medications.

Below we demonstrate in detail the data from our research. and the categories that we create and the process for how the educational program was created is presented in a schematic form in the Figures 22 and 23.

The category "clean–hydrate" included eight measures the patients should apply. Participants were required to take a daily bath or shower with non-irritating soaps and shampoos (weakly acidic to alkaline), avoid hot water during bath or shower (approx. 37 °C in summer and 39 °C in winter), wash the skin gently with the palm of the hand, and thoroughly rinse the soap/shampoo (Kiyohara et al., 2013). Measures like wiping the skin lightly with a clean towel without rubbing and avoiding sulfur-containing bath salts (cause of skin dryness) were also included in our list (Kiyohara et al., 2013). The last two measures for the category concerned moisturizing the skin after the bath with an alcohol-free cream and applying hypoallergenic and fragrance-free moisturizers (Jatoi et al., 2010).

The second category of the educational program was dedicated to 'sun protection'. The participants were required to use high protection sunscreen (Jatoi et al., 2010) and applying it on a daily basis to all the exposed skin, even on cloudy days (American academic of dermatology, 2022). Additionally, if they were experiencing chemo-induced hair loss, sunscreen was required to be applied to the scalp as well (researcher experience). For this measure, patients were asked to use a new/fresh bottle of sunscreen as a previously opened/used bottle may no longer be effective (researcher experience). The use of objects that blocked ultraviolet radiation such as umbrellas, hats, sunglasses, scarves, gloves, and clothes with minimal exposed areas was also recommended (Potthoff et al., 2011; American academic of dermatology, 2022; American Cancer Society, (2020). For when outside of a building, further recommendations were given to the participants: finding a place in the shade under a

tree or sitting under an umbrella, carrying a sun umbrella or even walking along paths sheltered by trees (Potthoff et al., 2011; American academic of dermatology, 2022; American Cancer Society, (2020). As wigs can be hot in the sun, a cotton scarf was recommended instead as it could be comfortable while providing protection at the same time (Potthoff et al., 2011; American academic of dermatology, 2022; American Cancer Society, (2020). Finally, another important measure the patients were required to follow as of this category, was to avoid sun exposure from 10 am to 4 pm (Potthoff et al., 2011; American academic of dermatology, 2022; American Cancer Society, (2020).

The "protection from other external stimulations" category included eight requirements, some of which were the protection of the skin during manual shaving (Potthoff et al., 2011) and during the use of an electronic razor; the avoidance of scratching by covering the itchy area, i.e., with a cold, wet cloth; and nail trimming (Potthoff et al., 2011). Wearing gloves when sleeping to avoid scratching unintentionally and avoiding wool clothing in order to help the skin "breathe" and feel less itchy were also included in the instructions given for this category (Potthoff et al., 2011; American academic of dermatology, 2022; American Cancer Society, (2020). The protection of any skin wounds as per the doctor's instructions, as well as the use of sterile, non-stick gauze and the use of paper tape, were also part of the guidelines given (Potthoff et al., 2011; American academic of dermatology, 2022; American Cancer Society, (2020).

The category regarding 'cosmetic products' included measures concerning their usage. At the same time, only "non-chemical" cosmetics could be used in order to cover the face while the use of colored moisturizers or even colored sunscreens was encouraged in order to achieve skin coverage and at the same time hydrate and protect it from the sun (researcher experience).

For the last category of the educational program, the 'note – update' category, participants were required to monitor their skin on a daily basis and inform their doctor immediately if any itching, photosensitivity, rash or new sores appeared on their skin (American academic of dermatology, 2022; American Cancer Society, 2020).

The final format of the educational program assembled by the researchers of the present study, regarding the management of skin pruritus, rash and photosensitivity dermatitis induced by immunotherapy, EGFRI treatment and chemotherapy, is presented at Figure 24.

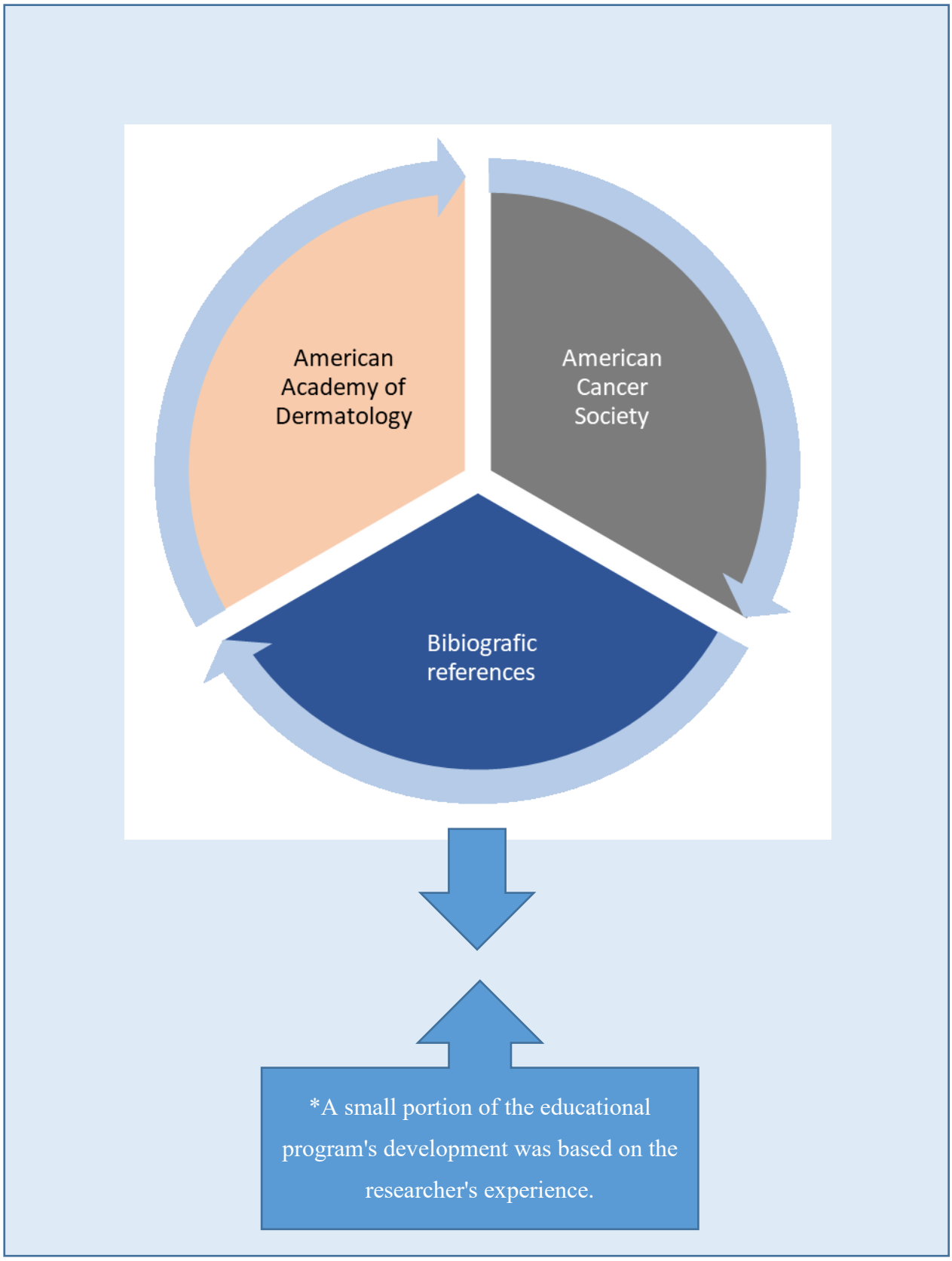


Figure 22 The process for how the educational program was created

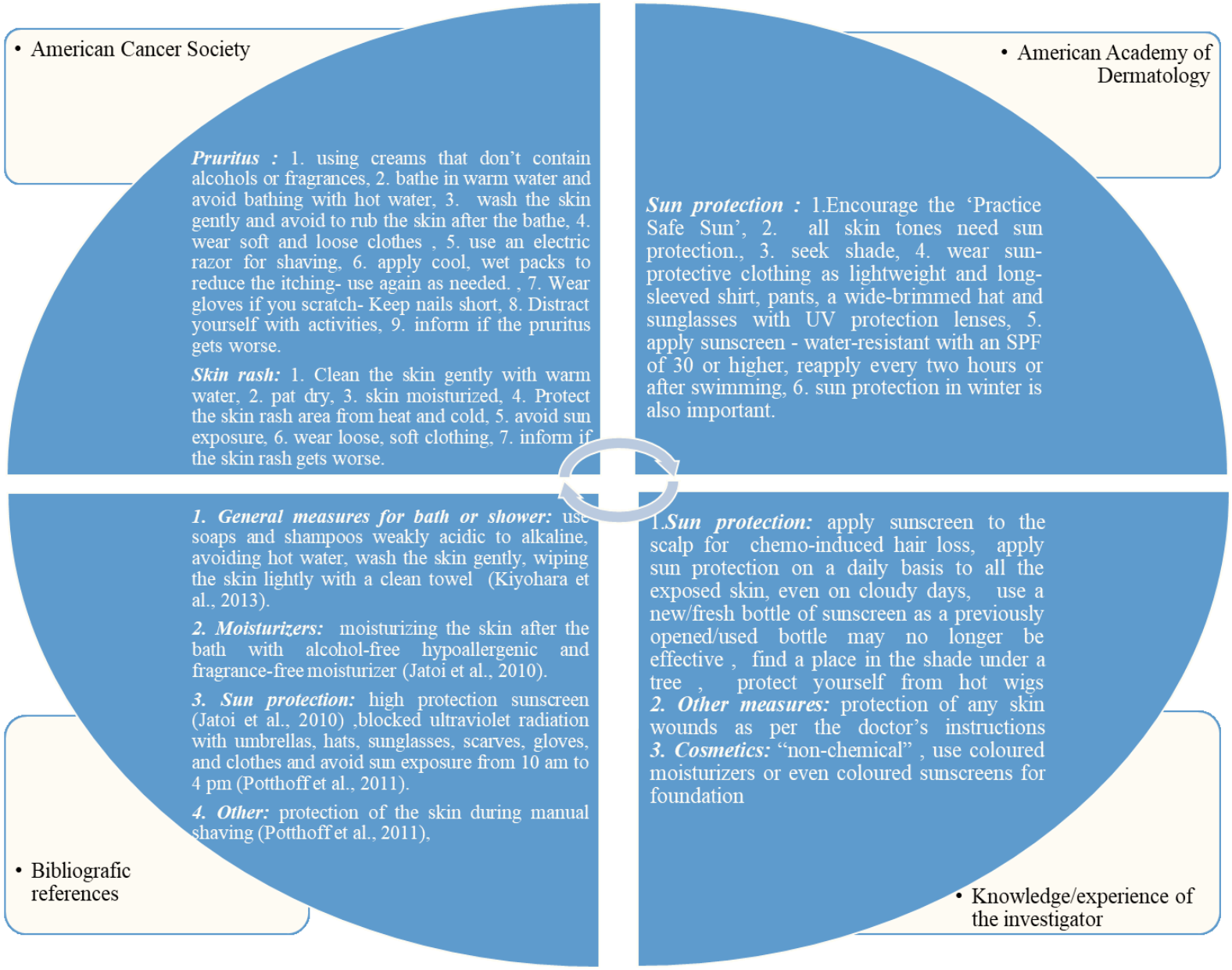
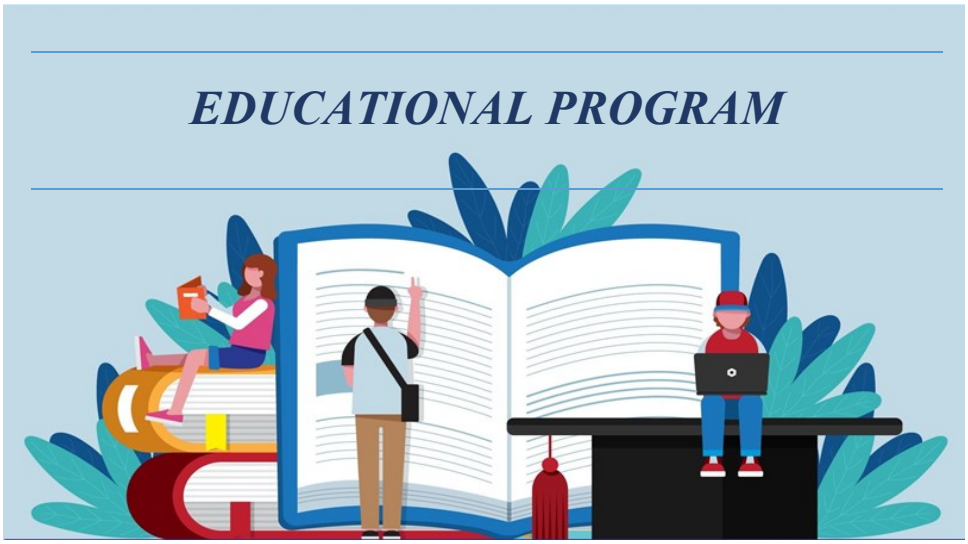


Figure 23 The process for how the educational program was created

Figure 24 Education program for skin pruritus, skin rash and photosensitivity dermatitis due to immunotherapies, EGFRI treatment and chemotherapies



The present educational program concerns the skin side effects that you have due to the treatment you are undergoing. You will see five categories, which are: 1. the category "clean – hydrate", 2. the category "protection from the sun", 3. the category "protection from other external stimulations", 4. the category "cosmetic products" and 5. the category "observe – inform".

For any questions or clarifications, do not hesitate to ask.

1. CLEANLINESS – HYDRATION

- Daily bath or shower with non-irritating soaps and shampoos (weakly acidic to alkaline).
- Avoid hot water for bath or shower (about 37 ° C in Summer and 39 ° C in Winter).
- Gently wash your skin using the palm of your hand.
- Good rinsing of the soap / shampoo

- Wipe lightly with a clean towel without rubbing.
- Sulfur-containing bath salts are not recommended because they cause dry skin.
- Moisturizing after the bath with a cream that does not contain alcohol.
- Apply hypoallergenic and fragrance-free moisturizer

2. SUN PROTECTION

- High protection sunscreen.
- Apply sunscreen daily to all exposed skin even on cloudy days.
- If chemo causes hair loss, be sure to apply sunscreen to your scalp, too.
- Make sure you have a fresh bottle of sunscreen. Last year's bottle may no longer be effective.
- Use of objects that block ultraviolet radiation such as umbrellas, hat, sunglasses, scarves, gloves, clothes with few exposed areas.
- Find a place in the shade under a tree or sit under an umbrella. You can also carry a sun umbrella.
- Walk along paths sheltered by trees.
- Wigs can be hot in the sun, but a cotton scarf can be comfortable while providing protection.
- Avoid sun exposure from 10 am to 4 pm

3. PROTECTION FROM OTHER EXTERNAL STIMULATIONS

- Carefully during shaving. An electronic razor is best used.
- Avoid scratching.
- Cover the itchy area if you can't keep from scratching it.
- In case of itching, use a wet cold cloth or ice and not scratch the area.
- Trim your nails to avoid scratching.

- Wear gloves when you sleep to avoid scratching.
- Avoid wool clothing
- Protect any wounds on your skin as doctor instructed.

4. COSMETICS PRODUCTS

- To cover the face, use moisturizers with color or even sunscreens with color. This way you will achieve coverage on your skin but at the same time you will keep your skin hydrated or protected from the sun.
- Prefer "non-chemical" cosmetics.

5. NOTE - UPDATE:

- Monitor your skin on a daily basis.
- Your doctor should be informed in time for any itching, photosensitivity, rashes.
- Tell to your doctor about any new sores on your skin.

10.7 Randomization

An important aspect of the clinical trial study is the randomization of the enrollment participants. The randomization is vital in these kind of studies in order to ensure the equality of the groups in the clinical trial.

Patients who consented to take part in the study and follow the baseline measurements, were randomly allocated to either the intervention or the control group, on a 1:1 ratio, with the use of a computer-based minimization algorithm able to stratify patients based on type of skin toxicity and type of treatment.

10.8 Blinding

Blinding is an important part of a clinical trial in order to minimize bias and maximize the validity of the results (Karanicolas, Farrokhyar and Bhandari, 2010). According to the study of Karanicolas, Farrokhyar and Bhandari, (2010) in any trial, blinding or "masking" can be the participants that are being treated; and/or the clinicians administering the appropriate therapy; and/or data collectors; and/or outcome adjudicators; and/or data analysts of the study. According to the above data, a clinical trial can be an open-label trial, a single-blind trial, a double-blind trial, a triple-blind trial, or a quadruple-blind trial. (Fellow, 2017).

The clinical trial study presented in this doctoral dissertation is a single-blind trial because the participants were unaware (blind) of which intervention they were receiving, but the researcher knew which group each patient was assigned to. The researcher, data collectors, outcome adjudicators, and data analysts of the study were not practical to be blind.

10.9 Statistical analysis

The validity of the models used in this study depends on four assumptions:

a. Homogeneity of residuals: The residuals are unaffected by the predicted value. We verified this by plotting residuals of the mixed effects models against the predicted values.

b. Normality of residuals: Errors in the predictions must be approximately normally distributed. We verified this with the use of histograms and Q-Q plots.

c. The normality of random effects: The random effects of each subject, are approximately normally distributed. We verified this with the use of histograms and Q-Q plots.

d. Independence between subjects: The scores of a subject are not related to the scores of other subjects. In other words, the clinical outcomes of a subject are not dependent on the clinical outcomes of any other subject. There is no statistical test for this holds true due to the nature of the research and the subjects involved.

Descriptive statistics are presented as frequencies (N) and proportions for the categorical variables (e.g. gender, grade, etc.) and with Mean + Standard deviation for the continuous variables. The homogeneity of the two groups at baseline was assessed with the X^2 test for the categorical variables and with the independent samples t-test for the continuous variables.

Cohen's d is utilized to assess the effect size differences between control and intervention at each time point (Baseline, week 1 to week 3) for the continuous scales (i.e, SF36 dimensions and DLQI), and the Relative Risk (RR) for the Dose Reduction and the Emergency Admission event.

The effect of the intervention on the Skin Reaction Grade (primary endpoint) was assessed using Generalised estimating equations (GEE) (Twisk, 2003) with an ordinal logistic response link due to the ordered levels of the grade status (1,2,3,4). The effect of the intervention on the Dose Reduction event and the Emergency Admission event, was assessed using the GEE with the binary logistic link due to the binary distribution of the event. The effect of the intervention on the secondary endpoints of DLQI score and the dimensions of the SF36 quality of life scale was assessed using Linear Mixed Models (LMM) with the patient as a random effect (random intercept model) using an unstructured covariance type. The models were adjusted for the gender, age, diagnosis and treatment type of the patient.

The data analyses were undertaken in SPSS v.28. A p value of <0.05 taken as the level of statistical significance.

10.10 Ethical considerations

The protocol was approved by the Cyprus National Bioethics Committee with the number: ΕΕΒΚ ΕΠ 2019.01.03 according to National Law. Specifically, after the application of the appropriate form the answer from the Cyprus National Bioethics Committee was: 'I refer to your application dated January 9, 2019 and I would like to inform you that the National Bioethics Committee of Cyprus gives its opinion in favor of conducting this research' (see Appendix 1 for the entire form from the Cyprus National Bioethics Committee).

Also, this trial was registered in the clinical trials.gov with identifier number NCT03992664.

Additionally, the study was conducted according to the provisions of the Declaration of Helsinki, which concerns the ethical principles of medical research involving human subjects and all patients gave their informed consent after a detailed description of the study before enrollment (see appendix 2). In particular, all study participants were informed of the purpose of the research, the study interventions, the voluntary and anonymous participation and that each candidate has the right to refuse to participate or discontinue participation, without this decision to affecting their personal treatment. Finally, it was also emphasized that their participation in the program does not entail any financial burden and contact details of the competent persons for any complaints or grievances were provided to the participants both in writing and verbally form (see appendix 2).

Finally, additional information is required for the study, such as the patient's age, educational level, job, date of diagnosis, and therapy protocol. For this reason, following each patient's registration in the research, an information sheet was filled out. (see appendix 3).

10.11 Results

Initially, demographic data and population characteristics are described. Various comparisons are made between and within the two groups (intervention and control

group) in order to assess the effectiveness of the intervention for the patients who suffer with skin toxicities (pruritus, rash and photosensitivity dermatitis).

10.11.1 Patient characteristics

Forty patients successfully completed the study. Twenty patients were assigned in the control group and twenty in the intervention group (Figure 25: CONSORT diagram).

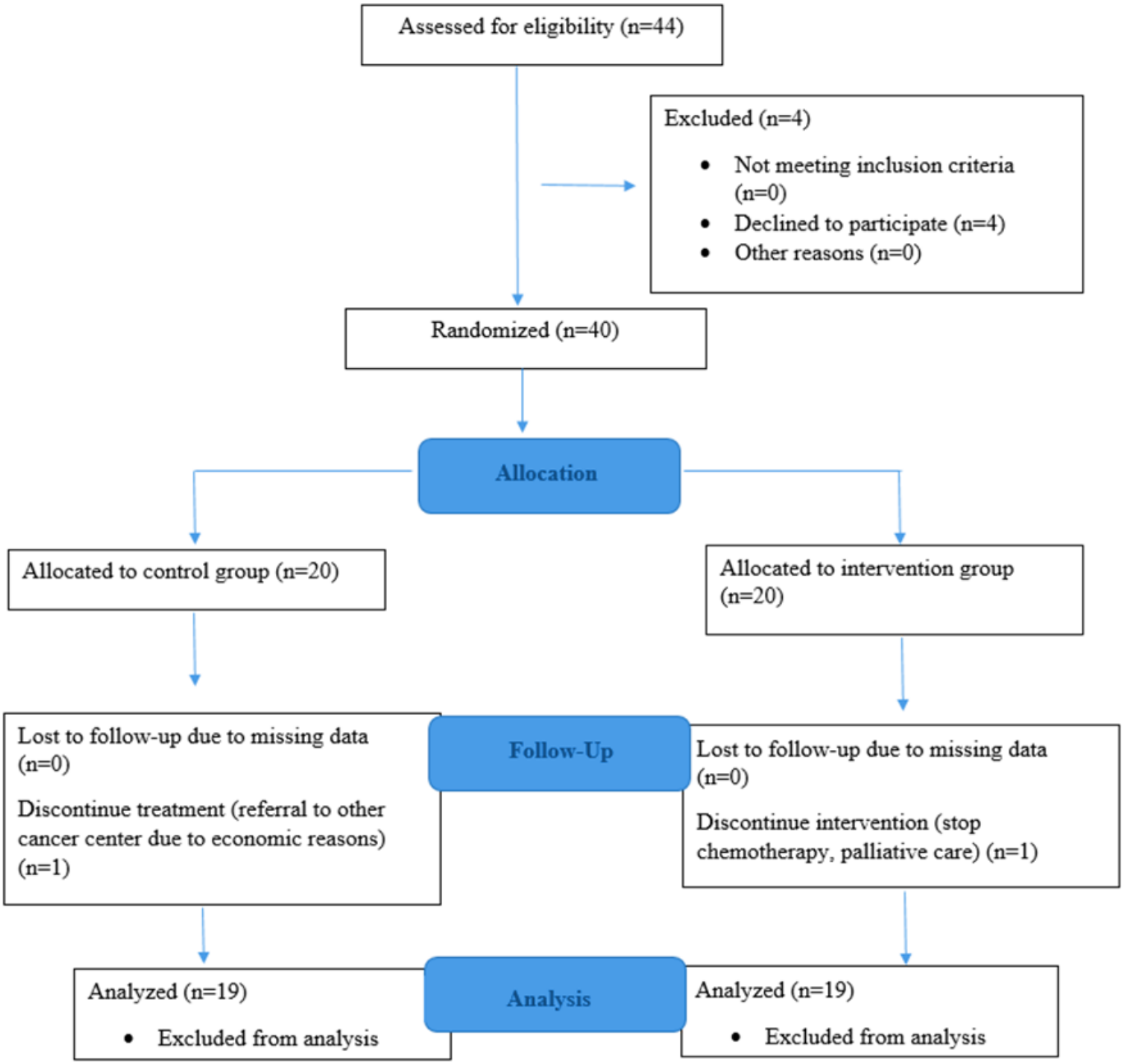


Figure 25 CONSORT diagram

Table 11 demonstrates demographic characteristics for the control group and the intervention group. There were no statistically significant differences in relation to the demographic characteristics between the two groups (Table 11).

Table 11 Patient demographics and clinical characteristics

		Control		**Intervention**		**Total**		
		N	%	N	%	N	%	p value
Gender	Male	11	55.0	10	50.00	21	52.5	0.752
	Female	9	45.0	10	50.00	19	47.5	
Age	(Mean, Standard Deviation)	57.6	13.7	62.8	12.6	60.2	1320.0	0.223
Job	Full Time	6	30.0	3	15.0	9	22.5	0.146
	Retired	5	25.0	11	55.0	16	40.0	
	Sick Leave	9	45.0	6	30.0	15	37.5	
Education	Secondary School	7	35.0	6	30.0	13	32.5	0.964
	High School	4	20.0	4	20.0	8	20.0	
	College	2	10.0	3	15.0	5	12.5	
	University	7	35.0	7	35.0	14	35.0	
Diagnosis	Breast Cancer	2	10.0	2	10.0	4	10.0	0.934
	Colon Cancer	4	20.0	5	25.0	9	22.5	
	Lung Cancer	3	15.0	3	15.0	6	15.0	
	Pancreatic Cancer	5	25.0	4	20.0	9	22.5	
	Head / Neck Cancer	0	0.0	1	5.0	1	2.5	
	Other	6	30.0	5	25.0	11	27.5	
Treatment	Chemotherapy	12	60.0	14	70.0	26	65.0	0.341
	EGFRI	6	30.0	6	30.0	12	30.0	
	Immunotherapy	2	10.0	0	0.0	2	5.0	
Treatment Type	EGFRI	6	30.0	6	30.0	12	30.0	0.664

	Gemcar - Abraxane	2	10.0	1	5.0	3	7.5	
	Doxorubicin	2	10.0	1	5.0	3	7.5	
	Avastin - Taxol - Carboplatin	3	15.0	4	20.0	7	17.5	
	Fluorouracil	2	10.0	5	25.0	7	17.5	
	Immunotherapy	2	10.0	0	0.0	2	5.0	
	Other	3	15.0	3	15.0	6	15.0	
Skin Reaction	Rash	6	30.0	6	30.0	12	30.0	
	Photosensitivity	8	40.0	7	35.0	15	37.5	0.931
	Pruritus	6	30.0	7	35.0	13	32.5	
Grade	Grade 1	9	45.0	11	55.0	20	50.0	0.527
	Grade 2	11	55.0	9	45.0	20	50.0	

According to the Table 11, in this clinical trial they participating 11 males and nine females in the control group and ten males and ten females in the intervention group. The category gender is not statistically significant in this study (p= 0.752). The mean value for the category age is 57.6 for the control group and 62.8 for the intervention group which is not statistically significant difference for the category age between the two groups (p= 0.223). For the category job and education, the results are not statistically significance with a p value equals to 0.146 and 0.964 respectively. Additionally, in this study, for the control group, two patients have breast cancer, four patients have colon cancer, three patients have lung cancer, five patients have pancreatic cancer and six patients classify to the category other type of cancer. In the intervention group, two patients have breast cancer, five patients have colon cancer, three patients have lung cancer, four patients have pancreatic cancer, one patient has head / neck cancer and five patients classify to the category other type of cancer. The result for the category diagnosis is not statistically significant between the control and intervention group (p=0.934). For the category treatment type, in the control group six patients receive EGFRI treatment, two patients receive Gemcar-Abraxane treatment, two patients receive Doxorubicin treatment, Fluorouracil treatment and immunotherapy

treatment respectively while three patients receive Avastin - Taxol – Carboplatin treatment and three patients classify to the category other type of treatment. In the intervention group, six patients receive EGFRI treatment, one patient receive Gemcar-Abraxane treatment and Doxorubicin treatment respectively, four patients receive Avastin - Taxol – Carboplatin treatment, five patients receive Fluorouracil treatment and three patients classify to the category other type of treatment. For the category treatment type, the results are not statistically significance between the control and intervention group (p=0.664). Finally, the results between the two groups for the category skin reaction and skin grades are not statistically significant respectively (p= 0.931, p =0.527 respectively).

10.12 Effect of the intervention

10.12.1 Primary endpoint

10.12.2 The effect of the educational program on skin reactions grades

The Generalised Estimating Equations (GEE) showed a significant interaction between Group and Week over the weekly measurements of skin reactions (rash, pruritus and photosensitivity) Grade (Walds X2 = 19,25, p = 0.004) (Table 12).

Table 12 General Estimating Equations (GEE) for the effect of the Intervention on Skin Reactions Grade

Effect	**Wald Chi-Square**	**df**	**Sig.**
Group	19.253	1	<.001
Week	1.282	3	0.733
Group * Week	13.141	3	**0.004**

10.12.3 Pruritus grades

At baseline, 50% of the patients in the control group experienced Grade 1 and Grade 2 pruritus, whereas in the intervention group 42.9% showed Grade 1 pruritus and 57.1 % Grade 2. At week 1, 33.3% of the patients in the control group experienced Grade 1 pruritus, 50% Grade 2, 16.7% Grade 3 and none of the patients demonstrated Grade 4. On the other hand, 71.4 % of the patients in the intervention group presented Grade 1 pruritus and 28.6% Grade 2. At week 2, 16.7% of the patients in the control group had Grade 1 pruritus and Grade 3, whereas 66.7% experienced Grade 2. At the same week, all of patients of the intervention group experienced Grade 1. Finally, in week 3, regarding the control group, 50% of the patients experienced pruritus Grade 2 and Grade 3, respectively. In the intervention group 85.7% of the patients presented Grade 1 pruritus and 14.3% Grade 2 (Table 13).

According to the findings (Table 13), patients in the intervention group outperformed those in the control group in weeks 1, 2, and 3. Week 1 was the best week for pruritus severity within the control group, while week 2 was the best week within the intervention group.

