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POSITION STATEMENT

Management of human epidermal growth factor receptor inhibitors-related acneiform rash: A position paper based on the first Europe/USA Delphi consensus process

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Abstract

Background: There is a need for unified guidance in the management of acneiform rash induced by epidermal growth factor receptor inhibitors (EGFRi) among dermatologists.

Objective: To establish unified international guidelines for the management of acneiform rash caused by EGFR inhibitors, based on an experts' Delphi consensus.

Methods: The initiative was led by five members of the European Academy of Dermatology and Venereology Task Force 'Dermatology for Cancer Patients' who developed a questionnaire that was circulated to a group of 32 supportive oncodermatology experts in Europe, Canada, Argentina, the US States and Asia. The questionnaire consisted of 84 statements in total, regarding diagnosis and treatment of EGFRi-induced acneiform rash. Experts responded to an anonymous 5-point Likert scale survey. The coordinators collected the first-round responses that were checked for consensus (≥75% agreement in positive [agree or strongly agree] or in negative [disagree or strongly disagree] vote). The statements that did not reach strong consensus in the first round were revised, according to experts' feedback, for a second-round survey.

Results: Strong consensus was reached in 75/84 (89.3%) of the statements, whilst moderate consensus was achieved in 6/84 elements. Key points include consideration of low-