Table 13 Distribution of Pruritus Grade over the weekly measurements

Skin Reaction-Pruritus	**Control Group**							
		Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%
	Baseline	3	50.0%	3	50.0%	0	0.0%	0	0.0%
	Week 1	2	33.3%	3	50.0%	1	16.7%	0	0.0%
	Week 2	1	16.7%	4	66.7%	1	16.7%	0	0.0%
	Week 3	0	0.0%	3	50.0%	3	50.0%	0	0.0%

	Intervention Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%
	Baseline	3	42.9%	4	57.1%	0	0.0%	0	0.0%
	Week 1	5	71.4%	2	28.6%	0	0.0%	0	0.0%
	Week 2	7	100.0%	0	0.0%	0	0.0%	0	0.0%
	Week 3	6	85.7%	1	14.3%	0	0.0%	0	0.0%

10.12.4 Rash grades

At baseline (week 0), 50% of the patients in the control group experienced Grade 1 and Grade 2 rash, whereas in the intervention group 83.3% presented Grade 1 rash and 16.7% Grade 2. At week 1, 16.7% of the patients in the control group experienced Grade 1 and Grade 3, while 33.3% presented Grade 2 and Grade 4. On the other hand, in the intervention group 50% of the patients had Grade 1 and Grade 2, respectively, and none of the patients experienced Grade 3 or Grade 4 rash.

At week 2, in the control group, 16.7% of the patients experienced Grade 1 and Grade 3 rash whereas 66.7% displayed Grade 2 rash. On the other hand, the percentage of the rash grades for the patients in the intervention group remained the same as in week 1. Finally, week 3 measurements demonstrate that 33.3 % of the patients in the control group experienced Grade 1 rash, 50% Grade 2 and 16.7% Grade 4, while in the intervention group patients experienced only Grade 1 and Grade 2 rash at 40% and 60% respectively (Table 14). Figure26 and figure 27 demonstrate the rash distribution within the control and intervention group respectively over the weekly measurements.

According to the results (table 14), the severity of the rash in weeks 1,2, and 3 was better in the intervention group compared to the control group. Within the control

group, the results in week 2 were better compared to the other weeks, and within the intervention group, weeks 1 and 2 were equally better compared to week 3.

Table 14 Distribution of Rash Grade over the weekly measurements

Skin Reaction – Rash	**Control Group**							
		Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%
	Baseline	3	50.0%	3	50.0%	0	0.0%	0	0.0%
	Week 1	1	16.7%	2	33.3%	1	16.7%	2	33.3%
	Week 2	1	16.7%	4	66.7%	1	16.7%	0	0.0%
	Week 3	2	33.3%	3	50.0%	0	0.0%	1	16.7%
	Intervention Group								
		Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%
	Baseline	5	83.3%	1	16.7%	0	0.0%	0	0.0%
	Week 1	3	50.0%	3	50.0%	0	0.0%	0	0.0%
	Week 2	3	50.0%	3	50.0%	0	0.0%	0	0.0%
	Week 3	2	40.0%	3	60.0%	0	0.0%	0	0.0%

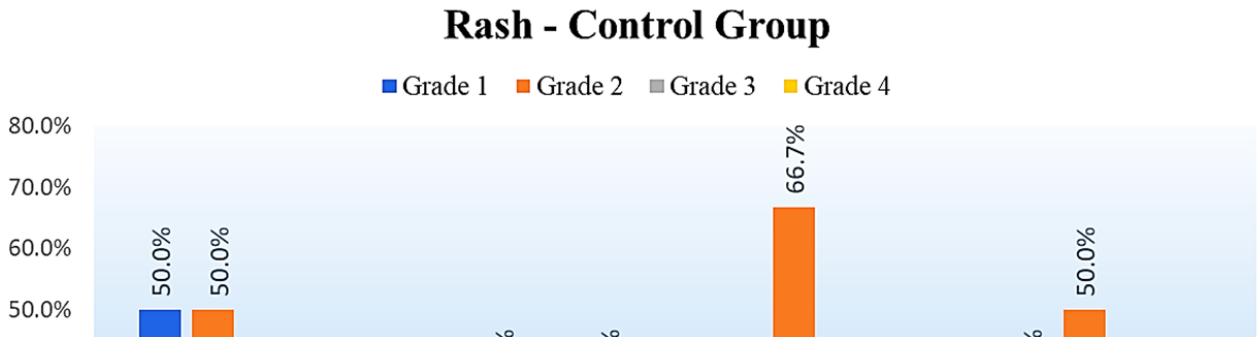


Figure 26 Distribution of rash grade in control group over the weekly measurements

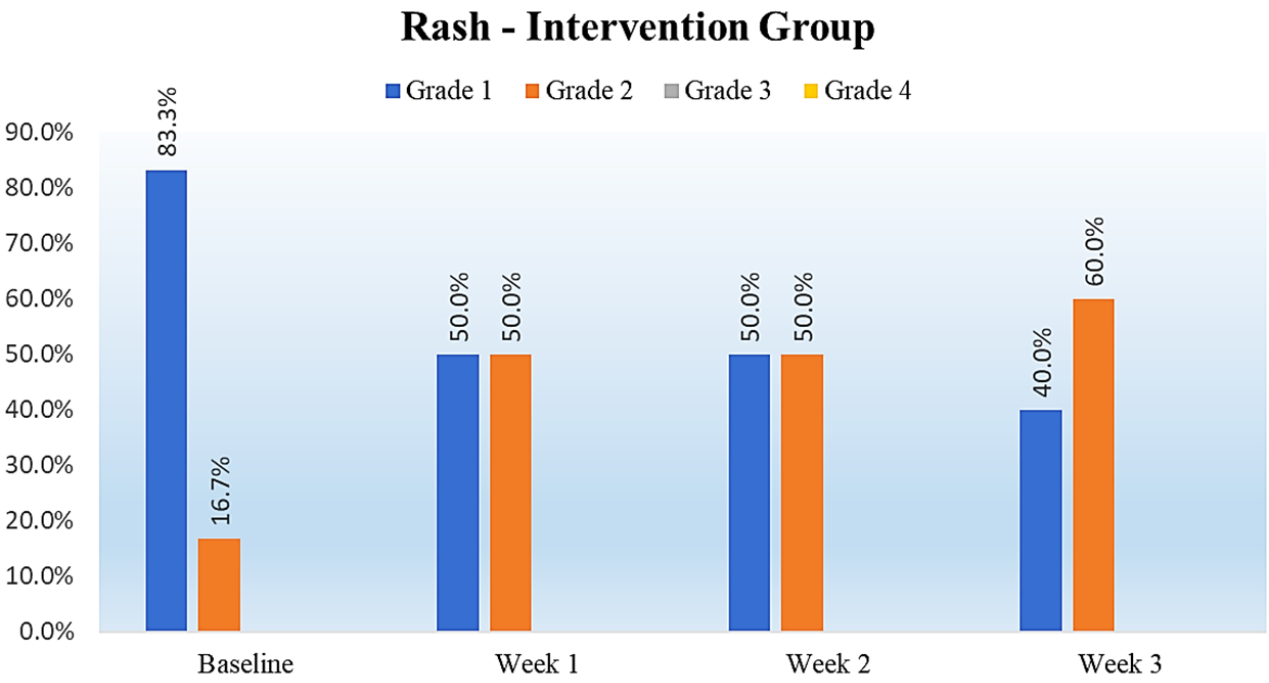


Figure 27 Distribution of rash grade in intervention group over the weekly measurements

10.12.5 Photosensitivity grades

At baseline, 37.5 % of the patients in the control group experienced Grade 1 photosensitivity and Grade 2 percentage was at 62.5%, whereas in the intervention

group 42.9% of the participants showed Grade 1 photosensitivity and 57.1 % showed Grade 2. Measurements from week 1 indicated that 28.6 % of the patients in the control group experienced Grade 1 photosensitivity while 57.1 % had Grade 2 and 14.3 % Grade 3. On the other hand, 71.4 % of the patients in the intervention group had Grade 1 photosensitivity and only 14.3% of the patients experienced Grade 2 and Grade 3, respectively. In week 2, 14.3 % of the patients in the control group experienced Grade 1 photosensitivity, 57.1% had Grade 2 and 28.6% presented Grade 3. During the same week, in the intervention group, 85.7% of the patients experienced Grade 1 and 14.3% Grade 2 photosensitivity. Finally, in week 3, none of the patients in the control group experienced Grade 1 and Grade 4, whereas 85.7% presented Grade 2 and 14.3% Grade 3. Finally, all of the patients in the intervention group expressed photosensitivity Grade 1 in this week (Table 15).

According to the results (Table 15) week 1, week 2 and week 3 was better in the intervention group compared to the control group. Week 3 within the intervention group was better about the severity of the photosensitivity, while week 1 within the control group was better regarding the severity of this adverse skin event.

Table 15 Distribution of Photosensitivity Grade over the weekly measurements

Skin Reaction-Photosensitivity	**Control Group**							
		Grade 1		**Grade 2**		**Grade 3**		**Grade 4**
	Time period	N	%	N	%	N	%	N	%
	Baseline	3	37.5%	5	62.5%	0	0.0%	0	0.0%
	Week 1	2	28.6%	4	57.1%	1	14.3%	0	0.0%
	Week 2	1	14.3%	4	57.1%	2	28.6%	0	0.0%
	Week 3	0	0.0%	6	85.7%	1	14.3%	0	0.0%

	Intervention Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time period	N	%	N	%	N	%	N	%
Baseline	3	42.9%	4	57.1%	0	0.0%	0	0.0%
Week 1	5	71.4%	1	14.3%	1	14.3%	0	0.0%
Week 2	6	85.7%	1	14.3%	0	0.0%	0	0.0%
Week 3	7	100.0%	0	0.0%	0	0.0%	0	0.0%

10.12.6 Compare the grades of skin reactions (pruritus, rash and photosensitivity) separately between control and intervention groups for week 0 (baseline) and week 3 (week 0 and week 3)

Table 16 Distributions of skin reactions grades between control and intervention group for baseline (week 0) and week 3

		Control Group								**Intervention Group**							
Pruritus		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Baseline	3	50%	3	50%	0	0%	0	0%	3	42.9%	4	57.1%	0	0%	0	0%
	Week 3	0	0%	3	50%	3	50%	0	0%	6	85.7%	1	14.3%	0	0%	0	0%
		Control Group								**Intervention Group**							
Rash		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	

	Time Period	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Baseline	3	50%	3	50%	0	0%	0	0%	5	83.3%	1	16.7%	0	0%	0	0%
	Week 3	2	33.3%	3	50%	0	0%	1	16.7%	2	40%	3	60%	0	0%	0	0%
		Control Group								**Intervention Group**							
Photosensitivity		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
	Baseline	3	37.5%	5	62.5%	0	0%	0	0%	3	42.9%	4	57.1%	0	0%	0	0%
	Week 3	0	0%	6	85.7%	1	14.3%	0	0%	7	100%	0	0%	0	0%	0	0%

According to the table above, pruritus skin reaction at baseline is approximately the same between control and intervention group (Control group: 50% had grade 1 and grade 2 respectively, Intervention group: 42.9% of the patients had Grade 1 and 57.1% had Grade 2). At the end of the follow up (week 3) patients in the intervention group had better results regarding the severity of the skin pruritus. Specifically, in the intervention group 85.7% of the patients had grade 1 and 14.3% of the patients had grade 2 whereas none of the patients expressed skin pruritus grade 3 and grade 4. On the other hand, in the control group 50 % of the patients had skin pruritus grade 2 and grade 3 respectively.

For the skin rash, patients in control group at baseline ad 50% grade 1 and grade 2 respectively whereas 83.3% of the patients in the intervention group had grade 1 and 16.7% of the patients had skin rash grade 2. At the end of the follow up (week 3) 33.3%, 50% and 16.7% of the patients in the control group had skin rash grade 1, grade 2 and grade 4 respectively, whereas in the intervention group at the end of the follow up 40% and 60 % of the patients had grade 1 and grade 2 skin rash and none of the patients expressed grade 3 or grade 4 skin rash.

Additionally, the distribution about skin photosensitivity at baseline in both groups (control and intervention) at week 0 was approximately the same. Specifically, in the control group 37,5% of the patients had grade and 62.5% had grade 2. In the intervention group 42.9% of the patients had grade 1 and 57.1% had grade 2 skin photosensitivity. At the end of the follow up, in the control group 85.7% of the patients had grade 2 and 14.3% of the patients had grade 3 whereas in the intervention group all of the patients (100%) had grade 1 skin photosensitivity.

10.12.7 To compare the grades of skin reactions (pruritus, rash and photosensitivity separately) within the control group for week 0 and week 3

Table 17 Distribution of all skin reactions grades within the control group for week 0 (baseline) and week 3

	Control Group							
Pruritus		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Baseline	3	50%	3	50%	0	0%	0	0%
	Week 3	0	0%	3	50%	3	50%	0	0%
Rash		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Baseline	3	50%	3	50%	0	0%	0	0%
	Week 3	2	33.3%	3	50%	0	0%	1	16.7%
Photosensitivity		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%

	Baseline	3	37.5%	5	62.5%	0	0%	0	0%
	Week 3	0	0%	6	85.7%	1	14.3%	0	0%

According to the table above patients in the control group had better distribution regarding the three skin reaction at week 0 (baseline) compared to the end of the follow up (week 3). Specifically, the patients on the control group about skin pruritus, at baseline 50% of the patients had grade 1 and grade 2 respectively whereas at week 3 50% of the patients had grade 2 and grade 3 skin pruritus respectively. About the skin rash at baseline 50% of the patients in the control group had grade 1 and grade 2 respectively whereas at the end of the follow up (week 3) 33.3% of the patients had grade 1 skin rash, 50% of the patients had grade 2 and 16.7% of the patients had grade 4 skin rash. Finally, for skin photosensitivity, at baseline, 37,5% had grade 1 and 62.5% had grade 2 whereas at the end of the follow up 85.7% of the patients had grade 2 and 14.3% had grade 3.

10.12.8 To compare the grades of skin reactions (pruritus, rash and photosensitivity separately) within the intervention group for week 0 (baseline) and week 3 (end of follow up)

Table 18 Distribution of the grades of all skin reactions within the intervention group for week 0 (baseline) and week 3

	Intervention Group							
Pruritus		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Baseline	3	42.9%	4	57.1%	0	0%	0	0%
	Week 3	6	85.7%	1	14.3%	0	0%	0	0%
Rash		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
	Baseline	5	83.3%	1	16.7%	0	0%	0	0%
	Week 3	2	40%	3	60%	0	0%	0	0%
Photosensitivity		**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**	
	Time Period	N	%	N	%	N	%	N	%

	Baseline	3	42.9%	4	57.1%	0	0%	0	0%
	Week 3	7	100%	0	0%	0	0%	0	0%

According to the table above, the results regarding the skin pruritus and the skin photosensitivity were better at the end of the follow up (week 3) compared to the week 0 (baseline) whereas for the skin rash the results were better at baseline (week 0) compared to the end of the follow up (week 3). Specifically, for the skin pruritus at baseline, 42.9% and 57.1% of the patients had grade 1 and grade 2 whereas at week 3 85.7% and 14.3% of the patients has grade 1 and grade 2 respectively. For the skin rash, at baseline, 83.3% and 16.7% had grade 1 and grade 2 respectively whereas 40% of the patients had grade 1 and 60% of the patients had grade 2. Finally, regarding the skin photosensitivity, at baseline 42.9% had grade 1 and 57.1% had grade 2 whereas at week 3 all of the patients had grade 1.

10.12.9 Secondary endpoints

10.12.10 SF-36 Questionnaire

At baseline (week 0) the mean score for the 'physical functioning' dimension of the SF-36 questionnaire for the control and the intervention group was 46.5 ± 30.09 and 48±28.58 respectively. For the control group, the score dropped from 42.63 ± 30.06 to 27.89 ± 27.85 from week 1 towards week 3. Additionally, a drop is observed for all the examined parameters of the SF-36 questionnaire (physical health, emotional problem, energy/fatigue, emotional well-being, social activities, pain, general health).

On the other hand, the score for the intervention group remained approximately the same regarding the dimension of physical functioning during the baseline (48± 28.58), week 1 (49.25± 30.79) and week 2 (43.25± 30.32), while in week 3 the score dropped (39.47 ± 29.34). Additionally, the score for the 'physical health' and 'emotional problems' dimensions increased from baseline to week 1, whereas a drop is observed from week 2 to week 3. For the category 'energy/fatigue', a drop is observed for the baseline (54.25 ± 12.17) to week 3 (46.32±15.26). Similarly, a drop is observed for the 'emotional well-being', 'social functioning', 'pain' and 'general health' parameters (Table 19).

The Linear Mixed Models (LMM), adjusted for age, gender, diagnosis and type of treatment, did not show a significant interaction between Group and Time over the weekly measurements for the 'physical functioning' dimension ($F = 0.362$, $p=0.78$). Additionally, the Linear Mixed Models (LMM) did not show a significant interaction between Group and Time over the weekly measurements for the 'physical health' dimension either ($F = 0.054$, $p=0.983$). The same test was repeated for all of the other six dimensions and the results did not show a significant interaction between Group and Time over the weekly measurements for either of them; the emotional problems, energy/fatigue, emotional well-being, social activities, pain and general health dimension.

Table 19 Mean level (±SD) of the SF 36 Weekly measurements

Control Group								
Time Period	**Physical functioning**	**Physical health**	**Emotional problem**	**Energy/ Fatigue**	**Emotional well-being**	**Social functioning**	**Pain**	**General health**
Baseline	46.5 ± 30.09	45±32.04	60 ±31.72	50.5±14.32	52.8±13.21	47.5±21.69	39.88±24.73	41±23.32
Week 1	42.63 ±30.06	43.42±27.44	50.88±28.04	46.05±15.95	49.05±10.9	41.45±15.05	37.63±19.23	36.32±21.78
Week 2	31.84±26.89	40.79±29.12	50.88±30.16	44.21±13.87	47.79±12.89	37.5±19.54	34.21±18.28	33.42±17.95
Week 3	27.89±27.85	36.84±25.51	45.61±27.69	42.37±14.85	44.63±15.56	34.21±18.09	28.16±21.31	31.58±18.71
Intervention Group								

Time Period	Physical functioning	Physical health	Emotional problem	Energy /Fatigue	Emotional well-being	Social functioning	Pain	General health
Baseline	48±28.58	57.5±28.21	68.33±27.52	54.25±12.17	58±15.38	53.75±20.32	51.63±21.93	57.25±26.28
Week 1	49.25±30.79	60±28.56	71.67±27.09	51.5±15.23	55.8±16.29	50±18.14	49.5±21.65	49.75±27.7
Week 2	43.25±30.32	53.75±28.42	65±31.48	47.5±16.42	50.2±18.42	43.13±21.26	42.38±19.64	46.75±26.82
Week 3	39.47±29.34	52.63±34.25	59.65±36.14	46.32±15.26	49.47±17.65	39.47±19.21	41.58±21.8	44.21±25.18

According to the table above, the intervention group had better results in terms of the SF-36 questionnaire for week 1, week 2 and week 3 compared to the control group.

Furthermore, within each group a statistical analysis was performed separately for each dimension of the questionnaire. In this section of doctoral dissertation presented the statistical analysis for the dimension of pain and general health within the control group.

For the dimension of pain for the control group, the results were not statistically significant (p= 0.18) (Table 20).

Table 20 Wald Chi-Square Analysis for the dimension of pain of the SF-36 questionnaire within the Control group

	Wald Chi-Square	**df**	**Sig.**
Intercept	99.245	1	0
Time Period	4.894	3	0.18
Dependent Variable: Pain Model: (Intercept), Time Period Group: Control			

For the same dimension (pain) for the control group for week 1 and week 2 the results were statistically significant (week 1: Wald X2=4.01, p value=0.045, week 2: Wald X2=4.286, p value=0.038) (Table 21).

Table 21 Wald Chi-Square Analysis for the week 1 and week 2 for the dimension of pain from the SF-36 questionnaire within the Control group over the weekly measurements

Parameter	**Std. Error**	**95% Wald Confidence Interval**		**Hypothesis Test**		
		Lower	**Upper**	**Wald Chi-Square**	**df**	**Sig.**
Intercept	4.7559	18.921	37.564	35.265	1	0

Baseline	7.1004	-2.284	25.549	2.684	1	0.101
Week 1	4.7799	0.204	18.941	4.01	1	**0.045**
Week 2	2.943	0.324	11.861	4.286	1	**0.038**
Dependent Variable: Pain Model: (Intercept), Time Period Group: Control						

For the dimension of general health for the control group, the results were not statistically significant (p value=0.085) (Table 22).

Table 22 Wald Chi-Square Analysis for the dimension of general health of the SF-36 questionnaire within the Control group

	Wald Chi-Square	**df**	**Sig.**
Intercept	81.242	1	0
Time Period	6.617	3	0.085
Dependent Variable: General Health Model: (Intercept), Time Period Group: Control			

The same statistical analysis was performed within the intervention group. For the dimension of pain within the intervention group, the results were statistically significant (p= 0.015) (Table 23).

Table 23 Wald Chi-Square Analysis for the dimension of pain of the SF-36 questionnaire within the Intervention group

	Wald Chi-Square	**df**	**Sig.**
Intercept	122.215	1	0

Time Period	10.404	3	**0.015**
Dependent Variable: Pain Model: (Intercept), Time Period Group: Intervention			

For the dimension of general health within the intervention group for week 1 and week 2 the results were statistically significant (week 1: Wald X2=6.57, p value=0.01, week 2: Wald X2=4.256, p value=0.039) (Table 24).

Table 24 Wald Chi-Square Analysis for the dimension of General Health of the SF-36 questionnaire within the Intervention group over the weekly measurements

Parameter	**Std. Error**	**95% Wald Confidence Interval**		**Hypothesis Test**		
		Lower	**Upper**	**Wald Chi-Square**	**df**	**Sig.**
Intercept	5.581	31.663	53.54	58.267	1	0
Baseline	3.6303	7.533	21.764	16.282	1	0
Week 1	2.7888	1.682	12.614	6.57	1	**0.01**
Week 2	2.0108	0.207	8.089	4.256	1	**0.039**
Dependent Variable: General Health Model: (Intercept), Time Period Group: Intervention						

10.12.11 Evaluate the Health - Related Quality of Life using the SF-36 questionnaire for patients with skin pruritus, rash and photosensitivity between control and intervention group for week 0 (baseline) and week 3

Table 25 Mean level (±SD) of the SF 36 questionnaire between control and intervention group for week 0 (baseline) and week 3

SF-36 questionnaire (Dimensions)	**Control Group**		**Intervention Group**	
	Week 0 (Baseline)	**Week 3**	**Week 0 (Baseline)**	**Week 3**
Physical functioning	46.5 ± 30.09	27.89±27.85	48±28.58	39.47±29.34
Physical health	45±32.04	36.84±25.51	57.5±28.21	52.63±34.25
Emotional problem	60 ±31.72	45.61±27.69	68.33±27.52	59.65±36.14
Energy /Fatigue	50.5±14.32	42.37±14.85	54.25±12.17	46.32±15.26
Emotional well-being	52.8±13.21	44.63±15.56	58±15.38	49.47±17.65
Social functioning	47.5±21.69	34.21±18.09	53.75±20.32	39.47±19.21

Pain	39.88±24.73	28.16±21.31	51.63±21.93	41.58±21.8
General health	41±23.32	31.58±18.71	57.25±26.28	44.21±25.18

According to the data presented in Table 25, patients in both groups (control and intervention), presented better results in all dimensions of the SF-36 questionnaire at baseline week 0 compared to week 3 which represents the end of the follow up period. The lower the score of the dimension, the grater the disability/discomfort for the patient.

Specifically, in the control group about the physical functioning dimension the mean level at baseline was 46.5 ± 30.09 and at week 3 was 27.89±27.85 while in the intervention group at the same dimension the score at baseline was 48±28.58 and at week 3 the score was 39.47±29.34. The mean level of the physical health in the control group at baseline was 45±32.04 and the score at week 3 was 36.84±25.51 whereas in the intervention group the score at baseline was 57.5±28.21 and at week 3 the score was 52.63±34.25. Regarding the dimension of the emotional problem the mean levels in the control group at baseline was 60 ±31.72 and at week 3 the mean level was 45.61±27.69 while in the intervention group for the same dimension the mean level at baseline was 68.33±27.52 and at week 3 the mean level was 59.65±36.14. About the dimension energy/fatigue the mean level in the control group at baseline was 50.5±14.32 and at week 3 the mean level was 42.37±14.85 while in the intervention group the mean score at baseline was 54.25±12.17 and at week 3 the mean level was 46.32±15.26. About the dimension emotional well-being in the control group at baseline was 52.8±13.21 and at week 3 was 44.63±15.56 while in the intervention group the score at baseline was 58±15.38 and at week 3 the score was 49.47±17.65. For the social functioning dimension in the control group at baseline the score was 47.5±21.69 and at week 3 the score was 34.21±18.09 while in the intervention group the score at baseline was 53.75±20.32 and t week 3 the score was 39.47±19.21. For the dimension of pain in the control group the score at baseline was 39.88±24.73 and at week 3 the score was 28.16±21.31 while in the intervention group the score at baseline was 51.63±21.93 and at week 3 the score was 41.58±21.8. Finally, for the dimension of the general health, the score in the control group at baseline was 41±23.32 and at week 3 the score was 31.58±18.71 while in the intervention group at baseline the score was 57.25±26.28 and at week 3 the score was 44.21±25.18.

Even though baseline data were better compared to week 3 data for both groups, the scores of the intervention group were noticeably better compared to the control group, in all dimensions of the SF-36 questionnaire in week 3.

10.12.12 DLQI Questionnaire

The control group demonstrated an increase in the mean score from week 1 (7.9±6.2) to week 3 (9.7 ±5.3) regarding the DLQI measurements. On the other hand, the intervention group illustrated a decrease in the mean score from week 1 (8.7±7.4) to week 3 (7.5±4.7). At week 1, both groups presented a low effect size difference (d= -0.12) in the mean level of the DLQI questionnaire, whereas at week 3 the effect size difference was high (d= 0.44) (Table 26).

Table 26 Mean Level (±SD) of DLQI Questionnaire and Cohen's d test over the weekly measurements

Time Period	Control Group	Intervention Group	Cohen's d
Week 1	7.9±6.2	8.7±7.4	-0.12
Week 2	9.6±6.2	7.9±4.7	0.31
Week 3	9.7±5.3	7.5±4.7	0.44

According to the above table, the control group had a better quality of life compared to the intervention group in week 1, while in weeks 2 and 3, the intervention group had better results regarding the QLQI questionnaire.

The Linear Mixed Models (LMM) did not show a significant interaction between Group and Time over the weekly measurements for the DLQI score (F = 0.948, p=0.391).

Statistical analyzes were also performed within each group separately. Specifically, in the control group the results of the questionnaire were not statistically significant between control group and time over the weekly measurements for the DLQI score (p=0.331) (Table 27). Additionally, in the intervention group the results of the questionnaire were not statistically significant between intervention group and time over the weekly measurements (p= 0.72) (Table 28).

Table 27 Wald Chi-Square Analysis for the DLQI questionnaire within the Control group

	Wald Chi-Square	df	Sig.
Intercept	65.831	1	0
Time Period	2.211	2	0.331
Dependent Variable: DLQI Score Model: (Intercept), Time Period Group: Control			

Table 28 Wald Chi-Square Analysis for the DLQI questionnaire within the Intervention group

	Wald Chi-Square	df	Sig.
Intercept	66.788	1	0
Time Period	0.656	2	0.72
Dependent Variable: DLQI Score Model: (Intercept), Time Period Group: Intervention			

10.12.13 Evaluate the Health - Related Quality of Life using the DLQI questionnaire for patients with skin pruritus, rash and photosensitivity between control and intervention group for week 1 and week 3

As demonstrated in Table 29, the produced results regard the data from the previous weeks. For example, the results presented in week 1 concern the measurements during the baseline week (the week before) and the results presented in week 3 correspond to the data produced during week 2. Hence, it is for the only measure that we do not have results up until the end of the follow up on week 3, i.e the four week of follow ups.

At week 1 the control group had better results regarding the DLQI questionnaire compare to the results for the patients in the intervention group (higher score, more quality of life is impaired). The results for the intervention group was 8.7±7.4 and the

results in the control group was 7.9±6.2. On the contrary, week 3 results of the participants under intervention, were noticeably better compared to the results from patients in the control group. Specifically, the results for the intervention group at week 3 was 7.5±4.7 while the results in the control group was 9.7±5.3.

Table 29 Mean Level (±SD) of DLQI Questionnaire and Cohen's d test for week 1 and week 3

Time Period	Control Group	Intervention Group	Cohen's d
Week 1	7.9±6.2	8.7±7.4	-0.12
Week 3	9.7±5.3	7.5±4.7	0.44

10.12.14 Emergency admissions between control and intervention group for weeks 1 until week 3 (week 1 – week 3)

During week 1, 15.8% of the patients in the control group required emergency admission whereas for the intervention group the percentage was lower, at 10%. During week 2, 26.3% of the patients in the control group were admitted in the emergency ward while 15% of the experimental group participants required that. Finally, in week 3, 21.1% and 31.6% of the patients were urgently admitted in the control and the intervention group, respectively. The patients in the intervention group had 66% lower risk for an emergency admission in week 1, compared to those in the control group. Week 2 data indicated that the patients following the educational measures had 57% lower risk for an emergency admission compared to those who did not. On the other hand, during week 3, the patients participating to the educational program presented 50% increase in the risk of requiring an emergency admission compared to the patients in the control group (Table 30). According to the Generalised Estimating Equations (GEE) no significant interaction was shown between Group and Week over the weekly measurements regarding emergency admissions event (Walds $X2 = 2.234$, $p = 0.327$).

Table 30 Relative Risk and percentage (%) of the emergency admissions over the weekly measurements

Time Period	Control Group	Intervention Group	Relative Risk
Week 1	15.80%	10%	RR = 0.66 [0.12 - 3.57], **p = 0.63**
Week 2	26.30%	15%	RR = 0.57 [0.16 - 2.06], **p = 0.39**
Week 3	21.10%	31.60%	RR = 1.50 [0.50 - 4.48], **p = 0.47**

According to the table above, the control group had a higher percentage of emergency admissions in weeks 1 and 2 compared to the intervention group, while in week 3, the intervention group had a higher percentage of emergency admissions compared to the control group.

Figure 28 demonstrate the percentage (%) of the emergency admissions over the weekly measurements for control and intervention group.

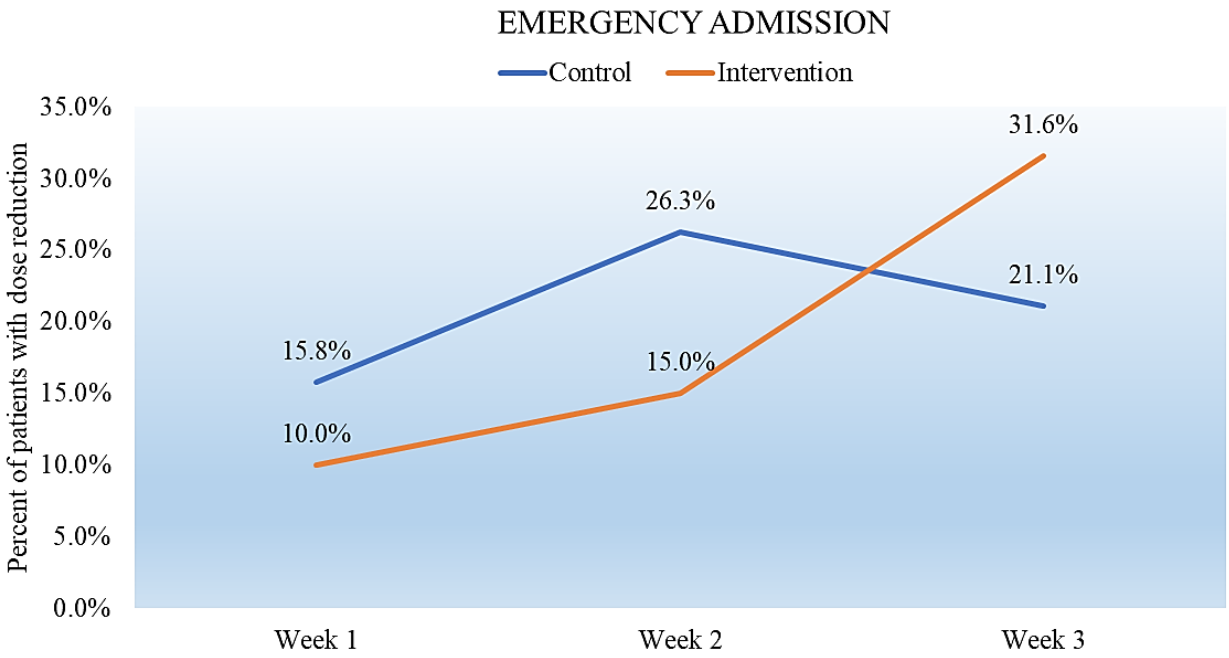


Figure 28 Percentage (%) of the emergency admissions over the weekly measurements

10.12.15 Dose reduction between control and intervention group for weeks 1 until week 3 (week 1 – week 3)

According to our analysis, a larger number of patients from the control group required a treatment dose reduction compared to the patients in the intervention group. Specifically, during week 1, 21.1 % of the patients in the control group and 10% of the patients in the intervention group required dose reduction. In week 2, the percentage in the control and the intervention group was 31.6% and 15%, respectively. Finally, in week 3, 31.6% of the control group participants and 10.5% of the intervention group participants required a treatment dose reduction. More specifically and according to the Relative Risk results, patients in the intervention group presented 50% lower risk to require dose reduction compared to control group participants in week 1. Additionally, in weeks 2 and 3 the patients in the intervention group presented 15% and 10.5% lower risk, respectively, for receiving dose reduction compared to the control group (Table 31 and Figure 29). Finally, as per the Generalised Estimating Equations (GEE) no significant interaction between Group and Week was shown over the weekly measurements of Dose Reduction event (Walds X2 = 0.182, p = 0.913).

Table 31 Relative Risk and percentage (%) of the dose reduction over the weekly measurements

Time Period	**Control Group**	**Intervention Group**	**Relative Risk**
Week 1	21.10%	10%	RR = 0.50 [0.10- 2.43], p = 0.39
Week 2	31.60%	15%	RR = 0.47 [0.13 - 1.63], p = 0.24
Week 3	31.60%	10.50%	RR = 0.33 [0.07 - 1.48], p = 0.14

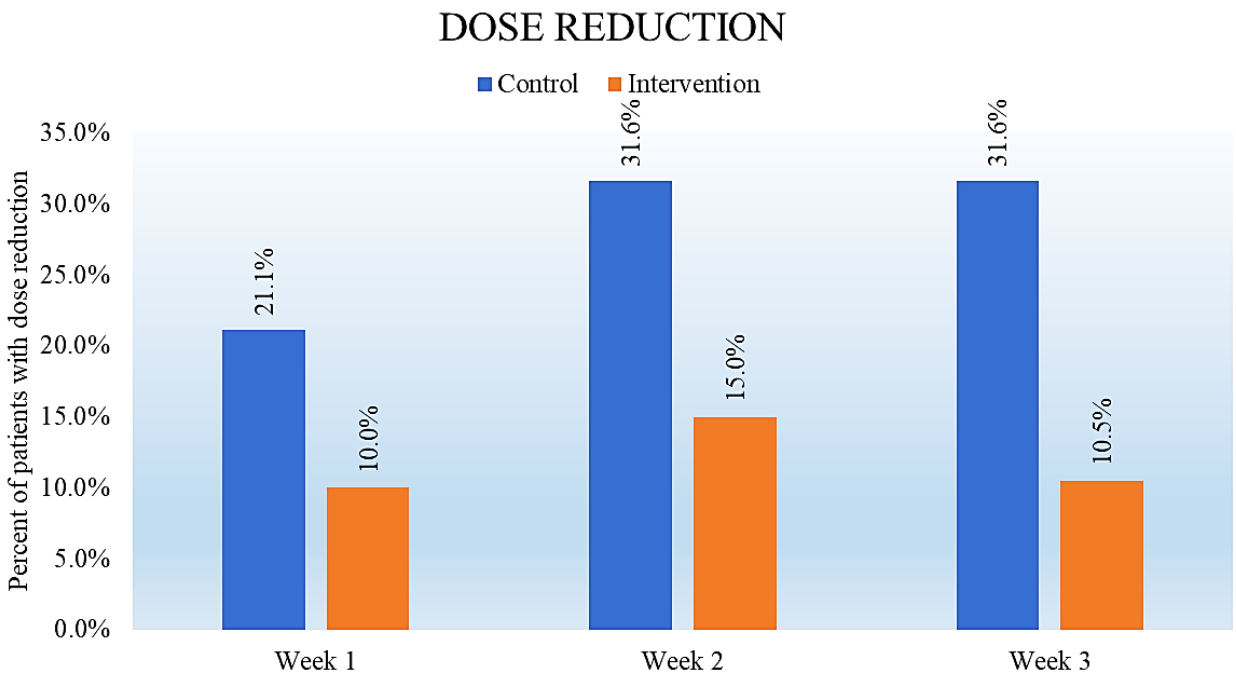


Figure 29 Percentage (%) of the dose reduction over the weekly measurements.

11 DISCUSSION

The present doctoral dissertation is comprised of two parts, the general section and the specific section. The general section regards the analysis of the theoretical background of the study through scientific publications, that being the cancer treatment-induced skin conditions of pruritus, rash and photosensitive dermatitis. Later, we examined the effects of these adverse skin conditions, for example the impact they have on patients' lives, and we analysed in depth the notions of the Quality of Life and the Health-Related Quality of Life.

Concurrently, we conducted a systematic review of studies published in the last decade so that we explore the effective interventions that exist for patients experiencing the aforementioned skin conditions (pruritus, rash, photosensitivity) due to the provision of cancer treatment.

A vast range of interventions has been examined so as to define effective measures in order to manage skin reactions for cancer patients who undergo treatment. The standard management for the EGFRI treatment-induced rash includes the use of antibiotics and cortisone products such as doxycycline and hydrocortisone (Melosky et al., 2009). Drug-induced photosensitivity is usually managed via the use of sun-protecting sunscreens and protective clothing (Moore, 2002). Pruritus management usually includes suggestions directed towards patients in order to reduce itching, like wearing light clothing, using a humidifier, restricting bath and shower time, using lukewarm water, and avoiding cleansers with a high pH or containing alcohol (Ensslin et al.,2013). Mild to moderate pruritus can be treated with topical corticosteroids and anesthetics like lidocaine and prilocaine, while antihistamines are the most common treatment for severe pruritus (Ensslin et al.,2013).

In-depth research regarding the available therapeutic options, for the management of cancer treatment-induced toxicities of the skin (pruritus, rash, photosensitivity), revealed that, apart from few expert opinion publications and clinical recommendations, there are no studies in bibliography that focus on the development and provision of educational programs for cancer patients as means of management (Pinto et al. 2011; Chu et al.,2017). Thus, the focus of this study's research section was to initially develop an educational program covering all the above requirements, and later proceed to a pilot

study in order to determine the effectiveness of the intervention/educational program for cancer patients experiencing pruritus, rash and photosensitivity induced by chemotherapy, EGFRI treatment and immunotherapy.

In order to achieve our goal and design a successful educational program, we initially reviewed the range of available educational methods and their effectiveness on patients, as well as the theoretical background behind learning. Based on this research, we decided that since we wanted to obtain the maximum effect from this intervention, we should base our program on the impactful Cognitive-Behavioral Theory of learning and that the educational material should be provided in the form of a printed booklet which is the most successful method of information distribution for patients (see chapter 7.3).

As soon as the educational material was prepared, we proceeded with the pilot study so as to examine the effectiveness of this educational program on cancer patients who presented pruritus, rash and photosensitivity induced by chemotherapy, EGFRI treatment and immunotherapies.

In order to evaluate the effectiveness of our educational program, we investigated changes in the skin reactions' grades (primary endpoint). The primary endpoint focuses on making comparisons between the control and intervention group along with comparisons within each group, from baseline (week 0) up to week 3 (fourth week of follow up), in order to decide whether the results were improved before or after the application of the educational program.

The results demonstrated an improved grade distribution for the three skin reactions (pruritus, rash, and photosensitivity). The Generalised Estimating Equations (GEE) indicated a statistically significant interaction between the Group and Week over the weekly measurements (week 1, week 2, and week 3) of all skin reactions investigated (rash, pruritus and photosensitivity) due to the educational program.

Patients in the intervention group had better results regarding pruritus, rash, and photosensitivity adverse events than those in the control group in weeks 1, 2, and 3. Within the control group, week 1 was the best week for pruritus severity, while week 2 was the best week within the intervention group. For the rash severity, the results within the control group were better in week 2 compared to the other weeks, and within the intervention group, weeks 1 and 2 were equally better compared to week 3. Finally, in

terms of the severity of the photosensitivity, week 1 was better within the control group while week 3 was better within the intervention group.

In more detail, within the groups, statistical analysis was also carried out. The results for the pruritus illustrate a better proportion in the intervention group compared to the control group. Specifically, patients in the control group showed grade 3 photosensitivity in weeks 1, 2, and 3, while patients in the intervention group did not manifest grade 3 pruritus at all. Furthermore, the results for the skin rash were better in the intervention group compared to the control group. In weeks 1 and 3, patients within the control group developed a grade 4 skin rash, whereas patients in the intervention group did not develop a grade 4 skin rash and had better results regarding the severity of their condition. Moreover, the results regarding the photosensitivity grades illustrate a better outcome in the intervention group compared to the control group. Specifically, all the patients within the intervention group had photosensitivity grade 1 in week 3 compared to the patients in the control group, who expressed photosensitivity grade 2 and grade 3 in the same week.

Within the control group, pruritus, rash and photosensitivity were improved at baseline compared to the end of the follow up, while for the intervention group skin pruritus and photosensitivity were improved at week 3 whereas skin rash was improved at baseline measurements.

The secondary endpoint of this trial concerned the results deriving from the SF-36 and DLQI questionnaires. The generic SF-36 questionnaire was used in both groups' patients in order to evaluate their Health-Related Quality of Life. At baseline the two groups presented the same results in many domains of the SF-36 questionnaire, with exception three dimensions (physical health, pain and general health) at which the intervention group participants performed better. The data from the DLQI questionnaire, the specific questionnaire utilized to meet the secondary endpoint of Health-Related Quality of Life, indicated that the results measured in week 1 (answers regarding the baseline week) show that intervention group participants' health appeared more affected from the skin condition in comparison with the control group. Although, according to measurements taken at the end of the follow up and after four weeks of intervention application, the intervention group ended up having better results regarding the effect of the condition over HR-QoL.

In detail, the intervention group presented an improved health status according to all SF-36 questionnaire dimensions (physical functioning, physical health, emotional problems, energy/fatigue, emotional well-being, social activities, pain, and general health) for week 1, week 2 and week 3 compared to the control group. Finally, the data from the DLQI questionnaire indicated that the control group had a better quality of life compared to the intervention group in weeks 2 and 3.

In particular, in terms of the SF-36 questionnaire, a drop in scores for the physical functioning dimension was observed in the control group. A downward trend in the score follows the physical health dimension, the energy/fatigue dimension, the emotional well-being dimension, the social functioning dimension, the pain dimension, and the general health dimension. The score for the emotional problem dimension is decreasing along with the other dimensions. Nevertheless, the results for weeks 1 and 2 for the emotional problem dimension are roughly equal (50.88 ±28.04 for week 1, 50.88 ±30.16 for week 2).

Additionally, for the DLQI questionnaire, the score within the control group from week 1 to week 3 increased (week 1: 7.9± 6.2, week 3: 9.7±5.3) whereas the score within the intervention group decreased from week 1 to week 3 (week 1: 8.7 ± 7.4, week 3: 7.5±4.7).

However, our results from the SF-36 and the DLQI questionnaires did not present a statistically significant interaction between Group and Time over the weekly measurements.

Emergency admissions for patients in the intervention group were lower for weeks 1 and 2 compared to the control group, whereas the emergency admissions in week 3 were higher in the intervention group. The percentage of emergency admissions increases within the control group, with the biggest percentage showing up in week 2 (26.30%), whereas the percentage increases within the intervention group, with the largest percentage showing up in week 3 (31.6%). Furthermore, patients in the intervention group had a lower possibility of requiring dose reduction in their treatment over weeks 1, 2, and 3. More specifically, patients in the intervention group presented a 50%, 15%, and 10.5% lower risk of requiring dose reduction compared to the control group for weeks 1, 2, and 3, respectively. Nevertheless, our results did not show a

significant interaction between Group and Week over the weekly measurements of emergency admissions and dose reduction events.

During the trial, one patient from the intervention group and one patient from the control group had to terminate their treatment. The termination of treatment in both cases was not associated with the skin reactions but due to metastasis (patient transited to palliative care) and economic reasons, respectively. Unfortunately, the authors had no access to the records of the participant who discontinued due to financial problems, as he/she continued at a public hospital, and thus the investigation could not be carried out until the end.

The importance of our study lays in the fact that we introduce a new and efficient management method for treatment-induced toxicities of the skin. Up to date, most effective management strategies for these conditions were considered the provision of pharmaceutical products such as antibiotics and steroids, the reduction of treatment dose or even the total interruption of cancer treatment (Papoui et al., 2021). The consequences of either of those options had a severe impact on the patients' treatment plan and, consequently, on their survival (Papoui et al., 2021).

Our intervention was designed based on the Cypriot patients' needs, the environment and weather of the island of Cyprus (for example, many sunny days through the year) and the Cypriot population's habits, as noted by the experience of this study's researcher.

Furthermore, as this study's main focus is the care of patients suffering from cancer, we took into consideration the principles that govern the wider context of caring for people with malignancies. According to Padrnos et al., (2016) patients with cancer demonstrate a significant lack of knowledge, from the phase of diagnosis up to post-treatment phase, while an astonishing 94% of them stated they desire as much information as possible, despite of them being positive or negative. The level of knowledge needs can persist over time as cancer status evolves (Padrnos et al., 2016). When their clinician cannot meet their information needs, due to limited time and/or expertise in cancer care, patients usually reach to additional information resources such as the Internet. A study by Rogers et al., (2012) demonstrated that 54 % of the interviewed patients with head and neck cancer, acquired information regarding their treatment and health maintenance from online sources. As of the health care system, this should proceed with identifying

the personal and population-specific information needs and challenges of cancer patients and provide effective ways of information provision and reassurance to patients seeking to gain and to improve their knowledge (Padrnos et al., (2016).

What is more, patient education and patient-centered care are notions that should be mandatory integrated in the cancer care pathway, as they represent an organized high-quality care that takes into consideration the complexity and vulnerability of patients and their need for greater awareness and information (Verot et al., 2020, Mead et al., 2021).

Thus, in order to achieve the maximum benefit from our educational program, we opted for an informative, patient-centered educational approach as cancer patients require a considerable amount of information in order to reach health-related decisions, understand treatment options, emerging side effects and health care system navigation, (Padrnos et al., 2016). This way, we relieved patients from the, often reported, burden of being unable to obtain appropriate health information or fully understand them and provided them with the needed so as to achieve greater patient satisfaction, stress management, improved mood, improved coping ability and improved communication (patient and its family) (Padrnos et al., 2016).

12 RECOMMENDATIONS BASED ON THE RESULTS OF THE STUDY

12.1 On clinical practice

It is a fact that the application of the appropriate cancer treatment protocol is nearly always affected by the adverse skin reactions (pruritus, rash, and photosensitivity) induced by chemotherapy, EGFRI treatment and immunotherapy. Our results show the importance of integrating the educational training program into clinical practice in order to minimize the impact of the toxicities. The advantages of our educational training program, as they emerged from the results, in clinical practice are illustrated below:

a) The intensity of the skin adverse events (pruritus, rash, and photosensitivity) seemed to be less severe for the patients who received the intervention during the educational program, compared to the patients who didn't receive the educational program.

b) The patients in the intervention group scored higher in both assessment questionnaires, the SF-36 questionnaire and the DLQI questionnaire, as they had improved health-related quality of life.

c) Patients who completed the educational program presented fewer limitations in their regular physical and social activities and experienced less physical pain and less emotional distress.

d) Patients who attended the training program had fewer emergency admissions, and the percentage of those requiring cancer treatment dose reduction was lower.

e) The information gained during the educational training program helped patients make informed clinical decisions.

f) The process of disseminating information via an educational training program facilitated a sturdy patient-clinician communication.

Based on the reasons listed above, the educational training program presented in this dissertation is recommended for use in clinical practice. As cancer patients require continuous empowerment and support to endure their situation, this training program it appears to provide many benefits for these individuals by boosting their and covering

many aspects of their needs. Additionally, this educational program gives the opportunity to nurses to provide a holistic nursing care to patients and achieve better patients' outcomes and satisfaction.

12.2 In education

Our findings are in agreement with the Kozuki study published in 2016; patient education provided by medical staffs is as important for the management of skin reactions, as the professional assessment of the treatment-associated skin toxicities, self-skin care (moisturizers, cream/lotion), cleanliness and use of protectants from external stimuli (Kozuki, 2016). Additionally, our data also agree with the study of Nicholson, Edwards and McArdle (2017) noting that interventions aimed at enhancing patient knowledge are related to greater patient satisfaction, while increased knowledge leads to greater patients' ability to take control and manage their side effects themselves.

In general though, it is not possible for our results to be properly compared with another publication since - as per the search we performed in scientific literature - this is the first study that examines this type of educational measures in a clinical trial. Despite that, our intervention is a small, readable and easy-to-use educational program designed based on bibliographic references and guidelines from the American Academy of Dermatology and the American Cancer Society, that achieved to decrease the severity of skin toxicities, improve HR-QoL, decrease dose reduction cases and emergency admissions, and help patients take informed decisions regarding their medical condition.

In terms of education, this study provides the steps on how an educational training program for cancer patients could be designed and developed. The value of the concept of the educational training program, would be reinforced when becomes a realization that a structured evidence-based knowledge could be offered to patients, in the oncology field, through such programs. Our study made this way an important step towards this direction, but continuation of this research is required in order to achieve better results in patient education in the future.

12.3 In research

According to our knowledge, deriving from extensive research in bibliography, this is the first time that a pilot study is contacted in order to examine the effectiveness of an educational program for cancer patients experiencing treatment-related skin pruritus, rash and photosensitivity, and is based on a randomized clinical study. The tested educational training program provided important benefits, yet further research with larger sample size is required so as to validate our findings. Additionally, further research into the pathophysiology of pruritus, skin rash and photosensitive dermatitis, induced by immunotherapies, EGFRI treatments and chemotherapies, is needed to provide recommendations on preventive measures and treatment that are more specific.

Another future study proposal is the assessment of patient satisfaction, following the training program, in terms of the obtained cancer knowledge, therapy insights and side effects management. Furthermore, the proper timing for delivering the educational training program could also prove critical, as some patients might prefer to receive the education program at the onset of the disease, while others on the first day of drug treatment.

As knowledge is important to cancer patients, future studies could focus on offering personalized knowledge (Padrnos et al., 2016). The health care system can identify the required types and modes of patient information, for each of them, by firstly assessing the individual’s knowledge level and following its sources of information and desire for additional information (Padrnos et al., 2016).

As this type of educational programs can give the opportunity to nurses to further involve with patient education and offer a holistic nursing care resulting in improved patient outcomes and satisfaction, the nurse's feedback regarding them could also be a future research field of research.

All in all, this study could be the start of research for evidence-based educational programs in the field of oncology related to cancer patients who suffer from skin toxicities induced by treatment. It could also serve as an encouragement for further research development in Cyprus and lay the foundations for personalized research on the Cypriot population.

13 STUDY STRENGTHS AND LIMITATIONS

As with all trials, our study presents both strengths and limitations.

To start, the sample size of this clinical trial was small. Given the fact though, that this trial is a pilot study, the small sample size is acceptable. However, further studies with a larger sample size would be required to provide support for our findings. As a result of the small sample size, participants included in the trial came solely from two private hospitals in Cyprus, increasing this way the risk of bias in our results. The heterogeneous nature of the study population, in terms of cancer type, was another limitation this study had.

Another limitation of this trial was the single-blind methodological design. During the trial, only participants were blinded while blinding of the researcher could not be achieved. It should also be noted that intervention was always provided by the same person, something that may have increased the consistency of the intervention's method, but also increased the possibility of researcher's influence (researcher's effect) on the study's outcome.

The possibility of a biased selection of patient could be another limitation of the present study. Individuals who were seeking information and were interested about condition-related education, may have been easier to be recruited compared to the general cancer patient population.

Beyond limitations, our study had several strengths too. To our knowledge, this study introduced, for the first time to the clinical trial concept, an intervention (educational program) that did not utilize medications of any form (oral or topical). Another strength of this trial was the use of various time points for better assessment of the interventions' effectiveness. This allowed the researchers to record how the intervention progressively affected the patients' skin conditions.

This patient-centered educational training program appears to be a novel method of health care information provision, especially within the health care system of Cyprus. The adoption of this type of educational programs, that use evidence-based knowledge, would be ideal so as to improve the island's health care system. Hopefully, this study becomes the beginning of improvement and a trigger for future studies.

14 CONCLUSION

The present study is a pilot randomized, controlled trial evaluating the effectiveness of a newly designed educational training program on the management of pruritus, rash and photosensitivity skin reactions induced by chemotherapies, EGFRI treatments and immunotherapies.

This trial illustrated that patients who followed the guidelines of the educational training program presented improvement of skin reaction grades, compared to those who did not. A statistically significant interaction was demonstrated between the Group type and Week in the program over the weekly grade measurements of skin reactions (rash, pruritus and photosensitivity).

The patients participating at the intervention group presented improved health status scores in all dimensions of the SF-36 questionnaire (physical functioning, physical health, emotional problems, energy/fatigue, emotional well-being, social activities, pain, and general health), while the data extracted from the DLQI questionnaire demonstrated that skin problems affected patients following the intervention less, compared to patients in the control group. Moreover, the patients in the intervention group required fewer emergency admissions compared to the control group, additionally to the fact that they presented a lower treatment dose reduction rate.

Further research is required in order to establish effective strategies to manage treatment-induced pruritus, rash and photosensitivity dermatitis, so as to achieve maximum treatment benefits for cancer patients who suffer from such skin reactions. Our study has provided the first solid evidence that could ensure the feasibility of a larger scale randomized controlled trial on the use of patient education as a measure to reduce skin reactions induced by immunotherapy, EGFRI treatment and chemotherapy.

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16 APPENDIX

16.1 Appendix 1: Cyprus national bioethics committee

ΚΥΠΡΙΑΚΗ ΔΗΜΟΚΡΑΤΙΑ

ΕΘΝΙΚΗ ΕΠΙΤΡΟΠΗ ΒΙΟΗΘΙΚΗΣ ΚΥΠΡΟΥ

Αρ. Φακ.: ΕΕΒΚ ΕΠ 2019.01.03
Αρ. Τηλ.: 22809038/039
Αρ. Φαξ: 22353878

18 Ιανουαρίου, 2019

Κυρία Ελένη Παπουή
Λεωφ. Γρίβα Διγενή 55
7600 Αθηένου
Λάρνακα

Αγαπητή κυρία Παπουή,

Αίτηση γνωμοδότησης για την πρόταση με τίτλο:
«Αποτελεσματικότητα εκπαιδευτικής παρέμβασης στην διαχείριση του εξανθήματος σε άτομα που λαμβάνουν θεραπεία με EGFRis»

Αναφέρομαι στην αίτησή σας ημερομηνίας 09 Ιανουαρίου 2019 για το πιο πάνω θέμα, και επιθυμώ να σας πληροφορήσω ότι από τη μελέτη του περιεχομένου των εγγράφων που έχετε καταθέσει, που αφορούν την πιο πάνω έρευνα, η Εθνική Επιτροπή Βιοηθικής Κύπρου (ΕΕΒΚ) **γνωμοδοτεί υπέρ της διεξαγωγής της εν λόγω έρευνας.**

2. Παρακαλούμε σημειώστε ότι **η έγκριση της ΕΕΒΚ δίδεται υπό τον όρο ότι στο πλαίσιο της πιο πάνω αναφερόμενης έρευνας δεν θα γίνει οποιαδήποτε παρέμβαση στην θεραπεία ή/και φαρμακευτική αγωγή που λαμβάνουν οι ασθενείς που θα συμμετέχουν.**

3. Περαιτέρω, σημειώνεται ότι τα έντυπα αίτησης ΕΕΒΚ 02 και συγκατάθεσης ΕΕΒΚ 03 δεν έχουν ληφθεί υπόψη καθότι αφενός δεν είναι κατάλληλα συμπληρωμένα και αφετέρου πρόκειται για αίτηση γνωμοδότησης.

4. Η Επιτροπή επιθυμεί να τονίσει ότι παραμένει ευθύνη δική σας η διεξαγωγή της έρευνας με τρόπο που να τηρούνται οι πρόνοιες του νέου Ευρωπαϊκού Γενικού Κανονισμού Προστασίας Προσωπικών Δεδομένων (2016/679) και του περί της Προστασίας των Φυσικών Προσώπων Έναντι της Επεξεργασίας των Δεδομένων Προσωπικού Χαρακτήρα και της Ελεύθερης Κυκλοφορίας των Δεδομένων αυτών Νόμος του 2018 (Ν. 125(Ι) /2018).

5. Σας ενημερώνουμε ότι για σκοπούς καλύτερου συντονισμού και αποφυγής επανάληψης ερευνών με το ίδιο θέμα ή/και υπό εξέταση πληθυσμό μέσα σε σύντομο σχετικά χρονικό διάστημα, η ΕΕΒΚ δημοσιεύει στην ιστοσελίδα της το θέμα της έρευνας, τον φορέα και τον υπό εξέταση πληθυσμό.

.../2

6. Κατά τη διάρκεια εκπόνησης της έρευνας, ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώνει την ΕΕΒΚ για κάθε τροποποίηση των αρχικά κατατεθειμένων εγγράφων (πρωτόκολλο ή άλλα ερευνητικά έγγραφα) και θα υποβάλλει τις απαιτούμενες έντυπες τροποποιήσεις στην Επιτροπή.

7. Σε περίπτωση διακοπής της έρευνας, ο συντονιστής/ επιστημονικός υπεύθυνος θα ενημερώσει γραπτώς την Επιτροπή κάνοντας αναφορά και στους λόγους διακοπής της έρευνας.

8. Ο συντονιστής/ επιστημονικός υπεύθυνος θα ενημερώσει την Επιτροπή σε περίπτωση αδυναμίας να συνεχίσει ως συντονιστής και θα υποβάλει τα στοιχεία επικοινωνίας του αντικαταστάτη του.

9. Με το πέρας της ερευνητικής πρότασης, ο συντονιστής / επιστημονικός υπεύθυνος θα ενημερώσει εγγράφως την Επιτροπή ότι το υπό αναφορά ερευνητικό πρωτόκολλο ολοκληρώθηκε.

10. Σας ευχόμαστε κάθε επιτυχία στη διεξαγωγή της έρευνάς σας.

Με εκτίμηση,

Καθ. Κωνσταντίνος Ν. Φελλάς
Πρόεδρος
Εθνικής Επιτροπής Βιοηθικής Κύπρου

16.2 Appendix 2: Consent form

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ
για συμμετοχή σε πρόγραμμα έρευνας
(Τα έντυπα αποτελούνται συνολικά από 4 σελίδες)

Καλείστε να συμμετάσχετε σε ένα ερευνητικό πρόγραμμα. Πιο κάτω (βλ. **«Πληροφορίες για Ασθενείς ή/και Εθελοντές»**) θα σας δοθούν εξηγήσεις σε απλή γλώσσα σχετικά με το τι θα ζητηθεί από εσάς ή/και τι θα σας συμβεί σε εσάς, εάν συμφωνήσετε να συμμετάσχετε στο πρόγραμμα. Θα σας περιγραφούν οποιοιδήποτε κίνδυνοι μπορεί να υπάρξουν ή ταλαιπωρία που τυχόν θα υποστείτε από την συμμετοχή σας στο πρόγραμμα. Θα σας επεξηγηθεί με κάθε λεπτομέρεια τι θα ζητηθεί από εσάς και ποιος ή ποιοι θα έχουν πρόσβαση στις πληροφορίες ή/και άλλο υλικό που εθελοντικά θα δώσετε για το πρόγραμμα. Θα σας δοθεί η χρονική περίοδος για την οποία οι υπεύθυνοι του προγράμματος θα έχουν πρόσβαση στις πληροφορίες ή/και υλικό που θα δώσετε. Θα σας επεξηγηθεί τι ελπίζουμε να μάθουμε από το πρόγραμμα σαν αποτέλεσμα και της δικής σας συμμετοχής. Επίσης, θα σας δοθεί μία εκτίμηση για το όφελος που μπορεί να υπάρξει για τους ερευνητές ή/και χρηματοδότες αυτού του προγράμματος. **Δεν πρέπει να συμμετάσχετε, εάν δεν επιθυμείτε ή εάν έχετε οποιουσδήποτε ενδοιασμούς που αφορούν την συμμετοχή σας στο πρόγραμμα.** Εάν αποφασίσετε να συμμετάσχετε, πρέπει να αναφέρετε εάν είχατε συμμετάσχει σε οποιοδήποτε άλλο πρόγραμμα έρευνας μέσα στους τελευταίους 12 μήνες. Εάν αποφασίσετε να μην συμμετάσχετε και είστε ασθενής, η θεραπεία σας δεν θα επηρεαστεί από την απόφασή σας. **Είστε ελεύθεροι να αποσύρετε οποιαδήποτε στιγμή εσείς επιθυμείτε την συγκατάθεση για την συμμετοχή σας στο πρόγραμμα.** Εάν είστε ασθενής, η απόφασή σας να αποσύρετε την συγκατάθεση σας, δεν θα έχει οποιεσδήποτε επιπτώσεις στην θεραπεία σας. Έχετε το δικαίωμα να υποβάλετε τυχόν παράπονα ή καταγγελίες, που αφορούν το πρόγραμμα στο οποίο συμμετέχετε, προς την Επιτροπή Βιοηθικής που ενέκρινε το πρόγραμμα ή ακόμη και στην Εθνική Επιτροπή Βιοηθικής Κύπρου.
Πρέπει όλες οι σελίδες των εντύπων συγκατάθεσης να φέρουν το ονοματεπώνυμο και την υπογραφή σας.

Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε
ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΕΚΠΑΙΔΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΤΗΝ ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΔΕΡΜΑΤΙΚΟΥ ΕΞΑΝΘΗΜΑΤΟΣ ΣΕ ΑΤΟΜΑ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΘΕΡΑΠΕΙΑ ΜΕ EGFRis: ΜΙΑ ΤΥΧΑΙΟΠΟΙΗΜΕΝΗ ΚΛΙΝΙΚΗ ΔΟΚΙΜΗ ΣΚΟΠΙΜΟΤΗΤΑΣ
Υπεύθυνος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε
Επιστημονικός Υπεύθυνος : Δρ. Ανδρέας Χαραλάμπους

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία:	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ για συμμετοχή σε πρόγραμμα έρευνας (Τα έντυπα αποτελούνται συνολικά 4 από σελίδες)
Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε
ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΕΚΠΑΙΔΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΤΗΝ ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΔΕΡΜΑΤΙΚΟΥ ΕΞΑΝΘΗΜΑΤΟΣ ΣΕ ΑΤΟΜΑ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΘΕΡΑΠΕΙΑ ΜΕ EGFRis: ΜΙΑ ΤΥΧΑΙΟΠΟΙΗΜΕΝΗ ΚΛΙΝΙΚΗ ΔΟΚΙΜΗ ΣΚΟΠΙΜΟΤΗΤΑΣ

Δίδετε συγκατάθεση για τον εαυτό σας ή για κάποιο άλλο άτομο;	
Εάν πιο πάνω απαντήσατε για κάποιον άλλο, τότε δώσετε λεπτομέρειες και το όνομα του.	

Ερώτηση	ΝΑΙ ή ΟΧΙ
Συμπληρώσατε τα έντυπα συγκατάθεσης εσείς προσωπικά;	
Τους τελευταίους 12 μήνες έχετε συμμετάσχει σε οποιοδήποτε άλλο ερευνητικό πρόγραμμα;	
Διαβάσατε και καταλάβατε τις πληροφορίες για ασθενείς ή/και εθελοντές;	
Είχατε την ευκαιρία να ρωτήσετε ερωτήσεις και να συζητήσετε το Πρόγραμμα;	
Δόθηκαν ικανοποιητικές απαντήσεις και εξηγήσεις στα τυχόν ερωτήματά σας;	
Καταλαβαίνετε ότι μπορείτε να αποσυρθείτε από το πρόγραμμα, όποτε θέλετε;	
Καταλαβαίνετε ότι, εάν αποσυρθείτε, δεν είναι αναγκαίο να δώσετε οποιεσδήποτε εξηγήσεις για την απόφαση που πήρατε;	
(Για ασθενείς) καταλαβαίνετε ότι, εάν αποσυρθείτε, δεν θα υπάρξουν επιπτώσεις στην τυχόν θεραπεία που παίρνετε ή που μπορεί να πάρετε μελλοντικά;	
Συμφωνείτε να συμμετάσχετε στο πρόγραμμα;	
Με ποιόν υπεύθυνο μιλήσατε;	

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία:	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ

για συμμετοχή σε πρόγραμμα έρευνας

(Τα έντυπα αποτελούνται συνολικά από 5 σελίδες)

Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΕΚΠΑΙΔΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΤΗΝ ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΕΞΑΝΘΗΜΑΤΟΣ ΣΕ ΑΤΟΜΑ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΘΕΡΑΠΕΙΑ ΜΕ EGFRI

ΠΛΗΡΟΦΟΡΙΕΣ ΓΙΑ ΑΣΘΕΝΕΙΣ ή/και ΕΘΕΛΟΝΤΕΣ

Το ερευνητικό έργο «***ΕΚΠΑΙΔΕΥΤΙΚΗ ΠΑΡΕΜΒΑΣΗ ΣΤΗΝ ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΕΞΑΝΘΗΜΑΤΟΣ ΣΕ ΑΤΟΜΑ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΘΕΡΑΠΕΙΑ ΜΕ EGFRI***» στο οποίο καλείστε να συμμετάσχετε πραγματοποιείται από το **Τεχνολογικό Πανεπιστήμιο Κύπρου** σε συνεργασία με το **American Medical Centre**.

Η συμμετοχή σας στο ερευνητικό έργο είναι **εθελοντική** ενώ μη συμμετοχή σας **δεν θα επηρεάσει** με οποιοδήποτε τρόπο την **θεραπεία και την φροντίδα** σας. Επιστημονικός υπεύθυνος του έργου είναι ο Αναπληρωτής Καθηγητής Δρ. Ανδρέας Χαραλάμπους.

Το ερευνητικό έργο στο οποίο καλείστε να συμμετάσχετε έχει σαν **στόχο** την λήψη εκπαιδευτικής παρέμβασης σε συνδυασμό με την συνήθη θεραπεία ως προς την διαχείριση του δερματικού εξανθήματος σε άτομα που λαμβάνουν θεραπεία με EGFRI.

Η κύρια ανεπιθύμητη αντίδραση της εν λόγω θεραπείας, είναι το εξάνθημα. Τα άτομα που λαμβάνουν αυτή την θεραπεία έχουν 24-95% πιθανότητα ανάπτυξης εξανθήματος.

Η σημασία του εκπαιδευτικού προγράμματος τονίζεται στο ότι οι πλείστες έρευνες που έχουν γίνει για την διαχείριση του εξανθήματος, αναφέρονται στην αναγκαιότητα των εκπαιδευτικών μέτρων χωρίς όμως να έχουν μελετήσει την αποτελεσματικότητα τους.

Για να επιτευχθεί ο σκοπός της μελέτης, ο ερευνητής θα συναντά τον ασθενή στην κλινική (American Medical Centre) την πρώτη εβδομάδα που θα εμφανίσει το εξάνθημα και θα ζητηθεί να απαντηθούν τα ερωτηματολόγια που θα δοθούν από τον ερευνητή. Η ενημέρωση του ερευνητή για την εμφάνιση του εξανθήματος θα γίνετε τηλεφωνικώς από τον ίδιο τον ασθενή. Ο ερευνητής θα σημειώνει την ακριβή ημερομηνία εμφάνισης του εξανθήματος.

Η επαναξιολόγηση του δέρματος καθώς και η επανάληψη των ερωτηματολογίων θα γίνετε κάθε εβδομάδα για 4 εβδομάδες. Σε κάθε συνάντηση το εξάνθημα θα φωτογραφίζετε.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία:	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ
για συμμετοχή σε πρόγραμμα έρευνας
(Τα έντυπα αποτελούνται συνολικά από 5 σελίδες)

Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΕΚΠΑΙΔΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΤΗΝ ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΕΞΑΝΘΗΜΑΤΟΣ ΣΕ ΑΤΟΜΑ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΘΕΡΑΠΕΙΑ ΜΕ EGFRI

Η **επεξεργασία των (ανώνυμων) δεδομένων** που θα ληφθούν μέσα από την εργασία γίνεται επίσης και για την διερεύνηση της ποιότητας ζωής σε σχέση με την σοβαρότητα του εξανθήματος. Επίσης δίνεται η ευκαιρία για την μελέτη των ενδεχόμενων παρενεργειών από το εξάνθημα όπως για παράδειγμα τυχών λοιμώξεις.

Τέλος με τα στοιχεία που θα παρθούν θα μπορεί να εντοπιστεί το ποσοστό των ασθενών που χρειάζονται μείωση της δόσης ή διακοπή της θεραπείας λόγω του εξανθήματος.

Με τον τρόπο αυτό θα δοθεί η ευκαιρία για τη **λήψη των ενδεδειγμένων εκπαιδευτικών μέτρων** σε μεταγενέστερο στάδιο τα οποία **θα έχουν ευεργετική επίδραση** στα άτομα που λαμβάνουν θεραπεία με EGFRI.

Η **συλλογή και επεξεργασία** των δεδομένων αφορά **αποκλειστικά και μόνο** την παρούσα έρευνα.

Σχετικά με το πιο πάνω ερευνητικό πρόγραμμα, εφόσον πληρείτε τα κριτήρια εισδοχής θα κληθείτε να συμμετάσχετε σε αυτό το ερευνητικό πρόγραμμα. **ΤΟΝΙΖΕΤΑΙ ότι η συμμετοχή σας στην έρευνα ΔΕΝ θα έχει οικονομική επιβάρυνση**.

Όπως έχει αναφερθεί και πιο πάνω, όλα τα δεδομένα που θα συλλεγούν ως μέρος του προγράμματος θα είναι **ανώνυμα και κωδικοποιημένα,** ενώ το αρχείο με τα δεδομένα θα διατηρηθούν 2 χρόνια μετά την ολοκλήρωση των επιστημονικών δημοσιεύσεων.

Διατηρείτε το δικαίωμα πρόσβασης στα δεδομένα που θα συλλεγούν από εσάς μέσω επικοινωνίας με τον επιστημονικό υπεύθυνο της έρευνας Δρ Ανδρέα Χαραλάμπους.

Δρ. Ανδρέας Χαραλάμπους, PhD, RN.
Αναπληρωτής Καθηγητής, Τεχνολογικό Πανεπιστήμιο Κύπρου
Προηγμένη Ογκολογική Νοσηλευτική
Τηλ. 25002011
andreas.charalambous@cut.ac.cy

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία:	

ΕΝΤΥΠΑ ΣΥΓΚΑΤΑΘΕΣΗΣ

για συμμετοχή σε πρόγραμμα έρευνας

(Τα έντυπα αποτελούνται συνολικά από 5 σελίδες)

Σύντομος Τίτλος του Προγράμματος στο οποίο καλείστε να συμμετάσχετε

ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ ΕΚΠΑΙΔΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΤΗΝ ΔΙΑΧΕΙΡΙΣΗ ΤΟΥ ΕΞΑΝΘΗΜΑΤΟΣ ΣΕ ΑΤΟΜΑ ΠΟΥ ΛΑΜΒΑΝΟΥΝ ΘΕΡΑΠΕΙΑ ΜΕ EGFRI

Η υποβολή τυχόν παραπόνων ή καταγγελιών θα μπορεί να γίνει άμεσα στον υπεύθυνο έρευνας του φορέα στον οποίο διεξάγεται το ερευνητικό πρόγραμμα :

Δρ. Χαράλαμπο Χρυσοστόμου, Προϊστάμενο Υπηρεσίας Έρευνας Διεθνών και Δημοσίων Σχέσεων (ΥΕΔΔΣ) – ΤΕΠΑΚ.

Στοιχεία Επικοινωνίας:

Τεχνολογικό Πανεπιστήμιο Κύπρου

Αθηνών 80 ΤΤ 3036 Λεμεσός

Τηλ 00357 25002562 Fax 0035725002763

Ηλεκτρονικό Ταχυδρομείο c.chrisostomou@cut.ac.cy

Επίσης για παράπονα μπορείτε να αποταθείτε και στους υπεύθυνους του American Medical Centre : Δρ. Μάριο Γεωργίου – υπεύθυνο προσωπικού και στον διευθυντή του American Medical Centre - κ. Κωνσταντίνο Μιχαηλίδη.

Στοιχεία Επικοινωνίας:

American Medican Centre

215, Spyrou Kyprianou Ave. 2047 Strovolos

P.O. Box 25610, 1311 Nicosia, Cyprus

Τηλ. 22476777 Fax 357 22 819 667

Συγκατάθεση:

Έχω ενημερωθεί για την πιο πάνω έρευνα από την ερευνητική ομάδα και δίνω τη συγκατάθεση μου για επεξεργασία των δεδομένων που αφορούν σε μένα αποκλειστικά και μόνο για σκοπούς της πιο πάνω επιστημονικής έρευνας.

Επίθετο:	.....	Όνομα:	.....
Υπογραφή:		Ημερομηνία:	

16.3 Appendix 3: Γενικές πληροφορίες

ΠΛΗΡΟΦΟΡΙΕΣ ΘΕΡΑΠΕΙΑΣ

Φύλο:

Άνδρας [ ]
Γυναίκα [ ]

Ηλικία (χρόνια): _____

Εργασία

Πλήρης [ ]
Μερική [ ]
Άνεργος [ ]
Συνταξιούχος [ ]
Άδεια ασθενείας [ ]

Εκπαίδευση

Γυμνάσιο [ ]
Λύκειο [ ]
Κολλέγιο [ ]
Πανεπιστήμιο [ ]

Ημερομηνία διάγνωσης: _____

Διάγνωση

Καρκίνος Μαστού [ ]
Καρκίνος Παχέος εντέρου [ ]
Καρκίνος Πνεύμονα [ ]
Καρκίνος παγκρέατος [ ]
Καρκίνος κεφαλής/τραχήλου [ ]

ΑΛΛΟ.....

Θεραπεία

Χημειοθεραπεία EGFR [ ]
ΧημειοθεραπείαEGFR + Ακτινοθεραπεία [ ]
Χημειοθεραπεία EGFR + Χειρουργική επέμβαση [ ]

Είδος και Σχήμα Χημειοθεραπείας

Erlotinib [ ]
Gefitinib [ ]
Cetuximab [ ]
Panitumumab [ ]

Ημερομηνία Έναρξης Θεραπείας :.....

ΣΥΜΠΛΗΡΩΣΗ ΣΤΗΝ ΕΠΟΜΕΝΗ ΣΥΝΑΝΤΗΣΗ Η ΟΠΟΤΕ ΧΡΕΙΑΣΤΕΙ

Μείωση της δόσης: ΝΑΙ / ΟΧΙ

Τερματισμός θεραπείας : ΝΑΙ/ΟΧΙ

Έκτακτες εισαγωγές ανά εβδομάδα: ΝΑΙ / ΟΧΙ

Εάν ΝΑΙ τότε:

Αριθμός εισαγωγών ανά εβδομάδα: .....

Αιτία εισαγωγής: .....

16.4 Appendix 4: DLQI Questionnaire

16.4.1 Permission to use the DLQI Questionnaire

Dear Elena,

I am writing this email on behalf of Professor Finlay. Thank you for your interest in the DLQI for your PhD study.
We are happy to assist you in receiving a license for your use of the DLQI for the non-commercial purpose that you have described. There will be no charge, but you will still need to apply to register on-line for a license. Please go to https://licensing.dermy.org. Please also see our website https://cardiff.ac.uk/dermatology(click on Quality of Life). This will give you all the information you may need about the index including the translations available and references describing its use. It is a requirement that the copyright statement is clearly shown at the bottom of every copy of the questionnaire. Please also note that the wording of the questionnaire must not be altered in anyway. This is a new online registration site. If you have any problems or queries about the registration process, please email us directly at dermqol@cf.ac.uk

Best wishes,
Faraz

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Dermatoleg Clinigol Ymchwil Cyd

Adran Dermatoleg, Ysgol Feddygaeth

Prifysgol Caerdydd, 3ydd Llawr Tŷ Morgannwg, Parc y Mynydd Bychan
Caerdydd, Cymru, y DU, CF14 4XN

16.4.2 DLQI questionnaire (Greek version)

ΔΕΙΚΤΗΣ ΠΟΙΟΤΗΤΑΣ ΖΩΗΣ - ΔΕΡΜΑΤΟΛΟΓΙΑ

Στόχος αυτού του ερωτηματολογίου είναι να εκτιμήσει το βαθμό κατά το οποίο το δερματολογικό σας πρόβλημα επηρέασε την ζωή σας ΤΗΝ ΠΕΡΑΣΜΕΝΗ ΕΒΔΟΜΑΔΑ. Παρακαλώ επιλέξτε μία απάντηση για κάθε ερώτηση, σημειώνοντας με ☑ το κατάλληλο τετραγωνάκι.

1.	Την περασμένη εβδομάδα, πόσο νοιώσατε το δέρμα σας να **φαγουρίζει**, να **ενοχλεί** να **πονάει** η να **τσούζει**;	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	
2.	Την περασμένη εβδομάδα, πόσο σας **ενόχλησε** ή σας **απασχόλησε** η κατάσταση του δέρματός σας ;	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	
3.	Την περασμένη εβδομάδα, πόσο σας επηρέασε η δερματική σας κατάσταση στο να πάτε **για ψώνια** ή **να ασχοληθείτε με το σπίτι ή το κήπο σας;**	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐
4.	Την περασμένη εβδομάδα, πόσο σας επηρέασε η δερματική σας κατασταση στην επιλογή των **ρούχων** σας ;	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐
5.	Την περασμένη εβδομάδα πόσο σας επηρέασε η δερματική σας κατάσταση στις **κοινωνικές** σας **δραστηριότητες** ή στα **χόμπυ** σας;	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐
6.	Την περασμένη εβδομάδα, πόσο σας δυσκόλεψε η δερματική σας κατάσταση στο να ασχοληθείτε με **σπόρ;**	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐
7.	Την περασμένη εβδομάδα, σας εμπόδισε η δερματική σας κατάσταση να **εργαστείτε ή να μελετήσετε;**	Ναι Όχι	☐ ☐	Άσχετο ☐
	Εάν «Όχι», κατά πόσο το δέρμα σας σας δημιούργησε πρόβλημα στη **δουλειά** ή στη **μελέτη** την περασμένη εβδομάδα;	Πολύ Λίγο Καθόλου	☐ ☐ ☐	
8.	Την περασμένη εβδομάδα, κατά πόσο η δερματική σας κατάσταση σας προκάλεσε προβλήματα στην σχέση σας με τον **σύντροφό σας** ή με κάποιον από τους **στενούς σας φίλους ή συγγενείς;**	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐
9.	Την περασμένη εβδομάδα, κατά πόσο η δερματική σας κατάσταση σας δημιούργησε προβλήματα στην **σεξουαλική σας ζωή;**	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐
10.	Την περασμένη εβδομάδα, κατά πόσο η **θεραπεία** του δέρματός σας αποτέλεσε πρόβλημα, για παράδειγμα δημιουργώντας ακαταστασία στο σπίτι, ή απαιτώντας αρκετό από το χρόνο σας;	Πάρα πολύ Πολύ Λίγο Καθόλου	☐ ☐ ☐ ☐	Άσχετο ☐

Ελέγξτε ότι απαντήσατε σε ΟΛΕΣ τις ερωτήσεις. Ευχαριστούμε.

16.5 Appendix 5: SF-36 Questionnaire

16.5.1 Permission to use the SF-36 Questionnaire

Terms and Conditions for Using the 36-Item Short Form Survey (SF-36):

RAND hereby grants permission to use RAND 36-Item Short Form Health Survey in accordance with the following conditions, which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

Changes to the Health Survey may be made without the written permission of RAND. However, all such changes shall be clearly identified as having been made by the recipient.

The user of this Health Survey accepts full responsibility, and agrees to indemnify and hold RAND harmless, for the accuracy of any translations of the Health Survey into another language and for any errors, omissions, misinterpretations, or consequences thereof.

The user of this Health Survey accepts full responsibility, and agrees to indemnify and hold RAND harmless, for any consequences resulting from the use of the Health Survey.

The user of the 36-Item Health Survey will provide a credit line when printing and distributing this document acknowledging that it was developed at RAND as part of the Medical Outcomes Study.

No further written permission is needed for use of this Health Survey.

16.5.2 SF-36 questionnaire (Greek version)

ΕΡΩΤΗΜΑΤΟΛΟΓΙΟ ΕΚΤΙΜΗΣΗΣ ΥΓΕΙΑΣ

& ΚΑΘΗΜΕΡΙΝΩΝ ΔΡΑΣΤΗΡΙΟΤΗΤΩΝ

Παρακαλούμε απαντήστε στις παρακάτω 36 ερωτήσεις του RAND Health Survey 1.0 ολοκληρωμένα ,ειλικρινά και χωρίς διακοπές.Σημειώσατε με «Χ» την απάντηση που σας αντιπροσωπεύει.

ΓΕΝΙΚΑ ΠΕΡΙ ΥΓΕΙΑΣ

Γενικά,θα λέγατε ότι η υγεία σας είναι:
(Επιλέξτε μία απάντηση)

- ○ Εξαιρετική
- ○ Πολύ καλή
- ○ Καλή
- ○ Μέτρια
- ○ Φτωχή

Συγκρίνοντας με τον προηγούμενο χρόνο, πώς θα χαρακτηρίζατε την υγεία σας **τώρα;**
(Επιλέξτε μία απάντηση)

- ○ Πολύ καλύτερη τώρα,από τον προηγούμενο χρόνο
- ○ Λίγο καλύτερη,από τον προηγούμενο χρόνο
- ○ Περίπου ίδια
- ○ Λίγο χειρότερη τώρα,από τον προηγούμενο χρόνο
- ○ Πολύ χειρότερη τώρα,από τον προηγούμενο χρόνο

Περιορισμοί των δραστηριοτήτων

Οι παρακάτω στήλες αφορούν δραστηριότητες που θα μπορούσατε να κάνετε κατά τη διάρκεια μιας τυπικής ημέρας.. **Το επίπεδο της υγείας σας τώρα σας περιορίζει** στις παρακάτω δραστηριότητες ;Αν ναι ,πόσο; **(Επιλέξτε μία απάντηση σε κάθε σειρά)**

	Ναι,με Περιορίζει πολύ	Περιορίζει λίγο	Περιορίζει καθόλου
Έντονες δραστηριότητες, όπως τρέξιμο, άρση βαρέων αντικειμένων, συμμετοχή σε δυναμικά σπορ	○	○	○
Μέτριας έντασης δρασηριότητες, όπως η μετακίνηση τραπεζιού, χρήση ηλεκτρικής σκούπας,παίζοντας μπόουλινγκ ή γκολφ	○	○	○
Άρση ή μεταφορά τροφίμων	○	○	○
Ανεβαίνοντας τη σκάλα **μερικές** φορές	○	○	○
Ανεβαίνοντας τη σκάλα **μία** φορά	○	○	○
Γονάτισμα ή σκύψιμο	○	○	○

Περπάτημα **πάνω από ένα χιλιόμετρο**	○	○	○
Περπάτημα **μερικών οικοδομικών τετραγώνων**	○	○	○
Περπάτημα **ενός οικοδομικού τετραγώνου**	○	○	○
Κάνοντας μπάνιο ή ντύνοντας τον εαυτό σας	○	○	○

Προβλήματα σωματικής υγείας

Κατά τη διάρκεια των **τελευταίων 4 εβδομάδων**, είχατε κάποιο πρόβλημα από τα παρακάτω στη δουλειά σας ή σε κάποιες καθημερινές δραστηριότητες, **ως αποτέλεσμα της σωματικής σας υγείας;** **(Επιλέξτε μία απάντηση σε κάθε σειρά)**

	Ναι	**Όχι**
Αναλογιστήκατε **πόσο χρόνο** ξοδέψατε στη δουλειά ή σε άλλες δραστηριότητες	○	○
Αξιολογήσατε τον εαυτό σας κατώτερο, από αυτό που θα θέλατε	○	○
Είχατε **κάποιον περιορισμό** στη δουλειά ή σε άλλες δραστηριότητες	○	○
Είχατε **δυσκολία** στην εκπλήρωση της δουλειάς σας ή σε άλλες δραστηριότητες (π.χ. χρειαστήκατε επιπλέον προσπάθεια)	○	○

Προβλήματα ψυχικής υγείας

Κατά τη διάρκεια των **τελευταίων 4 εβδομάδων**,είχατε κάποιο πρόβλημα από τα παρακάτω στη δουλειά σας ή σε κάποιες καθημερινές δραστηριότητες, **ως αποτέλεσμα κάποιων ψυχικών προβλημάτων** (π.χ.αίσθημα καταπίεσης ή άγχους) **(Επιλέξτε μία απάντηση σε κάθε σειρά)**

	Ναι	**Όχι**
Αναλογιστήκατε πόσο χρόνο ξοδέψατε στη δουλειά ή σε άλλες δραστηριότητες	○	○
Αξιολογήσατε τον εαυτό σας κατώτερο,από αυτό που θα θέλατε	○	○
Δεν κάνατε τη δουλειά σας ή άλλες δραστηριότητες **τόσο προσεχτικά** ωςσυνήθως	○	○

Κοινωνικές δραστηριότητες

Κατά τη διάρκεια των **4 τελευταίων εβδομάδων**,σε ποιά έκταση επέδρασαν τα ψυχικά προβλήματα ή η σωματική σας υγεία στις φυσιολογικές κοινωνικές δραστηριότητές σας με την οικογένεια,φίλους,γείτονες ή παρέες; **(Επιλέξτε μία απάντηση)**

- ○ Καθόλου
- ○ Ελάχιστα
- ○ Λίγο
- ○ Μέτρια
- ○ Πάρα πολύ

Πόνος

Πόσο πονέσατε σωματικά τις **τελευταίες 4 εβδομάδες;**
(Επιλέξτε μία απάντηση)

- Καθόλου
- Πολύ ήπια
- Ήπια
- Μέτρια
- Αρκετά
- Πολύ

Κατά τη διάρκεια των **τελευταίων 4 εβδομάδων** ,πόσο **ο πόνος** επέδρασε στη δουλειά σας (συμπεριλαμβανομένων και των δύο εργασιών μέσα κι έξω απ᾽ το σπίτι);
(Επιλέξτε μία απάντηση)

- Καθόλου
- Λίγο
- Μέτρια
- Αρκετά
- Πολύ

Ενέργεια και συναισθήματα

Αυτές οι ερωτήσεις έχουν σχέση με το πως νιώσατε και πώς ήταν η κατάστασή σας τις **4 τελευταίες εβδομάδες**.
Για κάθε ερώτηση,δώστε την απάντηση που προσεγγίζει τον τρόπο με τον οποίο νιώσατε.

(Επιλέξτε μία απάντηση σε κάθε σειρά)

Πόσο χρόνο κατά τη διάρκεια των **4 τελευταίων εβδομάδων...**	Ολο το χρόνο	Πολύ χρόνο	Αρκετό χρόνο	Λίγο χρόνο	Πολύ Λίγο χρόνο	Καθόλου χρόνο
Αισθανθήκατε γεμάτοι από ζωντάνια;	○	○	○	○	○	○
Είσαστε πάρα πολύ νευρικοί;	○	○	○	○	○	○
Αισθανθήκατε τόσο κατηφείς,ώστε τίποτα δε μπορούσε να σας φτιάξει τη διάθεση;	○	○	○	○	○	○
Αισθανθήκατε ήρεμοι και γαλήνιοι;	○	○	○	○	○	○
Είχατε πολύ ενέργεια;	○	○	○	○	○	○
Αισθανθήκατε μελαγχολικοί;	○	○	○	○	○	○
Αισθανθήκατε νευρικοί;	○	○	○	○	○	○
Αισθανθήκατε ευτυχείς;	○	○	○	○	○	○

Αισθανθήκατε κουρασμένοι;	○	○	○	○	○	○

Κοινωνικές δραστηριότητες

Κατά τη διάρκεια των **4 τελευταίων εβδομάδων**,πόσες φορές **η σωματική σας υγεία ή τα συναισθηματικά σας προβλήματα**, αναμείχθηκαν στις κοινωνικές σας δραστηριότητες (επίσκεψη σε φίλους,συγγενείς κ.τ.λ.);
(Επιλέξτε μία απάντηση)

- ○ Συνεχώς
- ○ Τις περισσότερες φορές
- ○ Μερικές φορές
- ○ Λίγες φορές
- ○ Καθόλου

Γενικά περί υγείας

Πόσο σωστές ή λάθος είναι για σας οι παρακάτω προτάσεις;

(Επιλέξτε μία απάντηση σε κάθε σειρά)

	Αληθής	Αρκετά αληθής	Δεν ξέρω	Αρκετά ψευδής	Ψευδής
Αρρωσταίνω ευκολότερα από τους άλλους ανθρώπους	○	○	○	○	○
Είμαι υγιής όσο οι άλλοι άνθρωποι	○	○	○	○	○
Περιμένω η υγεία μου να χειροτερέψει	○	○	○	○	○
Η υγεία μου είναι εξαιρετική	○	○	○	○	○

16.5.3 Appendix 6: Educational program (Greek version)

Το παρόν εκπαιδευτικό πρόγραμμα αφορά τις δερματικές παρενέργειες που έχετε λόγω της θεραπείας που υποβάλλεστε. Θα δείτε πέντε κατηγορίες, οι οποίες είναι: 1. η κατηγορία «καθαρό – ενυδατωμένο», 2. η κατηγορία «προστασία από τον ήλιο», 3. η κατηγορία «προστασία από άλλα εξωτερικά ερεθίσματα», 4. η κατηγορία «καλλυντικά προϊόντα» και 5. η κατηγορία «παρατήρηση – ενημέρωση ».

Για οποιαδήποτε απορία ή διευκρίνιση μη διστάσετε να ρωτήσετε.

1. **<u>ΚΑΘΑΡΙΟΤΗΤΑ – ΕΝΥΔΑΤΩΣΗ</u>**

- Καθημερινό μπάνιο ή ντους με μη ερεθιστικά σαπούνια και σαμπουάν (ασθενώς όξινα έως αλκαλικά).
- Αποφύγετε να κάνετε μπάνιο ή ντους με ζεστό –καυτό νερό (η θερμοκρασία του νερού να είναι περίπου 37 ° C το καλοκαίρι και 39 ° C το χειμώνα).
- Πλένετε απαλά το δέρμα σας χρησιμοποιώντας την παλάμη του χεριού σας.
- Καλό ξέβγαλμα του σαπουνιού / σαμπουάν
- Σκουπίστε ελαφρά το βρεγμένο δέρμα με μια καθαρή πετσέτα χωρίς να τρίβετε την επιδερμίδα.
- Τα άλατα μπάνιου που περιέχουν θείο δεν συνιστώνται γιατί προκαλούν ξηροδερμία.

- Ενυδατώστε το δέρμα σας μετά το μπάνιο με κρέμα που δεν περιέχει αλκοόλ.
- Εφαρμόστε υποαλλεργική και χωρίς άρωμα ενυδατική κρέμα

2. ΑΝΤΗΛΙΑΚΗ ΠΡΟΣΤΑΣΙΑ

- Χρησιμοποιήστε αντηλιακό υψηλής προστασίας.
- Εφαρμόστε καθημερινά αντηλιακό σε όλα τα εκτεθειμένα δέρματα ακόμα και τις συννεφιασμένες μέρες.
- Εάν έχετε απώλεια μαλλιών εξαιτίας της θεραπείας σας, φροντίστε να εφαρμόσετε αντηλιακό και στο τριχωτό της κεφαλής σας.
- Φροντίστε να χρησιμοποιείται φρέσκο μπουκάλι αντηλιακού. Αντηλιακά προϊόντα περασμένου έτους μπορεί να μην είναι πλέον αποτελεσματικά.
- Χρήση αντικειμένων που εμποδίζουν την υπεριώδη ακτινοβολία όπως ομπρέλες, καπέλο, γυαλιά ηλίου, κασκόλ, γάντια.
- • Βρείτε μια θέση στη σκιά για παράδειγμα κάτω από ένα δέντρο ή καθίστε κάτω από μια ομπρέλα. Μπορείτε επίσης να έχετε μαζί σας μια ομπρέλα για να προστατευτείτε από τον ήλιο.
- Περπατήστε στη φύση και σε μονοπάτια που να περιβάλλονται από δέντρα αφού παρέχουν σκιά και εμποδίζουν την υπεριώδη ακτινοβολία.
- Οι περούκες μπορεί να είναι ζεστές τους καλοκαιρινούς μήνες λόγω του ήλιου και των υψηλών θερμοκρασιών, αλλά ένα βαμβακερό μαντίλι μπορεί να προσφέρει άνεση ενώ παράλληλα μπορεί να παρέχει προστασία.
- Αποφύγετε την έκθεση στον ήλιο από τις 10 το πρωί έως τις 4 το απόγευμα.

3. ΠΡΟΣΤΑΣΙΑ ΑΠΟ ΑΛΛΑ ΕΞΩΤΕΡΙΚΑ ΕΡΕΘΙΣΜΑΤΑ

- Να είστε προσεκτικοί κατά το ξύρισμα. Μπορείτε να χρησιμοποιείται καλύτερα μια ηλεκτρονική ξυριστική μηχανή.
- Αποφύγετε να ξύνετε το δέρμα σας.
- Καλύψτε την περιοχή που έχετε φαγούρα εάν δεν το αντέχετε για να αποφύγετε τυχόν γρατσουνιές.
- Σε περίπτωση κνησμού, χρησιμοποιήστε ένα βρεγμένο κρύο πανί ή πάγο για να αποφύγετε το ξύσιμο της περιοχής.
- Κόψτε τα νύχια σας για να αποφύγετε τυχόν γρατσουνιές.

- Να φοράτε γάντια όταν κοιμάστε για να αποφύγετε το ξύσιμο κατά την διάρκεια του ύπνου.
- Αποφύγετε να φοράτε μάλλινα ρούχα.
- Προστατέψτε τυχόν πληγές στο δέρμα σας σύμφωνα με τις οδηγίες του γιατρού σας.

4. ΚΑΛΛΥΝΤΙΚΑ ΠΡΟΪΟΝΤΑ

- Για να καλύψετε το πρόσωπο σας από τυχόν ατέλειες χρησιμοποιήστε ενυδατικές κρέμες με χρώμα ή ακόμα και αντηλιακά με χρώμα. Έτσι θα πετύχετε κάλυψη στο δέρμα σας αλλά ταυτόχρονα θα διατηρήσετε το δέρμα σας ενυδατωμένο ή προστατευμένο από τον ήλιο.
- Προτιμήστε «μη χημικά» καλλυντικά.

5. ΠΑΡΑΤΗΡΗΣΗ – ΕΝΗΜΕΡΩΣΗ

- Παρακολουθήστε το δέρμα σας σε καθημερινή βάση.
- Ο γιατρός σας θα πρέπει να ενημερώνεται έγκαιρα για τυχόν κνησμό, εξανθήματα και φωτοευαισθησία στο δέρμα.
- Ενημερώστε τον γιατρό σας για τυχόν νέες πληγές στο δέρμα σας.

Σας Ευχαριστώ πολύ !

16.5.4 Appendix 7: Educational program (English version)

The present educational program concerns the skin side effects that you have due to the treatment you are undergoing. You will see five categories, which are: 1. the category "clean – hydrate", 2. the category "protection from the sun", 3. the category "protection from other external stimulations", 4. the category "observe – inform," and 5. the category "cosmetic products". For any questions or clarifications, do not hesitate to ask.

1. CLEANLINESS – HYDRATION

- Daily bath or shower with non-irritating soaps and shampoos (weakly acidic to alkaline).
- Avoid hot water for bath or shower (about 37 ° C in Summer and 39 ° C in Winter).
- Gently wash your skin using the palm of your hand.
- Good rinsing of the soap / shampoo
- Wipe lightly with a clean towel without rubbing.
- Sulfur-containing bath salts are not recommended because they cause dry skin.
- Moisturizing after the bath with a cream that does not contain alcohol.
- Apply hypoallergenic and fragrance-free moisturizer

2. SUN PROTECTION

- High protection sunscreen.
- Apply sunscreen daily to all exposed skin even on cloudy days.
- If chemo causes hair loss, be sure to apply sunscreen to your scalp, too.
- Make sure you have a fresh bottle of sunscreen. Last year's bottle may no longer be effective.
- Use of objects that block ultraviolet radiation such as umbrellas, hat, sunglasses, scarves, gloves, clothes with few exposed areas.
- Find a place in the shade under a tree or sit under an umbrella. You can also carry a sun umbrella.
- Walk along paths sheltered by trees.
- Wigs can be hot in the sun, but a cotton scarf can be comfortable while providing protection.
- Avoid sun exposure from 10 am to 4 pm

3. PROTECTION FROM OTHER EXTERNAL STIMULATIONS

- Carefully during shaving. An electronic razor is best used.
- Avoid scratching.
- Cover the itchy area if you can't keep from scratching it.
- In case of itching, use a wet cold cloth or ice and not scratch the area.
- Trim your nails to avoid scratching.
- Wear gloves when you sleep to avoid scratching.
- Avoid wool clothing
- Protect any wounds on your skin as doctor instructed, or use sterile, non-stick gauze, or use paper tape if you can.

4. COSMETICS PRODUCTS

- To cover the face, use moisturizers with color or even sunscreens with color. This way you will achieve coverage on your skin but at the same time you will keep your skin hydrated or protected from the sun.
- Prefer "non-chemical" cosmetics.

5. NOTE - UPDATE:

- Monitor your skin on a daily basis.
- Your doctor should be informed in time for any itching, photosensitivity, rashes.
- Tell to your doctor about any new sores on your skin.

16.6 Appendix 8. A systematic Review Publication

16.6.1 A systematic Review- approval form for publication

The information below relates to the article's final approval by the European Journal of Oncology Nursing on 03/01/2021:

Ref.: Ms. No. YEJON-D-20-00282R2

The extent to which the last decade has yielded additional treatment options for EGFR-associated rash besides classic treatment with antibiotics and corticosteroids - a systematic review

European Journal of Oncology Nursing

Dear Mrs. ELENI,

I am glad to inform you that your paper has been accepted for publication in the European Journal of Oncology Nursing.

Your accepted manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication.

We are aiming to publish your paper in about 6-9 months, although this is not a guarantee and will depend on a number of editorial factors. Nevertheless, the paper will be published online in about 2 weeks, after proof corrections are received.

Congratulations on your publication.

Yours sincerely,

Alexander Molassiotis, RN, PhD

Editor-in-Chief

European Journal of Oncology Nursing”

16.6.2 A systematic review – The published article

The extent to which the last decade has yielded additional treatment options for EGFR-associated rash besides classic treatment with antibiotics and corticosteroids - a systematic review

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ABSTRACT

Purpose: To investigate the effectiveness of different interventions for the prevention and treatment of EGFRI treatment-induced rash (EGFRIr) that appeared in the last decade, excluding antibiotics and cortisone products alone. Method: A systematic review was performed in 2019 and was updated in 2020. The search strategy was limited to studies published within the last 10 years on the Medline database accessed via Pubmed and the Cochrane database. The search was performed using keywords combined with AND, OR. Results: The search yielded thirteen studies. The studies were divided into two categories, based on the intervention method used: four studies used creams containing vitamin K1 or vitamin K3 (henceforth classified as "Category A") and nine studies ("Category B") focused on different intervention methods such as laser treatment, Polydatin (PD) cream treatment, treatment with sunscreen, Adapalene gel treatment, topical aloe vera treatment, topical hydration treatment, the impact of a pre-emptive skin treatment and, finally, epidermal growth factor (EGF) ointment treatment. From "Category A", the results vary as two studies found no benefit from cream use, while two studies indicated a possible improvement on skin reactions from cream use. In "Category B", a benefit due to laser treatment was indicated, Polydatin-containing moisturizer showed a reduction in the incidence of rash grade ≥ II in patients treated

with afatinib, while treatment with sunscreen demonstrated no benefit for the prevention of EGFRIr. Additionally, Adapalene gel use is not recommended as prophylaxis for EGFRIr, topical aloe vera may be used in the management for EGFRIr due to cetuximab, topical hydration resolved the EFGRIr, the pre-emptive skin treatment routine was well tolerated and the epidermal growth factor ointment improved all the symptoms due to EGFRI. Conclusions: The results from the studies vary, although this study focuses on reviewing treatment interventions that can be utilised, apart from antibiotics and steroids, in order to alleviate the problems of the patients suffering from EGFRIr. More specifically, the authors of this review cannot draw a conclusion from "Category A", as the efficacy of vitamin K for the management of EGFRIr is controversial. From "Category B", some of the suggested treatments show encouraging results, while others may prove ineffective and rather harmful for the patients.

KEYWORDS

EGFR; PREVENT; RASH; TREATMENT; VITAMIN K1/K3

1. INTRODUCTION

In recent years the EGFRI (Epidermal Growth Factor Receptor Inhibitor) treatments have evolved into effective anti-cancer targeted therapies (Pinta et al., 2014). They are mainly employed in the treatment of colon and rectum cancer as well as to head and neck, lung, pancreas and breast malignancies (Li et al., 2015).

Epidermal Growth Factor Receptor (EGFR) is a tyrosine kinase of the ErbB family that affects various molecular pathways that induce protein synthesis, affect cell differentiation, increase metastatic ability, apoptosis and angiogenesis (Abdelmohsen et al., 2003). Some new era targeted treatments attenuate the function of the EGFR. These targeted treatments are called EGFR Inhibitor (EGFRI) treatments and they are divided into two categories: the monoclonal antibodies (cetuximab and panitumumab) and tyrosine kinase inhibitors – TKIs (gefitinib, erlotinib, and afatinib) (Abdelmohsen et al., 2003, Fuggetta et al., 2019).

The use of EGFRI treatments has been associated to numerous adverse effects of varying intensity and severity. The most common side effect reported in the literature is skin reactions (Lacouture et al., 2011). More specifically, these skin reactions can cause discomfort and pain to patients and result in treatment dose reduction or dose provision delay or even discontinuation of the therapy, in severe cases (Lacouture et al., 2011). The most prevalent side effect from EGFRI treatments is rash, usually occurring in the face, head, chest and back. Rashes typically develop within the first 1-2 weeks following the initiation of treatment and are observed in 50-100% of the patients (Fabbrocini et al., 2015). According to Fabbrocini et al., (2015), the incidence of rash in patients receiving gefitinib ranges from 24%-62%, while for patients receiving erlotinib the incidence rate is 49%-67% and 75%-95% in patients under cetuximab therapy (Fabbrocini et al., 2015). The percentage of patients that require discontinuation or delay in treatments due to rash ranges between 32% and 76% (Fabbrocini et al., 2015).

The standard treatment for the EGFRIr includes the use of antibiotics and cortisone products such as doxycycline and hydrocortisone, respectively (Melosky et al., 2009). The systematic review of Brown J et al. (2016) showed that the most common drug interventions for the management of rash are the usage of oral and topical antibiotics, topical corticosteroids, and antihistamines (Brown et al., 2016). Additionally, Petrelli et al. (2016) conducted a systematic review and meta-analysis to evaluate whether prophylactic antibiotics may reduce the occurrence and severity of rash related to EGFRI treatment (Petrelli et al., 2016). The results showed that prophylactic antibiotics can significantly reduce the incidence and severity of rash (Petrelli et al., 2016). Despite the fact that the above methods are the ones mostly used for the control of the EGFRIr both prophylactically and reactively, nowadays other innovative intervention methods can be used.

There are many studies on the management and treatment of the EGFRIr but most of these are based on expert opinions and not on clinical trials. Such a study is the study of Pinto et al. (2011), where a group of Italian experts voted twice for the final decision regarding the guidelines for the management of skin reactions for the patients (Pinto et al., 2011). Another study based on experts was the one conducted by Chu et al., 2017 that voted for recommendations regarding the prevention of EGFRIr through the Taiwanese Dermatological Association (TDA) consensus panel (Chu et al., 2017).

This systematic review aims to investigate the effectiveness of different interventions apart from antibiotics and cortisone products for the prevention and treatment of EGFRI treatment-induced rash (EGFRIr) that appeared in the last decade.

2. METHOD

2.1 Data sources and search

The authors decided to undertake a systematic review because in the literature they could not find a systematic review to include different interventions for the prevention and treatment of EGFRIr, excluding antibiotics and cortisone products.

This systematic review was performed between January 1 and March 30, 2019 and was updated in September of 2020. The search strategy was limited to studies published within the last 10 years in the Medline database accessed via Pubmed and the Cochrane database. The following keywords were used: Acneiform Eruptions, EGFRI, epidermal growth factor receptor, exanthema, skin rash, skin toxicity, rash, erlotinib, gefitinib, cetuximab, panitumumab, afatinib, management, and patient education. The search was performed using keywords combined with appropriate operators (AND, OR).

2.2 Inclusion and exclusion criteria

The inclusion criteria for this systematic review included studies in English which focused on prevention and/or treatment of EGFRIr or combinational treatments with EGFRI therapy, for example EGFRI + other chemotherapy medicines or EGFRI + radiotherapy. Also, all tumor types and all cancer stages were included in the study.

This systematic review excluded article types such as letters, guidelines, clinical recommendations, reviews, and meta-analyses (for some reviews and meta-analysis authors compared their results with this systematic review). Excluded from this review were also studies that investigate the treatment and /or management of the EGFRIr with

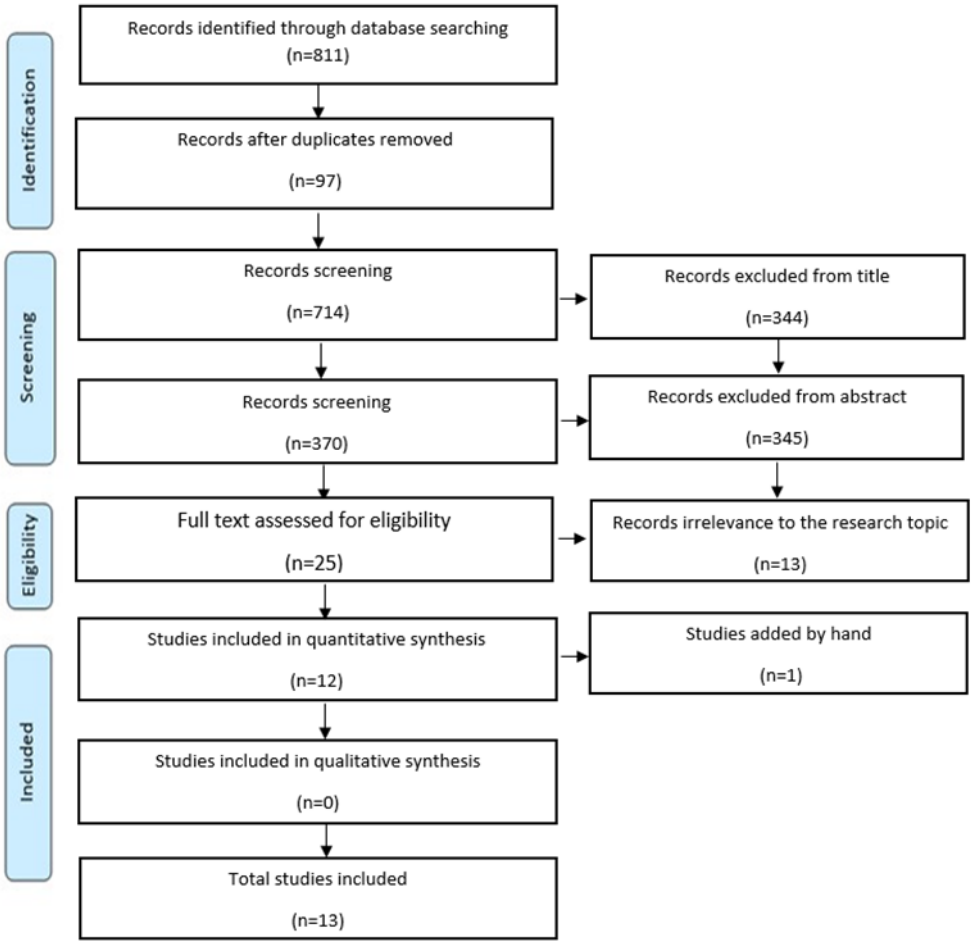
antibiotics and steroids, as these methods of treatment received extensive attention in the literature and their effectiveness is well established and documented. Furthermore, from this systematic review we excluded studies that examined the Objective Response (OR) of EGFRI treatments, Progression-Free Survival (PFS), the Disease Control Rate (DCR), as well as the cost regarding the EGFRI treatments or the cost deriving from the management of the side effects due to EGFRI treatments. Finally, studies that focused on the comparison of other chemotherapies and/or radiotherapy with EGFRI treatments were also excluded.

2.3 Screening

The authors screened the titles and abstracts based on the inclusion and exclusion criteria. The initial strategy was conducted in PubMed. No further studies were found in Cochrane. Due to the initial small number of studies used from the first screening (January-March, 2019), a second update was performed in September of 2020. This time we expanded our search criteria in order to include case series, case reports and other recently published studies in our systematic review.

A total of 811 studies were retrieved by the search strategy (PRISMA Flow Diagram). Primarily, 97 papers were rejected due to duplication, 344 studies were excluded due to their title, and 345 studies were excluded from the abstract contents as they did not meet the complete set of inclusion criteria. In total, 25 full text studies were read, of which 13 studies were excluded due to a lack of relevance to the research topic. From the bibliographies an additional article was identified by hand. Finally, a total of thirteen studies were selected to be included in this systematic review.

PRISMA Flow Diagram



2.4 Quality appraisal

To assess the scientific rigour of the studies used, Jadad (Jadad et al., 1996) and CASP tools (CASP, 2017) were utilized so as to evaluate the clinical trials and case-control studies, respectively, in order to limit any potential biases and exclude unreliable results from our literature review. Additionally, the NIH Quality Assessment Tool for Case Series Studies was used for the two case series reports and the CARE checklist was used (Gagnier et al., 2013) for the two case reports.

The Jadad tool used for the clinical trial studies examines three main parameters: randomization, withdrawals and loss of follow-up. The score for the studies carried out by of Eriksen et al. (2017), Jatoi et al. (2010) and Kim et al. (2020) was 5/5 as the methodological quality and the effectiveness of blinding and randomization were sufficient. The score for the study by Chayahara et al. (2019) was 3/5, as the study was only evaluator-blinded (Chayahara et al., 2019). In addition, the score for the study of

Lacouture et al. (2010) was 3/5 because the study was not blind (Lacouture et al., 2010). Three studies (Fuggetta et al., 2019; Hwang et al., 2016; Pinta et al., 2014) did not correspond to any of the Jadad criteria because they were not blind, non-randomized and they did not describe any dropouts or withdrawals.

The CASP tool, used for case control studies, does not suggest a scoring system but provides questions as key criteria. The CASP tool includes 11 questions divided into three sections; “Section A” examines if the results of the study are valid, “Section B” examines how the results are analyzed; and “Section C” examines whether the results will help locally.

The study of Ai-Min Li et al. (2015) evaluated with the CASP tool. This study did not mention if they used methods to minimize bias or to examine confounding factors. Additionally, the results of the study cannot be generalized as the population was solely Chinese (Li et al., 2015).

The studies of Tomková et al. (2013) and Gobbo et al. (2012) are case series studies evaluated with the NIH Quality Assessment Tool. This tool includes nine questions: Was the study question or objective clearly stated; Was the study population clearly and fully described, including a case definition; Were the cases consecutive; Were the subjects comparable; Was the intervention clearly described; Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants; Was the length of follow-up adequate; Were the statistical methods well described; Were the results well described. Based on the answers of the above questions, the quality rating can be good, fair or poor. Both studies lag behind the statistical method so the quality rating is fair.

The studies of Gürbüz et al. (2020) and Ferrari et al. (2016) were evaluated with the CARE checklist because they are case reports. The checklist includes thirteen questions about the title, the keywords, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic intervention, follow up and outcomes, discussion, patient perspective and informed consent. The aforementioned studies corresponded positively to the criteria of the CARE checklist except for three of them: the studies did not include in the keywords the phrase ‘case report’, they omitted to mention family and psycho-social history (this corresponded to the patient information question) of each patient including relevant genetic information and finally,

in both studies, information about the collection of informed consent from the patients was absent. Finally, the study of Ferrari et al. (2016) did not include the type of study in the title.

The major strengths identified in the studies reviewed regard the methodology: all studies described the eligibility criteria, sources, and methods of participant selection. A major weakness identified in some of the studies was the statistical method used: the failure to describe the efforts to address potential bias sources and the variable criteria, together with the fact that the majority of the studies did not report how potential confounders were addressed. Additionally, some other points that stand out are: the studies of Pinta et al. (2014) and Fugetta et al. (2019) did not describe their statistical method. Another study did not include the dates during which the population was selected (Eriksen et al., 2017), while a second study did not report the source of funding (Li et al., 2015). Finally, the case reports (Ferrari et al., 2016; Gürbüz et al., 2020) failed to provide the required patient history.

3. DATA SYNTHESIS

Retrieved data were combined and clustered into categories. The purpose of sorting the data in such a way was to investigate how the research question and important concepts were previously approached in the scientific literature.

Since the used studies in this review were outputs from a variety of fields (clinical, academic/research), structured synthesis methods were used during clustering of the findings. Subsequently, this systematic review mainly categorizes rather than expounds its retrieved data. Categories resulted following quality rating and classification based on the similarity of study conclusions.

In this systematic review, the authors extracted and congregated findings in the following two categories based on the intervention method used: four studies used “Category A” creams and nine studies focused on different intervention methods such as laser treatment, Polydatin (PD) cream treatment, treatment with sunscreen, Adapalene gel treatment, topical aloe vera treatment, topical hydration treatment, the

impact of a pre-emptive skin treatment, and finally epidermal growth factor ointment treatment (“Category B”).

4. RESULTS

All the studies included in this systematic review were quantitative. Eight studies were clinical trials (Chayahara et al., 2019; Eriksen et al., 2017; Fuggetta et al., 2019; Hwang et al., 2016; Jatoi et al., 2010; Kim et al., 2020; Lacouture et al., 2010; Pinta et al., 2014), one study was a case control (Li et al., 2015), two studies were case series (Gobbo et al., 2012; Tomková et al., 2013) and two studies were case reports (Ferrari et al., 2016; Gürbüz et al., 2020). More specifically, four studies were double-blinded placebo-controlled trials (Chayahara et al., 2019; Eriksen et al., 2017; Jatoi et al., 2010; Kim et al., 2020), the study of Pinta et al. (2014) and the study of Fuggetta et al. (2019) were pilot clinical trials and two studies were an open-label, multicenter, phase II trial (Hwang et al., 2016; Lacouture et al., 2010).

All of the studies were published between 2010 and 2020 and from the combined samples there were 576 patients in total. As previously mentioned, the studies were divided into two categories:

“Category A” included studies using creams containing vitamin K1 or vitamin K3, whilst “Category B” consisted of one article focused on laser treatment; another article focused on Polydatin (PD) cream treatment; another focused on treatment with sunscreen; another focused on treatment with Adapalene gel; one focused on topical use of aloe vera; another focused on topical hydration; one study focused on the impact of a pre-emptive skin treatment; and finally, two articles focused on epidermal growth factor ointment treatment.

More specifically, “Category A” included 151 patients and “Category B” included 425 patients. The patients in “Category A” carried diagnoses such as metastatic rectum cancer, colon, pancreas, esophagus, head and neck, or unknown primary cancer. “Category B” included patients with metastatic colorectal cancer, head and neck cancer and patients with lung, non-small cell lung, gastrointestinal, pancreatic and ‘other’ cancers.

The EGFRI treatments provided to patients of "Category A" studies included cetuximab or panitumumab, whereas for the patients of "Category B" they included cetuximab, panitumumab, afatinib, erlotinib, and gefitinib. The studies of Eriksen et al. (2017) and Gürbüz et al. (2020) used Cetuximab at a dose of 500mg/m2 every second week plus chemotherapy, while in the study of Fuggetta et al. (2019) the patients received afatinib at 40mg/die. In the case report of Ferrari et al. (2016), the patient was started with cetuximab at initial dose of 400mg/m2 infused over 2 hours and later was switched to 250 mg/m2 weekly over 1 hour followed by chemotherapy (Ferrari et al., 2016). In the study of Li et al. (2015), the patients were treated with either cetuximab plus FOLFOX or cetuximab plus FOLFIRI. The patients in the study of Pinta et al. (2014) were treated with one of the following therapeutic schemes containing cetuximab: cetuximab plus FOLFIRI/XERILI, cetuximab plus FOLFOX/XELOX, cetuximab plus irinotecan, cetuximab plus Fluoropyrimidine, or single-agent cetuximab (Pinta et al., 2014). In this study, each patient received the regimen either as first- or second-line therapy, or as single-agent therapy. In the study of Tomková et al. (2013), the patients received cetuximab or panitutumab with the dose ranging between 400mg to 800mg either alone or with irinotecan. The studies of Gobbo et al. (2012), Jatoi et al. (2010) and Chayahara et al. (2019) did not mention the dose of EGFRI treatment provided. In the study of Kim et al. (2020), the patients received gefitinib, erlotinib, afatinib, or cetuximab for the treatment of pancreatic cancer. The dose is provided only for the patients that received erlotinib, which was 100mg, whereas in the study of Hwang et al. (2016) the dose of erlotinib was 150 mg/100 mg. Finally, in the study of Lacouture et al. (2010) the patients were treated with panitumumab 6.0 mg/kg plus FOLFIRI every 2 weeks and panitumumab with 9.0 mg/kg plus irinotecan every 3 weeks.

For the rash's evaluation, three studies used the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Eriksen et al., 2017; Gürbüz et al., 2020; Kim et al., 2020). In addition, the study of Eriksen et al. (2017) used skin photos and skin biopsies were also obtained from ten patients one month before and after treatment, from each treatment area. Five studies used the CTCAE version 3.0 for the evaluation of the EGFRIr (Fuggetta et al., 2019; Jatoi et al., 2010; Li et al., 2015; Pinta et al., 2014,Hwang et al., 2016). Additionally, Jatoi et al. (2010) used the Skindex-16 questionnaire to evaluate the impact of rash on patients' quality of life, another brief

rash incidence questionnaire and a questionnaire on patient compliance with the EGFRI treatment (Jatoi et al., 2010). Finally, the study of Tomková et al. (2013) used the CTCAE version 4.03, while the study of Gobbo et al. (2012) used the visual analogue scale (VAS) and the CTR (Cetuximab-Related Toxicity) scale to assess the rash grade. The study of Chayahara et al. (2019) used two of the global skin assessment tools – the Investigator's Global Assessment (IGA) scale and the Multinational Association for Supportive Care in Cancer scale (MASSC), whereas two blinded dermatologists independently evaluated the endpoints from photographs. Additionally, one study used the Skin Toxicity Evaluation Protocol With Panitumumab (STEPP) study schema for the evaluation of the EGFRIr (Lacouture et al., 2010). On the other hand, one study failed to mention the grading system clearly, thus we hypothesised that they used the US National Cancer Institute catalogue of common toxicity criteria (NCI-CTC, version 4.0) (Ferrari et al., 2016). The reason for this hypothesis is because in the introduction of the study it says: "Among the many proposed criteria to grade the severity of cutaneous toxicity from EGFR inhibitors, the most commonly used are the NCI-CTC, version 4.0."

5. ANALYSIS OF THE FINDINGS

5.1 CATEGORY A - STUDIES USING VITAMIN K1 OR VITAMIN K3 CONTAINING CREAMS

Studies confirmed that Vitamin K is an EGFR activator which not only can rescue the skin reactions induced by cetuximab, but also enables direct action on skin for external use even with minimum absorption (Li et al., 2015; Ocvirk & Rebersek, 2008).

Vitamin K3 (menadione) is a stable and lipophilic molecule with a small molecular size, a synthetic pro-drug of vitamin K, and is suggested to be able to re-phosphorylate EGFR (Eriksen et al., 2017). Vitamin K3 is a potent phosphatase inhibitor and a potent EGFR activator and protector against erlotinib and cetuximab (Perez-Soler et al., 2011; Pinta et al., 2014).

At the time the study of Eriksen et al. (2017) was conducted, no commercial product with the exact required amount of vitamin K3 was available on the market, so the cream was manufactured at Glostrup Pharmacy in Denmark specifically for research purposes. The placebo cream consisted mainly of purified water (78.5%), sorbitol (7%), cetylanum (5%), paraffin liquid (5%) and 85% glycerol (4%). The vitamin K3 cream consisted of the ingredients of placebo cream along with 56.5 mg purified vitamin K3 per 100 mL placebo, corresponding to 1.5 mM/L. In this study the vitamin K3 concentration corresponds to 0.05% of menadione (Eriksen et al., 2017).

The study of Eriksen et al. included thirty patients (18 patients in the final analysis) who received cetuximab every second week plus chemotherapy. In each patient, vitamin K3 cream and placebo were applied twice daily on two separate areas either on the chest or back (application area set at 10x10cm). Each patient was their own control. The application of the vitamin-containing cream continued for up to 2 months. For some patients the cream was used in a prophylactic way from the start of the treatment while with other patients it was utilised as treatment when the rash appeared.

The mean number of rash spots that appeared was 4.9 for placebo cream area VS 5.1 for vitamin K3 cream area at baseline ($p = 0.9$), increased to 11.1 (placebo) VS 14.1 (vitamin K3) at 2 weeks ($p=0.5$) and 8.9 (placebo) VS 7.3(vitamin K3) at 6 weeks ($p=0.7$). At week 4, which was the primary endpoint, no difference at all was found, with results being 6.1 (placebo) VS 6.3 (vitamin K3). The study concluded that there was no benefit from the use of vitamin K3 for the patients who experienced EGFRIr due to cetuximab (Eriksen et al., 2017).

Vitamin K1 (also called phylloquinone, phytomenadione) is found in high amounts in green leafy vegetables. It is metabolized to vitamin K2 homologues (menaquinones), the active storage form in animals, via intermediate vitamin K3 (Hofheinz et al., 2018).

For the study of Li et al. (2015), vitamin K1 cream was manufactured at the Institute of Materia Medica, Chinese Academy of Medical Science. The main component was 0.1% Vitamin K1, with: (1) glycerin monostearate (ointment bases and stabilizer, making products smoothingly); (2) stearic acid (hydrophilic ointment bases); (3) liquid paraffin (adjusting the ointment consistency); (4) Vaseline (enhancing water absorption together with lanolin); (5) lanolin (with property close to the sebum, easy to penetrate the skin, suitable for drugs required to absorb); (6) sodium lauryl sulfate (anionic emulsifier); (7)

nipagin (common bacteriostatic agent in soft stalk); (8) triethanolamine (emulsifier, pH regulator); (9) distilled water (oil-in-water ointment diluent)(Li et al., 2015).

For the study of Pinta et al. (2014), Vigorskin cream was used. The cream contained 0.1% vitamin K1 (phytomenadione), urea, Triticum volgare germ oil, hydrolysed wheat protein, ceramides-1, -3, and -6 II, and phytosphingosine (Pinta et al., 2014).

In the study of Tomková et al., 2013 the cream was again manufactured for the purposes of the case series from phytomenadione (vitamin K1) solution containing 10 mg of phytomenadione (Hoechst-Biotika Ltd, Martin, Slovak Republic) in 1 mL, which was added to ambi-derman, a hydrophilic cream base, oil in water, to obtain the final concentration of 0.05% or 0.1% (Tomková et al., 2013).

The study of Li et al. (2015) included 60 patients with colorectal cancer that were divided into two groups: the experimental and control group (30 patients in each group). Patients in the experimental group applied vitamin K1 (0.1%) cream on their face, neck, chest, back and nails three times a day. The study found no statistically significant difference between the control and experimental group ($p= 0.642$). Additionally, no grade 4 rash cases occurred in any of the groups. More specifically, the occurrence rates of EGFRIr for Grades 0-3 in the experimental group were: 0%, 40%, 36.7%, and 23.3% respectively, while in the control group the rash for Grades 0-3 was: 0%, 36.7%, 33.3%, and 30% respectively. The occurrence rate of EGFRIr in Grade 2-3 for patients in the experimental group was smaller than in the control group (Li et al., 2015).

The study of Pinta et al. (2014) included 41 patients with metastatic colorectal cancer. The vitamin K1-containing cream was applied twice a day on the face and trunk on the first day of cetuximab provision. Data for the rash grade were recorded weekly by the investigators. The results regarding the occurrence rates of EGFRIr for this study were 15% for Grade 0, 45% for Grade 1, 25% for Grade 2, 15% for Grade 3, and 0% for Grade 4. The study concluded that there was a possible benefit of the vitamin K1 cream as prophylaxis from the cetuximab-induced rash in patients (Pinta et al., 2014).

The study of Tomková et al. (2013) included 20 patients with colorectal and head and neck cancer. The application of the cream on the face, chest and upper back was performed twice daily during the first month of cetuximab or panitumumab therapy. The initial application was performed in the morning before the first infusion of the

treatment. During the second month the application frequency was changed to once daily.

The beginning concentration of phytomenadione 0.05% was increased after 7 months to 0.1% for all patients that followed. The percentage of the patients with Grade 1 EGFRIr was 75%, while 25% had Grade 2 rash. This study concluded that topical pre-treatment with Vitamin K1 cream might become useful in EGFRI treatment-induced rash (Tomková et al., 2013).

5.2 CATEGORY B - STUDIES WITH DIFFERENT INTERVENTION METHODS

The study of Gobbo et al. (2012) used a diode laser K1200 by Eltech S.r.l. (Via Castagnole, 20/H– 31100 Treviso, number K-1200-00149) for the treatment of EGFRIr via the High-Level Laser Therapy (HLLT) method. The laser parameters used were: wavelength 970 nm, power 5.0 W, 10 J/cm2, duty cycle/ pulsed mode 50%, frequency 10-1,000 Hz, spot size diameter between 0.8 and 2.5 cm (Gobbo et al., 2012).

The study included four patients with metastatic colorectal cancer and two patients with head and neck cancer, all treated with cetuximab. For the purposes of the study, the patients were treated with two 8-minute consecutive sessions per day for 4 days of treatment. The two laser applications were provided with a 5-minute interval so the total duration of treatment was 21 minutes.

An evident decrease in the dimension of EGFRIr was recorded after the first two laser sessions for two patients, from Grade 2 to Grade 1, and after the third session for the remaining four individuals (again for Grade 2 to Grade 1). At the end of the treatment, all six patients showed complete healing of the EGFRIr and the study concluded there was a benefit from laser treatment.

Before HLLT treatment, four of the participating patients had been using topic compounds: (Aquacutis - emollient, vitamin K1, Hydracial™ Skin Vigor Cream and Fissan cream) on their skin lesions during the previous 10-12 months without clinical improvements. These compounds were prescribed to the patients by dermatologists, oncologists, and GPs without success, and all topical treatments were suspended before

the beginning of HLLT in order not to interfere with the laser therapy itself (Gobbo et al., 2012).

Polydatin (PD) is a glycosylated polyphenol (3,4′,5-trihydroxystilbene- 3-β-mono-D-glucoside, also known as piceid) with anti-inflammatory activity in human epidermal keratinocytes. It is a polyphenol extracted from the root stem of a traditional Chinese herb named Polygonum cuspidatum (Fuggetta et al.,2019).

The study of Fuggetta et al. (2019) included 34 patients in order to evaluate the effect of topical application of a moisturizer containing PD. One day before commencing the afatinib (a potent second generation irreversible ErbB family blocker that inhibits tyrosine kinase activity of EGFR and all relevant ErbB family dimmers), all patients were initiated on topical administration of a 1.5% PD-based cream twice a day, every day, until the end of afatinib treatment. The patients were monitored every 7 days for the first month and subsequently every twenty days or as needed. According to the study, the incidence of rash regarding all grades was 41.2% in total. For Grade 2 EGFRIr the percentage was 20.6%, while Grade 3 rash was not observed. Moreover, none of the patients discontinued therapy due to rash. In conclusion, this study indicated that a PD cream can reduce the incidence of Grade ≥2 in patients treated with afatinib.

Despite the fact that the study of Fugetta et al. (2019) mentions the small sample size as a large limitation, their results following the use of PD cream are equivalent to those of studies documenting benefit from tetracycline as prophylaxis from EGFRIr, a well-recognized therapeutic strategy. According to the author's knowledge of the present systematic review, the study of Fuggeta et al. was the only study that examined the effect of the PD cream treatment in patients treated with EGFRI.

For the management of EGFRIr, the study of Jatoi et al. (2010) used sunscreen provided by Pharmaceutical Specialties Incorporated (Rochester, MN), which included 7.5% titanium dioxide and 7.5% zinc oxide.

The study included fifty-four patients who received sunscreen with an SPF 60 (sun protection factor) while fifty-six patients received a placebo (Jatoi et al., 2010). The placebo formulation was identical to the sunscreen but lacked titanium dioxide and zinc oxide. The sunscreen or placebo were applied to the face, trunk, and extremities twice a day. During the 4-week intervention, ranging grades of rash occurred in 78% and 80%

of the patients using sunscreen and placebo, respectively (p=0.36). These results illustrated no significant difference in the EGFRIr between the two groups. However, Grade 2 rash recorded-percentage for the two study arms differed: 33% for patients using sunscreen and 52% for patients using a placebo (p=0.06). At eight weeks of intervention all grades rash percentages were 78% and 75% for the sunscreen arm and placebo arm, respectively (p=0.82). Here, Grade 2 EGFRIr percentage was recorded at 39% for sunscreen-using patients and at 52% for placebo-using patients (p=0.19). The above results were extracted from the physician-reported data and concluded that there was no benefit from the use of sunscreen to the prevention of EGFRI treatment-induced rash (Jatoi et al., 2010).

The study of Chayahara et al. (2019) evaluated the use of Adapalene gel versus a placebo as prophylaxis for EGFRIr. Adapalene gel 0.1% (trade name: Differin Gel 0.1%) is a topical retinoid and is used to treat acne vulgaris. In the study, the patients were randomly assigned to once-daily Adapalene gel 0.1% application on one side of the face and with a placebo on the other side. Additionally, all participants applied moisturizer to both sides of their face twice daily, and received oral antibiotic (minocycline 100mg) daily. The concurrent treatments with moisturizer and antibiotic were initiated on the day of the initiation of EGFR treatment. The results showed that areas treated with Adapalene gel had a greater lesion count than the placebo after twenty-eight days of use, although the difference was not statistically significant (mean, 12.6 vs. 9.8, p = .12). Also, no significant differences were observed in the complete control rate (CCR) of rash (54% vs. 50%) or the IGA scale (mean grade, 1.9 vs. 1.7). All in all, this study indicated that Adapalene gel is not recommended as a prophylaxis for rash due to EGFRI treatment (Chayahara et al., 2019).

The report of Gürbüz et al. (2020) presented the case of a 60-year-old male with colon adenocarcinoma with peritoneal, liver, lung and bone metastases. The patient received cetuximab plus chemotherapy and developed Grade 3 rash, despite prophylactic vitamin K1 0.1% cream provision, topical corticosteroid and doxycycline 100mg orally. Due to persisting rash, the patient expressed the wish to stop rash-related treatment and use topical aloe vera instead. Thus, he used topical aloe vera extract three times daily for two weeks. Aloe vera is an extract from a tropical cactus called Aloe and its leaf extract has anti-inflammatory, antioxidant, anticancer and immunomodulatory effects. In the

study, the patient used aloe vera for the treatment. The patient's lesions regressed significantly at the end of the second week to Grade 1, while after three weeks of use the lesions resolved completely. Skin toxicity did not relapse with the next doses of cetuximab. Based on this study, topical application of aloe vera may be used in the management of cetuximab-related EGFRIr without any side effects (Gürbüz et al., 2020).

The research group of Ferrari et al. (2016) studied the case of a patient diagnosed with metastatic colorectal cancer who received chemotherapy plus cetuximab. The patient developed EGFRIr and was managed with hydrating and moisturizing cream after the second cycle of treatment. Prior to the use of this cream, the patient had used vitamin K cream topically and oral minocycline, but developed grade 2 dermatitis. The rash disappeared completely after a twice-daily application of the hydrating and moisturizing cream that contained paraffin, silicone compounds, and macrogol. More specifically, the cream consisted of a mixture of glycerol, white soft and liquid paraffin, stearic acid, siloxane, silicone oil, macrogol 600, trolamin, propyl-hydroxybenzoate, and purified water (Dexeryl; Pierre Fabre, Paris, France). After the second day of administration of the hydrating and moisturizing cream, the skin became more hydrated and soft, the density of the EGFRIr was reduced, and the rash disappeared in about 2 weeks. Based on its findings, this study recommends the use of this hydrating and moisturizing cream as possible treatment for cetuximab- related rash (Ferrari et al., 2016).

The study of Kim et al. (2020) evaluated the efficacy of EGF ointment towards EGFRIr. Participating patients were randomly separated into three arms based on provided treatment: group 1 corresponded to the placebo arm, group 2 corresponded to use of 1 ppm of EGF ointment, and group 3 corresponded to use of 20 ppm of EGF ointment. Patients from all groups applied ointment to their skin lesions twice daily. Rash and pruritus were the main side effects of the participants in this study. There were no significant differences in baseline NCI-CTCAE ratings of ERSEs among the three arms. The response rates were measured 2 weeks after the treatment and every 4 weeks thereafter and indicated 44.4% response in group 1, 61.5% in group 2, and 77.8% in group 3($p = .042$). In arm 3 RRs were significantly different between arm 1 and the combination of arms 2 and 3 ($p = .028$). Fourteen of the participants (17.5%) received concomitant oral medication for the management of the rash and the pruritus, but this

did not affect the results between the three study groups. The study concluded that EGF ointment was effective in treating EGFRI treatment related rash and pruritus and this compound had a better effect at a higher dose (Kim et al., 2020).

The study of Hwang et al. (2016) also examined the efficacy of EGF ointment (Daewoong Pharmaceuticals Co. Ltd.). The ointment utilised contained 1 ppm of nepidermin and was evenly applied to the skin lesions twice daily for patients with Grade 2 lesions or greater. The results of the study were divided into two categories: Category 1 were lesions greater or equal to Grade 2 downgraded to Grade 1 or less, and Category 2, Grade 3 or 4 lesions were downgraded to Grade 2 and sustained for at least two weeks. For cases where the lesions did not improve after eight weeks of EGF ointment, the treatment was stopped and classified as "no effect." According to this study, the EGF ointment offered effective management up to a point for EGFR related lesions for 69.2 % of the participants, while ten participants showed no response to the ointment. Conclusively, this study showed that EGF ointment is effective for the adverse events due to EGFR treatment (Hwang et al., 2016).

In the study of Lacouture et al. (2010), the patients were divided into pre-emptive skin treatment and reactive skin treatment. Pre-emptive skin treatment started one day before the first dose of EGFRI treatment and continued for one to six weeks, whereas the reactive skin treatment was prescribed when skin reactions appeared. Pre-emptive skin treatment included skin moisturizer (face, hands, feet, neck, back, and chest) daily in the morning; sunscreen (SPF 15) applied to exposed skin areas before going outside; topical 1% hydrocortisone cream (steroid) to face, hands, feet, neck, back, and chest at bedtime; and doxycycline (antibiotic) 100 mg twice per day. On the other hand, the reactive skin treatment regimen consisted of any treatments the investigator considered necessary for the management of the EGFRI treatment-induced skin reactions. The results in the study of Lacouture et al. (2010) illustrated that in the pre-emptive group, the incidence of grade 2 skin toxicities was 29% versus 62% in the reactive group. Grade 2 skin toxicities of interest were reported in 23% of patients in the pre-emptive group, whereas in the reactive group the percentage was 40%, and grade 3 skin toxicities of interest were 6% in the pre-emptive group, and 21% of patients in the reactive groups.

A large gap exists regarding the management strategies for EGFRI reactions (Lowe et al., 2019). This systematic review investigates the effectiveness of different interventions for the prevention and treatment of EGFRIr, excluding the use of antibiotics and cortisone products. We choose to exclude the aforementioned as several studies have been conducted concerning the effectiveness of the treatment with antibiotics or steroids in EGFRIr which contributed to an improved statistical significance.

6.1 ACCEPTANCE FOR STUDIES

This systematic review systemically excluded studies which evaluated the impact of EGFRIr using antibiotics or steroid treatment. However, it is worth noting that two of the studies included in this systematic review used antibiotic or steroid treatment (Eriksen et al., 2017; Pinta et al., 2014). However, the results in Eriksen's study were independent from the use of systemic tetracycline and thus this study was not excluded from this systematic review. In addition, from the study of Pinta et al. 2014 we preserved solely the results for Grade 0 and Grade 1 rash because the study initiated patients on antibiotic or steroid treatment when they experienced Grade 2 and Grade 3 EGFRIr. The number of cases excluded from our review was small, as only 6 patients out of 41 advanced to Grade 3 rash and required minocycline and corticosteroids.

The study of Jatoi et al. (2010) examining the effectiveness of sunscreen use against EGFRIr made adjustments for sun intensity by gender, performance status score, geographical zone, season, photosensitivity medications and the treatment with corticosteroid products. This adjustment was a big asset for the study as the authors took into account the main factors that could affect the results in the two study arms. Despite the adjustments, no statistically significant difference in EGFRI treatment-induced rash development was noticed.

Despite the fact that the study of Kim et al. (2020) does not differentiate between the two EGFRI related adverse events, rash and pruritus, we have included it in our study as it describes an effective compound against the EGFRIr as a side effect.

The study of Hwang et al. (2016) was not excluded from this systematic review regardless of the fact that participants received antihistamines and antibiotics (6 patients: Ucerax, Azeptin antihistamine, 4 patients: minocycline oral antibiotic, 3 patients: both). This is due to the fact that there was no difference in the effectiveness of the EGF ointment in the patients who received the co-medication and those who did not.

In the study of Chayahara et al. (2019), all patients received an oral antibiotic and had topical moisturizer co-applied to both sides of the face, along with the use of a placebo and Adapalene gel. Thus, since all participants received the same intervention, the end result in regards to the effectiveness of the EGFRIr treatment was not differently affected.

Regarding the results from the clinical trial of Lacouture et al. (2010), the authors of this systematic review were initially reluctant to include them for two reasons: firstly, the Lacouture study was focused on comparing the importance of pre-emptive versus reactive treatments, while our work examines the universal effectiveness of treatment options against EGFRI-associated rash. Secondly, in the study of Lacouture et al. there were differences in the interventions used between the two groups; for patients undergoing reactive management the regimen consisted of any type of treatment that was considered necessary, while for patients undergoing preventive management all received moisturizer, sunscreen, steroids and antibiotics.

In the end, the study was included in our review for its results regarding solely the interventions used in the pre-emptive group (moisturizer, sunscreen).

6.2 COMPARING THE FINDINGS

Some of the studies in this systematic review can be compared with other studies which were not included in this systematic review.

A study which is comparable with the study of Eriksen et al. (2017) is an ongoing study with identifier number: NCT01393821 (as found on ClinicalTrials.gov) of which the results have not yet been published (Active, not recruiting).

The study of Li et al. (2015) investigated the effect of Vitamin K1 in a cream with 0.1% concentration of the substance, as the effects of such treatment were not examined and listed in Chinese patients by the time the study was conducted (Li et al., 2015). At the endpoint, the study found no benefit from the use of Vitamin K1 cream and this differs from other European studies that indicated a cumulative benefit from such treatment (Pinta et al., 2014; Tomková et al., 2013).

In addition, the results in the study of Tomková et al. (2013) were comparable with the results of the study of Ocvirk et al. (2008), which was the first study that demonstrated the efficacy of Vitamin K1 cream in the treatment of rash due to EGFRI treatment (Ocvirk & Rebersek, 2008). Data from the study of Ocvirk et al. illustrated a reduction of rash with Vitamin K1, 0.1% cream from grade 3 to Grade 2 after 1.2 weeks and from Grade 2 to Grade 1 after 2.3 weeks. The study of Tomková et al. concluded that topical pre-treatment with Vitamin K1 cream is useful in EGFRI treatment-induced rash.

As in the study of Chayahara et al. (2019) that is described in our systematic review, a similar study (Scope et al., 2007) examined the effectiveness of another retinoid as prophylaxis for EGFRIr. This study utilized tazarotene 0.05% cream for the management of rash and its use was eventually interrupted as it caused local irritation to participants (Scope et al., 2007). Conclusively, retinoids have proven ineffective and rather harmful for the management of EGFRIr.

Finally, both the study of Kim et al. (2020) and the study of Hwang et al. (2016) examined the effect of the epidermal growth factor ointment towards EGFRIr. Both studies concluded that the EGF ointment seems to be effective for the management of EGFRI treatment related rash (Hwang et al., 2016; Kim et al., 2020).

7. LIMITATIONS

This systematic review has both strengths and limitations. According to the authors' knowledge, there is a gap in relation to reviewing treatment interventions, except antibiotics and steroids, utilized for the prevention and/or treatment for EGFRIr.

This systematic review highlighted the necessity of conducted studies such as clinical trials, since the majority of the research studies based on the EGFRIr are expert opinions and reviews. The systematic review and meta-analysis study of Ocvirk et al. (2013) also expressed the above concern.

The studies included in this review show some heterogeneity: some studies use different grading systems in order to evaluate the severity of EGFRIr. For example, the study of Eriksen et al. (2017) assessed the EGFRIr using the CTCAE v. 4.0, whereas the study of Li et al. (2015) evaluated it with CTCAE v.3.0. Furthermore, this systematic review included studies with patients suffering from different primary cancers, as opposed to the recent systematic review of Lacouture et al. (2018) that included studies only with metastatic colorectal cancer patients. Moreover, the studies included in this review were published only in English, meaning that this might affect our findings.

Finally, the studies included in this review are studies with a different study design like clinical trials and case series, as opposed to the systematic review of Ocvirk et al. (2013), which included only clinical trials studies. The homogeneity in the studies of the review of Ocvirk et al. allowed the authors to proceed with a meta-analyisis in contrast to the present systematic review. In addition, this study did not proceed with a meta-analysis, as the studies included were clinically diverse, there was a mix of comparisons of different treatments and the range of tools used to investigate the EGFRIr would probably have made the meta-analysis meaningless.

8. CONCLUSION

The EGFRIr is an important side effect that can cause dose reduction or even discontinuation of targeted treatment (EGFRI) for patients that sometimes cannot afford this drawback.

This study investigated the effectiveness of different approaches for the prevention and treatment of rash due to EGFRI therapy, as opposed to the use of antibiotics and/ or steroid treatment as a primary intervention.

This review utilized studies from a variety of fields (clinical, academic/research) that evaluated the effectiveness of additional treatment options apart from classic treatments for EGFR-associated rash in the last decade. The authors of this review concluded that the use of some of the proposed interventions can yield a positive effect towards the management of EGFRIr, while others may prove ineffective and rather harmful for the patients. Specifically, the use of treatment with sunscreen alone and Adapalene gel is not encouraged by the studies reviewed, while the authors of this review cannot draw a conclusion regarding the use of vitamin K as the efficacy of the vitamin for the management of EGFRIr is controversial. On the other hand, the laser treatment, Polydatin-containing moisturizer, topical aloe vera, topical hydration, pre-emptive skin treatment routine with moisturizer and sunscreen and the epidermal growth factor ointment compounds were found to produce a positive effect for EGFRIr management and can be listed as effective interventions.

The authors of this review concluded that more studies are needed in order to provide more consistent evidence in this research field.

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CHARACTERISTICS OF THE STUDIES REVIEWED

CATEGORY A- VITAMIN K1 / VITAMIN K3

AUTHORS, YEAR	AIM	DESIGN	INSTRUMENTS	SAMPLE SIZE/ INCLUSION CRITERIA	ANALYSIS METHOD	OUTCOMES
(Eriksen et al., 2017)	To investigate the effect of a vitamin K3 cream on cetuximab - rash. Secondary aim: to investigate any possible side effects of	A randomized, double-blinded placebo-controlled trial.	CTCAE v. 4.0	n = 30 (n=18 for final analysis) Patients with metastatic cancer (rectum, colon, pancreas, esophagus, head & neck, unknown primary) receiving cetuximab 500 mg/m2 every second week plus chemotherapy.	Bland-Altman plots and linear regression, Descriptive statistics, Changes in the number of follicular eruptions- t test after	The mean number of elements: At baseline: 4.9 (placebo) versus 5.1 (vitamin K3) (p =0.9). Week 2: 11.1(placebo) versus 14.1 (vitamin K3) at (p=0.5).

	vitamin K3 cream.			At least 18 years old. No other diseases (including chronic skin disease) No concomitant treatment with vitamin K. No hypersensitivity to vitamin K3.	testing for normal distribution Using QQ-plots.	Week 6: 8.9 (placebo) versus 7.3 (vitaminK3) (p=0.7). Week 4: 6.1 (placebo) versus 6.3 (vitamin K3).
(Tomková et al., 2013)	To assess the possible effect of topical Vitamin K1 pre-treatment in diminishing the extent and severity of	Case series	CTCAE v.4.0	n=20 Patients with colorectal cancer or head and neck cancer. Treated with panitumumab or cetuximab	/	75%: grade I 25%: grade II

	acne-like follicular rash associated with epidermal growth factor receptor inhibitor therapy					
(Li et al., 2015)	To investigate the impact of 0.1% vitamin K1 cream on cetuximab-skin toxicity	Case-control study.	NCT-CTC v 3.0	n= 60 Patients with colorectal cancer. Patients taking cetuximab plus F0LF0X 4/14 days and cetuximab plus FOLFIRI/ 14 days. Exclusion criteria: Patients with skin disease and diabetes.	Wilcoxon rank-sum test	No grade 4 in both groups. There was no statistically significant difference between the two groups for the rash (P= 0. 642).

(Pinta et al., 2014)	Evaluate the prophylactic use of Vitamin K1 cream (Vigorskin) in patients taking Cetuximab.	Pilot Clinical Trial.	CTCAE v 3.0	n= 41 Patients with Metastatic Colorectal Cancer received cetuximab with or without other chemotherapy.	/	No grade 4 was reported. Grade 0 – 15% Grade 1 – 45%, Grade 2 – 25% Grade 3- 15%

CATEGORY B - STUDIES WITH DIFFERENT INTERVENTION METHOD

AUTHORS, YEAR	AIM	DESIGN	INSTRUMENTS	SAMPLE SIZE/ INCLUSION CRITERIA	ANALYSIS METHOD	OUTCOMES
(Gobbo et al., 2012)	Evaluate the effectiveness of high-level laser therapy in reducing the severity of facial acneiform rash induced by cetuximab, an epidermal	Case series	Visual analogue scale (VAS) and Cetuximab-Related Toxicity scale (CTR)	n=6 Patients with metastatic colorectal cancer, head and neck cancer showing cetuximab- Induced rash.	/	All the patients start with grade II rash, after the second laser application two patients had grade I rash and after the end of the laser application all the patients had grade I rash.

	growth factor receptor inhibitors.					
(Fuggetta et al., 2019)	Evaluate the effect of topical application of a moisturizer containing PD (Polydatin) to prevent skin rash due to EFGR therapy.	Pilot clinical trial.	CICTCAE v 3.0	N=34 patients. Patients with mutated non-small cell lung cancer (NSCLC) stage IV treated with afatinib 40mg/die. Patients (age≥18years). ECOG performance status of 0 to 2. Exclusion criteria: Poor patient compliance, allergic/sensitive to PD, concomitant skin diseases.	/	The incidence of skin rash (all grades) was 41.2% and grade 2 rash was 20.6%, and grade 3 rash was not observed. None of the patients discontinued therapy due to rash.
(Jatoi et al., 2010)	Determine whether	Placebo-controlled,	CTCAE v 3.0 Skindex-16	n=110	Fisher exact test, logistic regression.	During the 4-week intervention rash for any

	sunscreen prevents or mitigates rashes.	double-blinded Trial.		(54 patients received sunscreen, and 56 received placebo) Patients >18 years, a cancer diagnosis, an EGFR inhibitor started or about to be started by the patient within 3 days of randomization, patient appearing capable of applying sunscreen as instructed and of completing questionnaires independently or with help.		grade occurred in 78% and 80% for the sunscreen and the placebo respectively (p=0.36). No significant difference in rash between the two groups

Chayahara et al., 2019	To evaluate the prophylactic efficacy of adapalene. Primary endpoint: The difference in total facial lesion count of acne-like rash at 4 weeks. Secondary endpoints: 1. Complete control rate (CCR) of acne-like rash	Randomized, placebo-controlled, evaluator-blinded, left-right comparative trial.	CTCAE v 4.0, IGA scale, Multinational Association For Supportive Care in Cancer scale (MASSC)	n=36 patients were enrolled (of whom 26 were evaluable) Patients with head and neck cancers, non-small cell lung cancer, and colorectal cancer, ≥20 years of age, ECOG performance status of 0–2, Adequate organ function, Receive treatment with cetuximab, panitumumab, gefitinib, erlotinib, or afatinib.	Investigator's Analysis: Inactive because results did not meet primary endpoint	No statistically significant differences in any of the efficacy endpoints between adapalene treated and placebo-treated sides. On the IGA scale, 15 of 26 patients scored equally between the placebo and adapalene sides, and 8 of the remaining 11 patients had a higher score on the adapalene side VS placebo side. On the MASSC scale,

	(≤5 facial lesions) 2. Global skin assessment (Investigator's Global Assessment [IGA] scale, grade 0–4) at 4 weeks.					16 of 26 patients had the same score for both sides, 8 of the remaining 10 patients had a greater score on the adapalene side VS placebo side. The overall incidence for 4 weeks of therapy was: 51% (Adapalene) VS 48% (placebo)

Gürbüz et al., 2020	Presented a metastatic colon cancer case which developed acneiform rash under cetuximab treatment and was managed by aloe vera extract.	Case Report	NCCTCAE v 4.0	A 60-year-old male patient with malignant polypoid lesions in the sigmoid colon, and pathological examination revealed colonic adenocarcinoma. The patient had peritonitis carcinomatosa, liver, lung and bone metastases.	/	Cetuximab-related severe acneiform rash was effectively treated by topical aloe vera.
Ferrari et al., 2016	To tested a compound of a mixture of	Case Report	/	A 50-year-old woman with metastatic colorectal cancer.	/	The rash disappeared in about 2 weeks.

	paraffin, silicone and macrogol in a patient with rash treated with cetuximab.					Not observe any reactivation of the skin rash in the following weeks with cetuximab
Kim et al., 2020	To evaluate the efficacy of EGF ointment for EGFR inhibitor-related skin adverse events (ERSEs) Primary endpoint:	Placebo-controlled, double-blind, multicenter, pilot phase III trial	NCI-CTCAE v 4.0 Skindex-16 questionnaire	N=90 (n=80 for the final analysis) Between June 2015 and October 2017 Inclusion criteria: Patients with non-small cell lung cancer, pancreatic cancer, or colorectal cancer who are treated with gefitinib,	Pearson's chi-square test Cochran Armitage trend test Chi-squared test. Fisher's exact test Kruskal-Wallis test or Mann-Whitney U test	Acneiform rash and pruritus were the main ERSEs Grade 3 ERSEs were observed in 10% patients. There were no significant differences in baseline NCI-CTCAE ratings of ERSEs among the three arms.

	response rate (RR) of EGF ointment: (a) reduction of ERSEs from grade ≥2 to grade ≤ 1 or (b) grade ≥3 ERSEs downgrading to grade 2 and lasting for at least 2 weeks. Secondary endpoints: QoL and safety			erlotinib, afatinib, or cetuximab 11 institutions in South Korea, age ≥20 years, ECOG ≤2, an estimated life expectancy of at least 3 months. Exclusion Criteria: Dermatologic treatment for skin lesions within 4 weeks, prior organ transplantation,	SAS statistical software For continuous variables, summary statistics included number, mean, SD, median, and range	RR was 44.4% (arm 1), 61.5% (arm 2), and 77.8% (arm 3) (p = .042). RRs were significantly different between arm 1 and the combination of arms 2 and 3 (p = .028). There was a significant linear correlation between EGF concentration and response (p = .012). The RR was significantly higher in arm 3 than that in arm 1 (p = .049). In patients treated with

				history of hypersensitivity to EGF ointment or chemotherapeutic agents patients receiving immunosuppressive agents.		EGFR TKIs, RR was 50.0% in arm 1, 72.7% in arm 2, and 78.6% in arm 3 (p = .209) There were no significant concomitant medication differences among study arms (p = .662). There was no influence on response of EGF ointment by concomitant medication (p = .797) In patients not receiving concomitant oral medication

						for the management of ERSEs, RR in arm 2 (60.9%) or arm 3 (77.3%) was higher than that in arm 1 (42.9%, p = .070) although it was not significantly higher.
Hwang et al., 2016	Evaluated the effect of epidermal growth factor (EGF) ointment on erlotinib-related skin effects (ERSEs).	Open-label, non-comparative multicenter, phase II trial.	NCI-CTCAE v 3.0 Skindex-16	N=52 (n= 46 patients for final assessment) Patients from 7 institutes in Korea. Between October 2012 and November 2013 Inclusion criteria: Patients with NSCLC treated with erlotinib alone	$\chi 2$ tests or Fisher's exact tests. SPSS software v. 20.0	EGF ointment was effective in 69.2 % of the patients. No statistically significant differences in the effectiveness of the EGF ointment by gender (p = 0.465), age (p = 0.547), tumor type

	The effectiveness of the ointment was defined as follows: (1) grade 2, 3, or 4 ERSEs downgraded to ≤grade 1 or (2) grade 3 or 4 ERSEs downgraded to grade 2 and persisted for at least 2 weeks.			and PC treated with gemcitabine and erlotinib in combination with chemotherapy. Sufficient liver, kidney, and bone marrow functions to undergo treatment. All the patients had grade ≥2 ERSEs.		(p = 0.085), erlotinib dosage (p = 0.117), and number of prior chemotherapy sessions (p = 0.547) Rating of rash and itching improved from 2.02 ± 0.83 to 1.13 ± 0.89 and 1.52 ± 0.84 to 0.67 ± 0.90, respectively (p < 0.001)

Lacouture et al., 2010	Examine differences between pre-emptive and reactive skin treatment for specific skin toxicities in patients with mCRC for any EGFR inhibitor. Primary objective: 1.to estimate the difference in incidence of specific grade 2	Phase II, multicenter, open-label, randomized clinical trial	Medical Dictionary for Regulatory Activities (MedDRA) version 9.0. NCICTCAE v3.0 Modified CTCAE v. 3.0. for panitumumab-related skin toxicities.	N=95 patients Patients with metastatic adenocarcinoma of the colon or rectum, disease progression or unacceptable toxicity with first-line treatment containing 5-FU and oxaliplatin, with or without bevacizumab, age> 18 years old, ECOG 0 or 1. Adequate hematologic, renal, metabolic, and hepatic function, no prior irinotecan treatment or anti-EGFR	A logistic regression model, Wald method, Kaplan-Meier (KM) plots, Cox regression models	In the pre-emptive group, the incidence of grade 2 skin toxicities were 29% vs 62% in the reactive group. Grade 2 skin toxicities of interest were reported in 23% of patients in the pre-emptive group VS 40% of patients in the reactive group. Grade 3 skin toxicities of interest, with 6% and 21%of patients in the pre-emptive and reactive groups experiencing grade 3 events, respectively

	skin toxicities between patients in the pre-emptive and reactive skin treatment groups during the 6-week skin treatment period. Secondary objectives: 1. incidence rates of skin toxicities of any type during the 6-week skin		Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) DLQI	therapy or vaccine treatment for mCRC, no incidence of pulmonary embolism, deep vein thrombosis, or any other significant thromboembolic event within 8 weeks before random assignment.		Median time to first occurrence of specific grade 2 skin toxicities of interest was not reached in the pre-emptive group and was 2.1 weeks in the reactive group

	treatment period 2.efficacy and safety of panitumumab given concomitantly with second-line irinotecan.					

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16.7 Appendix 9: A pilot randomized controlled study – Publication

16.7.1 A pilot randomized controlled study - Approval form for publication

The information below relates to the article's final approval by the European Journal of Oncology Nursing on 10/08/2022:

“Ref : Ms. No. YEJON-D-22-00056R3

A pilot randomized controlled study on the effects of an educational training program on skin reactions induced by chemotherapies, Epidermal Growth Factor Inhibitors (EGFRI) treatments, and immunotherapies.

Dear Mrs. ELENI,

I am glad to inform you that your paper has been accepted for publication in the European Journal of Oncology Nursing.

Your accepted manuscript will now be transferred to our production department and work will begin on creation of the proof. If we need any additional information to create the proof, we will let you know. If not, you will be contacted again in the next few days with a request to approve the proof and to complete a number of online forms that are required for publication.

We are aiming to publish your paper in about 6-9 months, although this is not a guarantee and will depend on a number of editorial factors. Nevertheless, the paper will be published online in about 2 weeks, after proof corrections are received.

Congratulations on your publication. We appreciate and value your contribution to European Journal of Oncology Nursing. We regularly invite authors of recently published manuscript to participate in the peer review process. If you were not already part of the journal's reviewer pool, you have now been added to it. We look forward to your continued participation in our journal, and we hope you will consider us again for future submissions.

Yours sincerely,

Alexander Molassiotis, RN, PhD

Editor-in-Chief

European Journal of Oncology Nursing”

16.7.2 A pilot clinical randomized control study – The published article

A pilot randomized controlled study on the effects of an educational training program on skin reactions induced by chemotherapies, Epidermal Growth Factor Inhibitors (EGFRI) treatments, and immunotherapies.

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Abstract

Purpose: The aim of the present trial was to evaluate the effectiveness of an educational program for cancer patients who developed pruritus, rash or photosensitivity induced by their provided treatment plan of chemotherapy, Epidermal Growth Factor Inhibitors (EGFRI) treatments, or immunotherapy.

Method: This study is a pilot randomized controlled study. The patients in the experimental pool were assigned to attend the educational program once weekly, for a total of 4 consecutive weeks. Patients in the control group did not receive the specific information regarding the educational program. However, the usual information was provided to them, as with any cancer patient who initiates chemotherapy, immunotherapy or EGFRI treatment. Each participant's induction day to the program (symptoms initiation) was considered part of week 0, while participants were divided into two clusters, the control group and the intervention group. For the Primary endpoint of this study repeated measurements were taken weekly regarding the grade of skin

reaction while for the Secondary endpoint and the patients score as per the 36-Item Short Form Survey questionnaire (SF-36) was recorded. Additionally, details regarding possible dose reduction, emergency admissions or end of treatment were noted since week 1. The Dermatology Life Quality Index (DLQI) questionnaire measurements were also initiated during the second week of the program and were part of the Secondary endpoint.

Results: This pilot trial was conducted between 01/2019 and 12/2020 and included 40 patients undertaking chemotherapy, EGFRI or immunotherapy treatment. As per the weekly measurements, the grades of rash, pruritus or photosensitivity, indicating the spread and severity of the reaction, showed a statistically significant improvement in the intervention group compared to the control (Walds X2 = 19,25, p = 0.004). The retrieved data from the SF-36 questionnaire, showed that patients in the intervention group presented higher functional health and wellbeing status, compared to the control group, although the results did not indicate a significant interaction between Group and Time over the weekly measurements, for all the questionnaire parameters. As per the results of the DLQI questionnaire, the effect size difference between control and intervention groups was higher at week 3 (d= 0.44) while at week 1, the same patients presented 66% reduction of risk to require emergency admission and 50% reduction of risk to require dose reduction, compared to the control group.

Conclusions: The results of this trial provide preliminary evidence on the effectiveness of the provided educational program. Further validation of the effectiveness of the educational program in a full – powered study and over longer periods of time will be required.

Keywords: rash, photosensitivity, pruritus, educational, chemotherapy, EGFRI, immunotherapy

1. Introduction

Chemotherapies, EGFRI treatments and immunotherapies, intended to treat cancer, can often cause damage to the skin and its appendages. Such skin reactions may discontinue patient's therapy protocol and affect their quality of life (QoL), causing this way a negative impact to their cancer treatment and progression-free survival (Lacouture and Sibaud, 2018).

Pruritus, rash and photosensitivity are the most frequent skin reactions observed due to cancer treatments. Pruritus is a disorder characterized by an intense itching sensation and it is most commonly described to involve the scalp, head, neck, and acral areas. Its severity is characterized by three grades (Grade 1, Grade 2, Grade 3) according to the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Rash acneiform, according to the CTCAE v5.0, is a disorder characterized by eruption of papules and pustules, typically appearing on the face, scalp, upper chest and back. It is divided into 5 categories (Grades 1 to 5) depending also on the severity. Finally, the term photosensitivity describes the clinically recognized sunlight-induced dermatitis, characterized by cutaneous eruptions typically localized on sun-exposed areas such as the cheeks, nose, forehead, posterior nuchal area, V area of neck, dorsal of hands, extensor surface of forearms, and lower legs (Lembo et al., 2020).

Pruritus is among the most prevalent adverse skin reactions induced by immunotherapies. According to Sibaud's study, all-grades pruritus incidence ranges from 13 to 20% with nivolumab and pembrolizumab treatment. The incidence is even more frequent with ipilimumab when used as monotherapy or in combination (Sibaud, 2017). The systematic review and meta-analysis of Ensslin et al. (2013) that examined 17,368 patients from 141 clinical trials, treated with single agent targeted therapies indicated that the incidence of all-grade pruritus ranged between 3.0% (95% CI: 1.1%−7.8%) and 30.7% (95% CI: 15.9%−51.0%). The same study evaluated 15,927 patients from 132 clinical trials, treated with single agent targeted therapies for Grade 3 pruritus. The data are derived from these studies showed that the incidence of high-grade pruritus ranged between 0.5% (95% CI: 0.2%−1.5%) and 1.8% (95% CI: 1.5%−2.3%). The overall incidence of high-grade pruritus for all patients was 1.4% (95% CI: 1.2%−1.6%) (Ensslin et al., 2013).

Rashes typically develop within the first two weeks following the initiation of EGFRI treatment and are observed in 50 - 100% of the patients undergoing this type of therapy (Fabbrocini et al., 2015). According to Fabbrocini et al. (2015), the incidence of rash in patients receiving EGFRI treatment with gefitinib, ranges from 24% - 62%, while for patients receiving erlotinib the incidence rate rises to 49% - 67% and escalates to 75% - 95% for patients under cetuximab therapy. The percentage of patients that require discontinuation or delay in treatments due to EGFRI treatment-induced rash ranges between 32% - 76% (Fabbrocini et al., 2015).

Photosensitivity is one of the most reported adverse skin reactions related to BRAF inhibitor (BRAFi) therapies, while treatments with fluoroquinolones (5-FU) have also been reported to induce the same reaction (Lembo et al., 2020). The photosensitivity skin reactions range from 22.2% to 66.7% among treated patients, depending on their treatment type, and occur more frequently during the summer time. According to Lugović-Mihić et al. (2017), photosensitivity adverse skin reaction-inducing drugs involve anticancer therapies such as BRAF kinase inhibitors (vemurafenib, dabrafenib) and EGFR inhibitors (Lugović-Mihić et al., 2017). Paclitaxel, nab-paclitaxel (Abraxane) and docetaxel have also been associated with photosensitivity. A case report study by Beutler and Cohen (2015) presented a 69-year-old female, cancer patient with a rash on the extensor surfaces of her upper extremities, which was treated with carboplatin and pemetrexed as well as gemcitabine and vinorelbine. In this study, a diagnosis of nab-paclitaxel-associated photosensitivity skin reaction was also recognized (Beutler and Cohen, 2015).

These skin reactions can cause discomfort and pain to patients and lead to a treatment dose reduction or even treatment discontinuation, in severe cases (Lacouture et al., 2011). Therefore, appropriate management for these skin reactions is necessary in order to allow sufficient drug administration, maximize the treatment benefit and improve health-related quality of life (QoL).

1.1 Management of pruritus, rash and photosensitivity

According to Song et al. (2018), pruritus management includes: determining the causative factors, treating original diseases, avoiding all irritating factors, preventing

skin dryness, and keeping skin moisturized. In addition, medication with topical application such as low PH cleansing agents and moisturizers, coolants, local anesthetics, topical antihistamines, topical anti-inflammatory agents and corticosteroids are often used for the relief of pruritus (Song et al., 2018). The study of Vallely et al. (2019) suggested that pre-emptive monitoring of pruritus symptoms leads to better patient experience and may even lead to increased patient survival.

Skin rash is a common adverse event noted among cancer patients treated with EGFR inhibitors. Sun protection products, topical or systemic corticosteroids (creams or ointments), antibiotics like tetracycline, doxycycline or minocycline, topical retinoids like topical tazarotene and Vitamin K (Vitamin K1 cream or Vitamin K3 lotion) were some suggested measurements for chemotherapy-caused rash as per the study of Kozuki (2016).

Finally, according to a study conducted by Blakely et al. (2019), if a photosensitivity skin reaction occurs, it may become necessary to discontinue the provided medical treatment and manage the side effects with corticosteroid products. Physicians should be aware of the photosensitivity skin reaction potential risk induced by medications and should advise cancer patients regarding sun avoidance and sun protection (Blakely et al., 2019). The most serious adverse effect that may occur during the management of photosensitivity skin reaction is discontinuation of the chemotherapy drug (Blakely et al., 2019). Unfortunately, discontinuation of chemotherapy cannot be applied to all patient cases. Thus, when this is the case, secondary prevention measures such as sun avoidance, especially during peak daylight hours, and the use of sun protective clothing and sunscreens with UVA and UVB protection should be implemented (Blakely et al., 2019).

Most of the aforementioned measures for pruritus, rash and photosensitivity skin reaction are based on expert opinions, case reports, or retrospective analysis. Only a few randomized trial data are incorporated in these guidelines (Kozuki, 2016). The study of Blakely et al. (2019) concluded that inclusive reporting, that also incorporates randomized control trials, will assist in better characterizing these skin reactions and provide a more comprehensive list for the treatment of such chemotherapy side effects. Finally, clinicians such as oncologists and dermatologists should pay closer attention to these skin reactions induced by chemotherapies (Cho et al., 2019).

The aim of the present pilot randomized controlled study was to evaluate the effectiveness of an educational program with non-pharmacological interventions for cancer patients who presented pruritus or rash or photosensitivity induced by chemotherapies, EGFRI treatments, or immunotherapies. The study also provides evidence for the functional health and well-being of the patients, showcases how much the skin problem has affected their quality of life and indicates the impact of secondary events that occur, i.e. unplanned admissions and percentage of patients who required regiment dose reduction or discontinuation of treatment.

2. Methods

2.1 Design

This study is a pilot randomized controlled study and was register in the Clinical Trials Registry with the trial ID: NCT03992664.

2.2 Study population and sampling

In the literature, the sample size for similar pilot studies ranged from 24 patients (12 per group) (Julious, 2005) to at least 50 patients (Sim and Lewis, 2012). The study of Kieser and Wassmer (1996) recommended 20-40 patients while the study of Browne (1995) recommended 30 patients.

A study carried out by Johanson and Brooks (2009) noticed that the confidence intervals from pilot study data may prove useful. According to the writers, parameter estimation and confidence intervals are considered high quality when the number of patients included in the study, stated as N, ranges from 30 to 50 and when the sampling procedure is truly random. Johanson and Brooks (2009) concluded that 30 participants are recognized as a reasonable, minimum sample size for pilot studies. Furthermore, the impact of increasing sample size on the length of the confidence interval for Pearson correlations was examined. The data indicated that a sample size between 24 to 36 patients may be a reasonable sample size for that (Johanson and Brooks, 2009).

According to our knowledge, the present study is the first that evaluated the effectiveness of an educational training program regarding skin reactions induced by

chemotherapies, EGFRI treatments and immunotherapies without the use of any pharmaceutical factors such as antibiotics, steroids, topical creams or lotions. Therefore, there were no previously reported data on the expected effect size on this topic.

For the aforementioned reasons, this pilot trial included 40 patients who were randomly allocated into two groups the intervention and the control group each consisting of 20 participants. This trial included cancer patients who experienced pruritus or rash or photosensitivity and the onset of their symptoms was due to a provided chemotherapy treatment, an EGFRI treatment, or an immunotherapy.

Patients' demographic data (sex, age, occupational status, academic qualifications), type and initial date of cancer diagnosis, provided chemotherapy treatment name and date of initiation were required for the purposes of the study and were collected by one of the authors (E.P.).

Thereafter, patients in the experimental group were assigned to attend the educational program once a week, for a total of 4 weeks under the supervision of author E.P.. The educational program initiated day each participant signed the consent form.

The SF-36 and DLQI questionnaires were provided and completed by the intervention as well as the control group. The SF-36 questionnaire was presented to each participant on the first meeting (week 0 - the day they signed the consent form) and was completed every week (every seven days) for all 4 weeks of the program. The DLQI questionnaire was provided to all patients a week after the initial meeting, as its questions concerned the week that passed. In addition, one of the authors (E.P.) collected data about other events that occurred due to pruritus, rash or photosensitivity, such as secondary side effects, dose reduction, emergency admission or discontinuation of treatment.

2.2.1 Inclusion criteria

Prospective participants were assessed according to the following inclusion criteria:

a. Adult cancer patients (>18).

b. Patients who suffered with pruritus, or rash or photosensitivity, in the onset of the symptoms.

c. Willing to participate.

d. Ability to complete the questionnaires.

e. A performance status of two or less on the Eastern Cooperative Oncology Group (ECOG).

f. Patients with no pre-existing dermatological condition that may limit the interpretation of results.

3. Measures

3.1 Primary endpoint

Data about pruritus, rash and photosensitivity were recorded by one of the investigators (E.P.), who was adequately trained in the application of Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Pruritus Grade 1 is characterized by mild or localized symptoms, manageable via topical intervention. Grade 2, is described by widespread and intermittent eruptions and could also include skin changes caused by scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts). Patients experiencing Grade 2 pruritus are also characterized by limited instrumental Activities of Daily Living (ADL). Oral intervention treatment is indicated for Grade 2. Finally, Grade 3 is characterized by: widespread and incessant signs of pruritus, limited self-care ADL or sleep and the necessity of treatment with systemic corticosteroid or immunosuppressive therapy.

Rash Grade 1 is characterized by papules and/or pustules covering less than 10% of Body Surface Area (BSA) and is or is not associated with tenderness or symptoms of pruritus. Grade 2 is characterized by papules and/or pustules covering 10% to 30% of BSA and is or is not associated with symptoms of pruritus or tenderness, has psychosocial impact on patients' life and causes limited Activity of Daily Living (ADL). Grade 2 could also be represented by papules and/or pustules covering more than 30% of BSA and patients presenting or not mild symptoms. Grade 3 is characterized by papules and/or pustules covering more than 30% of BSA and could be associated with moderate or severe symptoms. This Grade is also characterized by limited self-care Activities of Daily Living and local superinfection requiring oral antibiotic treatment. Grade 4 is characterized by papules and/or pustules covering any

percentage of the Body Surface Area, is or is not associated with symptoms of pruritus or tenderness and has life-threatening impact. Grade 4 is also associated with extensive superinfection. Intravenous antibiotics are required for Grade 4 management. Grade 5 rash is categorized as lethal.

Photosensitivity Grade 1 is characterized by painless erythema covering less than 10 % of the Body Surface Area (BSA) while Grade 2 is described as tender erythema covering 10% to 30% of BSA. Grade 3 is described as erythema covering more than 30% of BSA characterized by blistering or photosensitivity which require management with oral corticosteroids. Additionally, pain control medications such as narcotics or nonsteroidal anti-inflammatory drugs (NSAIDs) are indicated for this grade's management. Urgent intervention is indicated for Grade 4 management due to its life-threatening consequences, whereas Grade 5 is characterized as lethal.

3.2 Secondary endpoints

For the Secondary endpoints we: a) investigated the functional health and well-being of patients by utilizing the SF-36 questionnaire, b) evaluated how much the skin reaction affected the patient's life over each past week during the educational program with the use of the Dermatology Life Quality Index (DLQI) questionnaire, c) investigated for secondary side effects such as infections and fever and recorder any unplanned admission of the patients (due to pruritus, rash and photosensitivity), d) identified the percentage of the patients who required reduction of the treatment dose or were forced to discontinue treatment due to pruritus, rash and photosensitivity.

The RAND developed the 36-Item Short Form Health Survey (SF-36), which is a practical, reliable and valid measure of physical and mental health. We chose to utilize the SF-36 questionnaire for this study because it provides a comprehensive list of 36 patient-reported questions that assist researchers in measuring the functional health and well-being of the patients from their point of view. The SF-36 measures eight parameters: physical functioning, physical health, emotional problems, energy/fatigue, emotional well-being, social functioning, pain and general health. Each parameter is rated on a 0-100 scale where the lower the score, the greater the disability the patient presents.

In addition, for the purposes of the study, the Dermatology Life Quality Index (DLQI) questionnaire was also used to evaluate participants in both groups. The aim of this questionnaire is to measure how much the skin problem has affected the patient's life over each of the previous weeks. The questionnaire includes 10 questions, which investigate the: occurring symptoms, treatment, embarrassment experienced, clothes chosen, shopping and home care, social life and leisure, sport, work or study, close relationships and sex. The score ranges from 0, meaning no impact of skin disease was reported over the patient's quality of life, to 30 meaning maximum impact was reported on quality of life.

Emergency admissions, dose reduction and treatment interruption were also evaluated in this trial. These parameters were evaluated per seven days for a total of 3 weeks (week 1 – week 3) starting from the day that patients signed the informed consent (week 0 - baseline).

3.3 Procedures and interventions

3.3.1 Educational program

The educational program was created by the research team and was addressed to cancer patients who presented pruritus or rash or photosensitivity. The program was developed with the use of bibliographic references, from references from the American Academy of Dermatology (American Academy of Dermatology, 2018) and the American Cancer Society (American Cancer Society, 2020) and also the knowledge/experience of the investigator.

The educational program was consisted out of five categories: 'clean – hydrate', 'protection from the sun', 'protection from other external stimulations', 'observe – inform' and 'cosmetic products' (see 'Box 1'). The educational program contained measures/actions that patients should take for the management of the skin reaction and excluded any oral or topical medicines.

The category 'clean – hydrate' included eight measures the patients should apply. Taking a daily bath or shower with non-irritating soaps and shampoos (weakly acidic to alkaline), avoiding hot water during bath or shower (approx. 37 ° C in summer and 39 ° C in winter), washing the skin gently using the palm of the hand and rinsing thoroughly

the soap / shampoo were some of the actions the participants were required to take (Kiyohara et al., 2013). Measures like wiping the skin lightly with a clean towel without rubbing and avoiding sulfur-containing bath salts (causative of skin dryness) were also included in our list (Kiyohara et al., 2013). The last two measures for the category regarded moisturizing the skin after the bath with an alcohol-free cream and applying hypoallergenic and fragrance-free moisturizer (Jatoi et al., 2010).

The second category of the educational program was dedicated to 'sun protection'. The participants were required to use high protection sunscreen (Jatoi et al., 2010) and applying it on a daily basis to all the exposed skin, even on cloudy days. Additionally, if they were experiencing chemo-induced hair loss, sunscreen was required to be applied to the scalp as well. For this measure, patients were asked to use a new/fresh bottle of sunscreen as a previously opened/used bottle may no longer be effective. The use of objects that blocked ultraviolet radiation, such as umbrellas, hats, sunglasses, scarves, gloves, and clothes with minimal exposed areas was also recommended (Potthoff et al., 2011). For when outside of a building, further recommendations were given to the participants: finding a place in the shade under a tree or sitting under an umbrella, carrying a sun umbrella or even walking along paths sheltered by trees. As wigs can be hot in the sun, a cotton scarf was recommended instead as it could be comfortable while providing protection at the same time. Finally, another important measure the patients were required to follow as of this category, was to avoid sun exposure from 10 am to 4 pm (Potthoff et al., 2011).

The 'protection from other external stimulations' category included eight requirements some of which were the protection of the skin during manual shaving (Potthoff et al., 2011) and during the use of electronic razor, the avoidance of scratching by covering the itchy area i.e. with a cold, wet cloth and nail trimming (Potthoff et al., 2011). Wearing gloves when sleeping to avoid scratching unintentionally and avoiding wool clothing in order to help the skin 'breathe' and feel less itchy were also included in the instructions given for this category. The protection of any skin wounds as per the doctor's instructions as well as the use of sterile, non-stick gauze and the use of paper tape were also part of the guidelines given.

The category regarding 'cosmetic products', included measures concerning their usage. Only "non-chemical" cosmetics could be used in order to cover the face while the use of

coloured moisturizers or even coloured sunscreens was encouraged in order to achieve skin coverage and at the same time hydrated and protected it from the sun.

For the last category of the educational program, the ‘note – update’ category, participants were required to monitor their skin on a daily basis and inform their doctor immediately if any itching, photosensitivity, rash or new sores appeared on their skin.

Box 1. Educational Program

EDUCATIONAL PROGRAM

CLEANLINESS – HYDRATION

- Daily bath or shower with non-irritating soaps and shampoos (weakly acidic to alkaline).
- Avoid hot water for bath or shower (about 37 ° C in Summer and 39 ° C in Winter).
- Gently wash your skin using the palm of your hand.
- Good rinsing of the soap / shampoo
- Wipe lightly with a clean towel without rubbing.
- Sulfur-containing bath salts are not recommended because they cause dry skin.
- Moisturizing after the bath with a cream that does not contain alcohol.
- Apply hypoallergenic and fragrance-free moisturizer

SUN PROTECTION

- High protection sunscreen.
- Apply sunscreen daily to all exposed skin even on cloudy days.
- If chemo causes hair loss, be sure to apply sunscreen to your scalp, too.
- Make sure you have a fresh bottle of sunscreen. Last year's bottle may no longer be effective.
- Use of objects that block ultraviolet radiation such as umbrellas, hat, sunglasses, scarves, gloves, clothes with few exposed areas.
- Find a place in the shade under a tree or sit under an umbrella. You can also carry a sun umbrella.
- Walk along paths sheltered by trees.
- Wigs can be hot in the sun, but a cotton scarf can be comfortable while providing protection.
- Avoid sun exposure from 10 am to 4 pm

PROTECTION FROM OTHER EXTERNAL STIMULATIONS

- Carefully during shaving. An electronic razor is best used.
- Avoid scratching.
- Cover the itchy area if you can't keep from scratching it.
- In case of itching, use a wet cold cloth or ice and not scratch the area.
- Trim your nails to avoid scratching.
- Wear gloves when you sleep to avoid scratching.
- Avoid wool clothing
- Protect any wounds on your skin as doctor instructed, or use sterile, non-stick gauze, or use paper tape if you can.

COSMETICS PRODUCTS

- To cover the face, use moisturizers with color or even sunscreens with color. This way you will achieve coverage on your skin but at the same time you will keep your skin hydrated or protected from the sun.
- Prefer "non-chemical" cosmetics.

NOTE - UPDATE:

- Monitor your skin on a daily basis.
- Your doctor should be informed in time for any itching, photosensitivity, rashes.
- Tell to your doctor about any new sores on your skin.

3.3.2 Procedures

The study was performed at two private hospitals specialized in cancer treatment, in Nicosia and Limassol, Cyprus. The patients were selected and monitored within the clinic either during their treatment or during scheduled weekly appointments. All the meetings took place within the two abovementioned private hospitals. Patient recruitment was completed within 23 months (January 2019 - December 2020).

Details and instructions regarding the educational program were provided in paper form to the participants in the intervention group, over the first day of their recruitment, right after they had signed the consent form. Author E.P. read and explained the details of the educational program to each patient and then proceeded with providing the paper with the information to him/her.

On the other hand, patients in the control group did not receive the specific information regarding the educational program. However, the usual information was provided to them, as with any cancer patient who initiates chemotherapy, immunotherapy or EGFRI treatment. The usual information was provided in the form of a 'treatment booklet' which included: explanation regarding the methods of drug administration (cannula, central venous access device, portable pump), forms of chemotherapy provision (oral chemotherapy, injections, cream, chemoembolization), tips on how to spend the time during chemotherapy (e.g. reading a book), safety precautions (e.g. what to notice while using the toilet, how to handle laundry carefully) and what to expect and how to prepare regarding side effects such as fatigue, nausea or emesis, diarrhea or constipation, hair loss, mouth sores, skin and nail changes, sexuality and fertility issues. Each time, the follow up appointments were also noted in the treatment booklet while on the first page of it the emergency numbers of the oncology team were provided.

The grades of skin reactions and the performance as per the SF-36 questionnaire were evaluated every week (since participant's selection day - week 0), for all participants in both groups. The DLQI questionnaire measurements initiated during the second week (week 1) as its questions referred to the previous week. Also, details about dose reduction, emergency admissions or discontinuation of treatment were collected from week 1 and onward.

3.4 Randomization

Patients who consented to take part in the study and follow the baseline measurements, were randomly allocated to either the intervention or the control group, on a 1:1 ratio, with the use of a computer-based minimization algorithm able to stratify patients based on the type of skin toxicity and type of treatment.

This is a single-blinded trial because participants were unaware in which group they would be allocated to, but the researcher, one of the authors alongside E.P., knew into which group each patient was classified.

3.5 Statistical Analysis

Descriptive statistics are presented as frequencies (N) and proportions for the categorical variables (e.g. gender, grade, etc.) and with Mean + Standard deviation for the continuous variables. The homogeneity of the two groups at baseline was assessed with the X2 test for the categorical variables and with the independent samples t-test for the continuous variables.

Cohen's d is utilized to assess the effect size differences between control and intervention at each time point (Baseline, week 1 to week 3) for the continuous scales (i.e, SF36 dimensions and DLQI), and the Relative Risk (RR) for the Dose Reduction and the Emergency Admission event.

The effect of the intervention on the Skin Reaction Grade (primary endpoint) was assessed using Generalised estimating equations (GEE) (Twisk, 2003) with an ordinal logistic response link due to the ordered levels of the grade status (1,2,3,4). The effect of the intervention on the Dose Reduction event and the Emergency Admission event, was assessed using the GEE with the binary logistic link due to the binary distribution of the event. The effect of the intervention on the secondary endpoints of DLQI score and the dimensions of the SF36 quality of life scale was assessed using Linear Mixed Models (LMM) with the patient as a random effect (random intercept model) using an unstructured covariance type. The models were adjusted for the gender, age, diagnosis and treatment type of the patient.

The data analyses were undertaken in SPSS v.28. A p value of <0.05 taken as the level of statistical significance.

3.6 Ethical considerations

The protocol was approved by the Cyprus National Bioethics Committee with the number: ΕΕΒΚ ΕΠ 2019.01.03 according to National Law. Also, this trial was registered in the clinical trials.gov with identifier number NCT03992664.

The study was conducted according to the provisions of the Declaration of Helsinki, and all patients after a detailed description of the study gave their informed consent before enrollment.

4. Results

4.1 Patient characteristics

Forty patients successfully completed the study. Twenty patients were assigned to the control group and twenty in the intervention group (Fig. 1: CONSORT diagram).

Table 1 demonstrates demographic characteristics for the control group and the intervention group. There were no statistically significant differences in relation to the demographic characteristics between the two groups. (Table 1).

4.2 Effect of the intervention

4.2.1 Primary endpoint

4.2.1.1 Rash grades

At baseline (week 0), 50% of the patients in the control group experienced Grade 1 and Grade 2 rash, whereas in the intervention group 83.3% presented Grade 1 rash and 16.7% Grade 2. At week 1, 16.7% of the patients in the control group experienced Grade 1 and Grade 3, while 33.3% presented Grade 2 and Grade 4. On the other hand, in the intervention group 50% of the patients had Grade 1 and Grade 2, respectively, and none of the patients experienced Grade 3 or Grade 4 rash.

At week 2, in the control group, 16.7% of the patients experienced Grade 1 and Grade 3 rash whereas 66.7% displayed Grade 2 rash. On the other hand, the percentage of the rash grades for the patients in the intervention group remained the same as in week 1. Finally, week 3 measurements demonstrate that 33.3 % of the patients in the control group experienced Grade 1 rash, 50% Grade 2 and 16.7% Grade 4, while in the intervention group patients experienced only Grade 1 and Grade 2 rash at 40% and 60% respectively (Table 2).

4.2.1.2 Pruritus Grades

At baseline, 50% of the patients in the control group experienced Grade 1 and Grade 2 pruritus, whereas in the intervention group 42.9% showed Grade 1 pruritus and 57.1 % Grade 2. At week 1, 33.3% of the patients in the control group experienced Grade 1 pruritus, 50% Grade 2, 16.7% Grade 3 and none of the patients demonstrated Grade 4. On the other hand, 71.4 % of the patients in the intervention group presented Grade 1 pruritus and 28.6% Grade 2. At week 2, 16.7% of the patients in the control group had Grade 1 pruritus and Grade 3, whereas 66.7% experienced Grade 2. In the same week, all patients in the intervention group experienced Grade 1. Finally, in week 3, regarding the control group, 50% of the patients experienced pruritus Grade 2 and Grade 3, respectively. In the intervention group, 85.7% of the patients presented Grade 1 pruritus and 14.3% Grade 2 (Table 3).

4.2.1.3 Photosensitivity Grades

At baseline, 37.5 % of the patients in the control group experienced Grade 1 photosensitivity and Grade 2 percentage was at 62.5%, whereas in the intervention group 42.9% of the participants showed Grade 1 photosensitivity and 57.1 % showed Grade 2. Measurements from week 1 indicated that 28.6 % of the patients in the control group experienced Grade 1 photosensitivity while 57.1 % had Grade 2 and 14.3 % Grade 3. On the other hand, 71.4 % of the patients in the intervention group had Grade 1 photosensitivity and only 14.3% of the patients experienced Grade 2 and Grade 3, respectively. In week 2, 14.3 % of the patients in the control group experienced Grade 1 photosensitivity, 57.1% had Grade 2 and 28.6% presented Grade 3. During the same

week, in the intervention group, 85.7% of the patients experienced Grade 1 and 14.3% Grade 2 photosensitivity. Finally, in week 3, none of the patients in the control group experienced Grade 1 and Grade 4, whereas 85.7% presented Grade 2 and 14.3% Grade 3. Finally, all of the patients in the intervention group expressed photosensitivity Grade 1 in this week (Table 4).

4.2.1.4 The effect of the Educational Program on Skin Reactions Grade

The Generalised Estimating Equations (GEE) showed a significant interaction between Group and Week over the weekly measurements of skin reactions (rash, pruritus and photosensitivity) Grade (Walds X2 = 19,25, p = 0.004) (Table 5).

4.2.2 Secondary endpoint

4.2.2.1 SF-36 questionnaire

At baseline (week 0) the mean score for the 'physical functioning' dimension of the SF-36 questionnaire for the control and the intervention group was 46.5 ± 30.09 and 48±28.58 respectively. For the control group, the score dropped from 42.63 ± 30.06 to 27.89 ± 27.85 from week 1 towards week 3. Additionally, a drop is observed for all the examined parameters of the SF-36 questionnaire (physical health, emotional problem, energy/fatigue, emotional well-being, social activities, pain, general health).

On the other hand, the score for the intervention group remained approximately the same regarding the dimension of physical functioning during the baseline (48± 28.58), week 1 (49.25± 30.79) and week 2 (43.25± 30.32), while in week 3 the score dropped (39.47 ± 29.34). Additionally, the score for the 'physical health' and 'emotional problems' dimensions increased from baseline to week 1, whereas a drop is observed from week 2 to week 3. For the category 'energy/fatigue', a drop is observed for the baseline (54.25 ± 12.17) to week 3 (46.32±15.26). Similarly, a drop is observed for the 'emotional well-being', 'social functioning', 'pain' and 'general health' parameters (Table 6).

The Linear Mixed Models (LMM), adjusted for age, gender, diagnosis and type of treatment, did not show a significant interaction between Group and Time over the

weekly measurements for the 'physical functioning' dimension (F = 0.362, p=0.78). Additionally, the Linear Mixed Models (LMM) did not show a significant interaction between Group and Time over the weekly measurements for the 'physical health' dimension either (F = 0.054, p=0.983). The same test was repeated for all of the other six dimensions and the results did not show a significant interaction between Group and Time over the weekly measurements for either of them; the emotional problems, energy/fatigue, emotional well-being, social activities, pain and general health dimensions.

4.2.2.2 DLQI questionnaire

The control group demonstrated an increase in the mean score from week 1 (7.9±6.2) to week 3 (9.7 ±5.3) regarding the DLQI measurements. On the other hand, the intervention group illustrated a decrease in the mean score from week 1 (8.7±7.4) to week 3 (7.5±4.7). At week 1, both groups presented a low effect size difference (d= -0.12) in the mean level of the DLQI questionnaire, whereas at week 3 the effect size difference was high (d= 0.44) (Table 7).

The Linear Mixed Models (LMM) did not show a significant interaction between Group and Time over the weekly measurements for the DLQI score (F = 0.948, p=0.391).

4.2.2.3 Emergency admissions

During week 1, 15.8% of the patients in the control group required emergency admission, whereas for the intervention group the percentage was lower, at 10%. During week 2, 26.3% of the patients in the control group were admitted in the emergency ward while 15% of the experimental group participants required that. Finally, in week 3, 21.1% and 31.6% of the patients were urgently admitted in the control and the intervention group, respectively. The patients in the intervention group had 66% lower risk for an emergency admission in week 1, compared to those in the control group. Week 2 data indicated that the patients following the educational measures had 57% lower risk for an emergency admission compared to those who did not. On the other hand, during week 3, the patients participating in the educational program presented 50% increase in the risk of requiring an emergency admission compared to the patients

in the control group (Table 8). According to the Generalised Estimating Equations (GEE) no significant interaction was shown between Group and Week over the weekly measurements regarding emergency admissions event (Walds X2 = 2.234, p = 0.327).

4.2.2.4 Dose reduction

According to our analysis, a larger number of patients from the control group required a treatment dose reduction compared to the patients in the intervention group. Specifically, during week 1, 21.1 % of the patients in the control group and 10% of the patients in the intervention group required dose reduction. In week 2, the percentage in the control and the intervention group was 31.6% and 15%, respectively. Finally, in week 3, 31.6% of the control group participants and 10.5% of the intervention group participants required a treatment dose reduction. More specifically and according to the Relative Risk results, patients in the intervention group presented 50% lower risk to require dose reduction compared to control group participants in week 1. Additionally, in weeks 2 and 3 the patients in the intervention group presented 15% and 10.5% lower risk, respectively, for receiving a dose reduction compared to the control group (Table 9). Finally, as per the Generalised Estimating Equations (GEE) no significant interaction between Group and Week was shown over the weekly measurements of Dose Reduction event (Walds X2 = 0.182, p = 0.913).

5. Discussion

This was a pilot, randomized controlled trial designed to evaluate the effectiveness of an educational training program over skin reactions induced by chemotherapies, EGFRI treatments, or immunotherapies.

A vast range of interventions have been examined so as to define effective measures in order to manage skin reactions for cancer patients who undergo treatment. The standard management for the EGFRI treatment-induced rash includes the use of antibiotics and cortisone products such as doxycycline and hydrocortisone (Melosky et al., 2009). Drug-induced photosensitivity is usually managed via the use of sun-protecting sunscreens and protective clothing (Moore, 2002). Pruritus management usually includes suggestions towards patients in order to reduce itching like: wearing light clothing, using a humidifier, restricting the bath and shower time, using lukewarm water

and avoiding cleansers with a high pH or containing alcohol. Management of mild to moderate pruritus consists of topical corticosteroids and anesthetics (ie. lidocaine, prilocaine), whereas for severe pruritus antihistamines are the most widely used therapy (Ensslin et al., 2013).

It appears that the most effective strategy for the management of the aforementioned skin reactions remains the dose-reduction or end-of-treatment strategy. Unfortunately, the consequences of either of the options have a severe impact on the patient's treatment plan and consequently on its survival. Thus, this randomized placebo-controlled pilot clinical trial examined the effectiveness of an educational program for cancer patients who presented pruritus, rash and photosensitivity induced by chemotherapies, EGFRI treatments, or immunotherapies, so as to determine further ways for the management of these skin reactions.

In order to evaluate the effectiveness of our educational program, to meet our primary endpoint we investigated changes in the skin reactions' grades. The results demonstrated an improved grade distribution for all skin reactions, the rash, pruritus and photosensitivity. The Generalised Estimating Equations (GEE) indicated a statistically significant interaction between the Group and Week over the weekly measurements (week 1, week 2, week 3) of all skin reactions investigated (rash, pruritus and photosensitivity), due to the effect of the Educational Program.

The secondary endpoint of this trial regarded the results deriving from the SF-36 and DLQI questionnaires. In addition, our study examined the emergency admissions and the need for treatment dose reduction for the participating patients. The intervention group presented an improved health status according to all SF-36 questionnaire dimensions (physical functioning physical health, emotional problems, energy/fatigue, emotional well-being, social activities, pain and general health). The data from the DLQI questionnaire indicated that for weeks 2 and 3, skin reactions affected less the lives of patients in the intervention group in comparison to the control group. However, our results from the SF-36 and the DLQI questionnaires did not present a statistically significant interaction between Group and Time over the weekly measurements.

Emergency admissions for patients in the intervention group were lower for weeks 1 and 2 compared to the control group, whereas the emergency admissions in week 3 were higher in the intervention group. Furthermore, patients in the intervention group

had a lower possibility to require dose reduction to their treatment over weeks 1, 2 and 3. More specifically, patients in the intervention group presented 50%, 15% and 10.5% lower risk to require dose reduction compared to the control group for weeks 1, 2 and 3, respectively. Nevertheless, our results did not show a significant interaction between Group and Week over the weekly measurements of Emergency Admissions and Dose Reduction events.

During the trial, one patient from the intervention group and one patient from the control group had to terminate their treatment. The termination of treatment in both cases was not associated with the skin reactions but due to metastasis (patient transited to palliative care) and economic reasons, respectively. Unfortunately, the authors had no access to the records of the participant who discontinued due to financial problems, as he/she continued at a public hospital, thus the investigation could not be carried out until the end.

Preceding studies were reviewed in order to identify appropriate management measures for the studied skin reactions and compare them with our data. According to a study by Kozuki (2016), the use of sunscreen may be effective for the EGFRI-treatment induced rash, if combined with other methods such as the use of topical or systemic corticosteroids, systemic or topical use of antibiotics, topical retinoids and vitamin K3 (menadione). Our findings agree with the Kozuki study; that patient education by medical staffs is as important as the professional assessment of EGFR-associated skin toxicities, self-skin care (moisturizers, cream/lotion), cleanliness and use of protectants from other external stimuli before and during EGFRI treatment (Kozuki, 2016).

Our trial concurs with the study of Moore (2002) regarding photosensitivity, where fully protective clothing and eyewear are recommended along with the application of high protection sunscreen formulation. The study also suggested that medical treatment provision is necessary when severe photosensitivity occurs. In the case of a phototoxic reaction, the treatment is usually the same as applied to sunburn. Furthermore, the study concluded that antibacterial creams should be applied to prevent infection if the skin develops blisters that burst, while antihistamines and corticosteroids may be required to manage the inflammation arising from photosensitivity (Moore, 2002).

For pruritus induced by chemotherapies, EGFRI treatments, or immunotherapies our trial suggested management via the topical application of moisturizers, the elimination

of skin dryness and the avoidance of bathing with hot water for prolonged periods. These measures agree with the study of Ebata (2016) where further interventions are suggested such as: avoiding mental stress, spicy food, and irregular lifestyle habits regarding sleep and nutrition.

In general, it is not possible for our results to be compared with a similar study since, based on our knowledge, this is the first study that examines this type of educational measurements in a clinical trial study. However, we managed to develop a small, readable and easy-to-use educational program with the use of bibliographic references as the aforementioned, references and guidelines from the American Academy of Dermatology (American Academy of Dermatology, 2018) and the American Cancer Society (American Cancer Society, 2020) and also the knowledge and experience of the investigators.

5.1 Study strengths and limitations

The sample size of this clinical trial was small. Given the fact though that this trial is a pilot study, the small sample size is acceptable. However, further studies with a larger sample size would be required in order to provide further support to our findings. In addition, participants included in the trial come solely from two private hospitals in Cyprus, increasing this way the risk of bias in our results. All in all, this trial is a good step for future studies. According to Kozuki (2016) and Lacouture et al. (2011), most of the statements for the management of skin reactions induced by cancer treatments are based on expert opinions or consensus, case reports, single-arm prospective trials or retrospective analysis, and only a few randomized trial data are incorporated in these guidelines.

Another limitation of this trial is the single-blind methodological design. Specifically, only trial participants were blinded in this study whereas blinding for the researcher was not achievable.

It should also be noted that intervention was always provided by the same person, researcher E.P. This may have increased consistency in the intervention's method, but it could also have increased the possibility of a researcher effect on the study outcome as well.

According to our knowledge, a study which introduces an educational program that does not utilize oral or topical medications has not been conducted before in a clinical trial form. Another strength of this trial was the various time points used for the assessment of the interventions' effectiveness. This allowed us to progressively record how the interventions affected the patients' skin toxicities.

6. Conclusion

The present study is a pilot randomized, controlled trial evaluating the effects of an educational training program over pruritus, rash and photosensitivity skin reactions induced by chemotherapies, EGFRI treatments, or immunotherapies.

This trial illustrated that patients who followed the guidelines of the aforementioned training program presented improved skin reaction grades compared to those who did not. Additionally, a statistically significant interaction between the Group and Week over the weekly grade measurements of all skin reactions (rash, pruritus and photosensitivity) was demonstrated.

The patients of the intervention group presented an improved health status in all dimensions of the SF-36 questionnaire (physical functioning, physical health, emotional problems, energy/fatigue, emotional well-being, social activities, pain and general health). The data extracted from the DLQI questionnaire demonstrated that the skin problem affected less the patients following the interventions for weeks 2 and 3, in comparison to the control group patients. Moreover, the patients in the intervention group presented lower numbers regarding emergency admissions for weeks 1 and 2, compared to the control group, additionally to the fact that they also presented lower treatment dose reduction rate for weeks 1, 2 and 3. All the above results highlight the great importance of educating oncology patients regarding dermatological care.

All in all, further research is required in order to establish effective strategies to manage pruritus, rash and photosensitivity dermatitis induced by cancer treatments, in order to be able to achieve maximum treatment benefit for cancer patients who suffer from such skin reactions.

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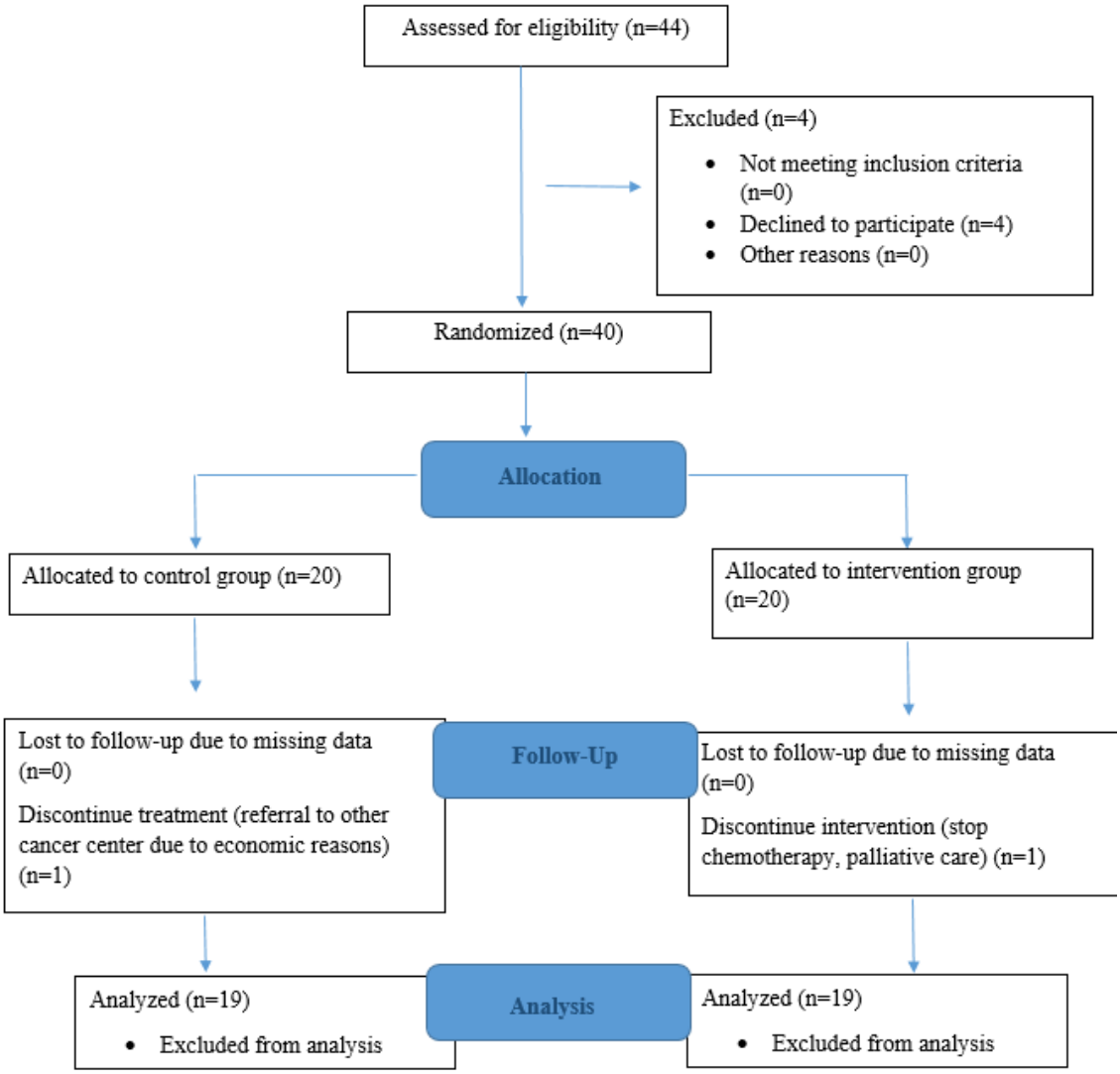
Declaration of competing interest

The authors declare no conflict of interest.

Figures

Figure 1: Consort Flow Diagram



Tables

Table 1 Patient demographics and clinical characteristics

		Control		Intervention		Total		
		N	%	N	%	N	%	p value
Gender	Male	11	55.0	10	50.00	21	52.5	0.752
	Female	9	45.0	10	50.00	19	47.5	
Age	(Mean, Standard Deviation)	57.6	13.7	62.8	12.6	60.2	1320.0	0.223
Job	Full Time	6	30.0	3	15.0	9	22.5	0.146
	Retired	5	25.0	11	55.0	16	40.0	
	Sick Leave	9	45.0	6	30.0	15	37.5	
Education	Secondary School	7	35.0	6	30.0	13	32.5	0.964
	High School	4	20.0	4	20.0	8	20.0	
	College	2	10.0	3	15.0	5	12.5	
	University	7	35.0	7	35.0	14	35.0	
Diagnosis	Breast Cancer	2	10.0	2	10.0	4	10.0	0.934
	Colon Cancer	4	20.0	5	25.0	9	22.5	
	Lung Cancer	3	15.0	3	15.0	6	15.0	
	Pancreatic Cancer	5	25.0	4	20.0	9	22.5	
	Head / Neck Cancer	0	0.0	1	5.0	1	2.5	
	Other	6	30.0	5	25.0	11	27.5	
Treatment	Chemotherapy	12	60.0	14	70.0	26	65.0	0.341
	EGFRI	6	30.0	6	30.0	12	30.0	
	Immunotherapy	2	10.0	0	0.0	2	5.0	
Treatment Type	EGFRI	6	30.0	6	30.0	12	30.0	0.664
	Gemcar - Abraxane	2	10.0	1	5.0	3	7.5	
	Doxorubicin	2	10.0	1	5.0	3	7.5	
	Avastin - Taxol - Carboplatin	3	15.0	4	20.0	7	17.5	
	Fluorouracil	2	10.0	5	25.0	7	17.5	
	Immunotherapy	2	10.0	0	0.0	2	5.0	

	Other	3	15.0	3	15.0	6	15.0	
Skin Reaction	Rash	6	30.0	6	30.0	12	30.0	0.931
	Photosensitivity	8	40.0	7	35.0	15	37.5	
	Pruritus	6	30.0	7	35.0	13	32.5	
Grade	Grade 1	9	45.0	11	55.0	20	50.0	0.527
	Grade 2	11	55.0	9	45.0	20	50.0	

Table 2. Distribution of Rash Grade over the weekly measurements

Skin Reaction - Rash	**Control Group**							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time Period	N	%	N	%	N	%	N	%
Baseline	3	50.0%	3	50.0%	0	0.0%	0	0.0%
Week 1	1	16.7%	2	33.3%	1	16.7%	2	33.3%
Week 2	1	16.7%	4	66.7%	1	16.7%	0	0.0%
Week 3	2	33.3%	3	50.0%	0	0.0%	1	16.7%
	Intervention Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time Period	N	%	N	%	N	%	N	%
Baseline	5	83.3%	1	16.7%	0	0.0%	0	0.0%
Week 1	3	50.0%	3	50.0%	0	0.0%	0	0.0%
Week 2	3	50.0%	3	50.0%	0	0.0%	0	0.0%
Week 3	2	40.0%	3	60.0%	0	0.0%	0	0.0%

Table 3. Distribution of Pruritus Grade over the weekly measurements

Skin Reaction-Pruritus								
	Control Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time Period	N	%	N	%	N	%	N	%
Baseline	3	50.0%	3	50.0%	0	0.0%	0	0.0%
Week 1	2	33.3%	3	50.0%	1	16.7%	0	0.0%
Week 2	1	16.7%	4	66.7%	1	16.7%	0	0.0%
Week 3	0	0.0%	3	50.0%	3	50.0%	0	0.0%
	Intervention Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time Period	N	%	N	%	N	%	N	%
Baseline	3	42.9%	4	57.1%	0	0.0%	0	0.0%
Week 1	5	71.4%	2	28.6%	0	0.0%	0	0.0%
Week 2	7	100.0%	0	0.0%	0	0.0%	0	0.0%
Week 3	6	85.7%	1	14.3%	0	0.0%	0	0.0%

Table 4. Distribution of Photosensitivity Grade over the weekly measurements

Skin Reaction-Photosensitivity								
	Control Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time period	N	%	N	%	N	%	N	%
Baseline	3	37.5%	5	62.5%	0	0.0%	0	0.0%
Week 1	2	28.6%	4	57.1%	1	14.3%	0	0.0%
Week 2	1	14.3%	4	57.1%	2	28.6%	0	0.0%
Week 3	0	0.0%	6	85.7%	1	14.3%	0	0.0%
	Intervention Group							
	Grade 1		**Grade 2**		**Grade 3**		**Grade 4**	
Time period	N	%	N	%	N	%	N	%
Baseline	3	42.9%	4	57.1%	0	0.0%	0	0.0%
Week 1	5	71.4%	1	14.3%	1	14.3%	0	0.0%
Week 2	6	85.7%	1	14.3%	0	0.0%	0	0.0%
Week 3	7	100.0%	0	0.0%	0	0.0%	0	0.0%

Table 5			
General Estimating Equations (GEE) for the effect of the Intervention on Skin Reactions Grade			
Effect	**Wald Chi-Square**	**df**	**Sig.**
Group	19.253	1	<.001
Week	1.282	3	0.733
Group * Week	13.141	3	0.004

Table 7			
Mean Level (±SD) of DLQI Questionnaire and Cohen's d test over the weekly measurements			
Time Period	**Control Group**	**Intervention Group**	**Cohen's d**
Week 1	7.9±6.2	8.7±7.4	-0.12
Week 2	9.6±6.2	7.9±4.7	0.31
Week 3	9.7±5.3	7.5±4.7	0.44

Table 8			
Relative Risk and percentage (%) of the emergency admissions over the weekly measurements			
Time Period	**Control Group**	**Intervention Group**	**Relative Risk**
Week 1	15.80%	10%	RR = 0.66 [0.12 - 3.57], p = 0.63
Week 2	26.30%	15%	RR = 0.57 [0.16 - 2.06], p = 0.39
Week 3	21.10%	31.60%	RR = 1.50 [0.50 - 4.48], p = 0.47

Table 9			
Relative Risk and percentage (%) of the dose reduction over the weekly measurements			
Time Period	**Control Group**	**Intervention Group**	**Relative Risk**
Week 1	21.10%	10%	RR = 0.50 [0.10- 2.43], p = 0.39
Week 2	31.60%	15%	RR = 0.47 [0.13 - 1.63], p = 0.24
Week 3	31.60%	10.50%	RR = 0.33 [0.07 - 1.48], p = 0.14

Table 6

Mean level (±SD) of the SF 36 Weekly measurements

Control Group

Time Period	Physical functioning	Physical health	Emotional problem	Energy /Fatigue	Emotional well-being	Social functioning	Pain	General health
Baseline	46.5 ± 30.09	45±32.04	60 ±31.72	50.5±14.32	52.8±13.21	47.5±21.69	39.88±24.73	41±23.32
Week 1	42.63 ±30.06	43.42±27.44	50.88±28.04	46.05±15.95	49.05±10.9	41.45±15.05	37.63±19.23	36.32±21.78
Week 2	31.84±26.89	40.79±29.12	50.88±30.16	44.21±13.87	47.79±12.89	37.5±19.54	34.21±18.28	33.42±17.95
Week 3	27.89±27.85	36.84±25.51	45.61±27.69	42.37±14.85	44.63±15.56	34.21±18.09	28.16±21.31	31.58±18.71

Intervention Group

Time Period	Physical functioning	Physical health	Emotional problem	Energy /Fatigue	Emotional well-being	Social functioning	Pain	General health
Baseline	48±28.58	57.5±28.21	68.33±27.52	54.25±12.17	58±15.38	53.75±20.32	51.63±21.93	57.25±26.28
Week 1	49.25±30.79	60±28.56	71.67±27.09	51.5±15.23	55.8±16.29	50±18.14	49.5±21.65	49.75±27.7
Week 2	43.25±30.32	53.75±28.42	65±31.48	47.5±16.42	50.2±18.42	43.13±21.26	42.38±19.64	46.75±26.82
Week 3	39.47±29.34	52.63±34.25	59.65±36.14	46.32±15.26	49.47±17.65	39.47±19.21	41.58±21.8	44.21±25.18

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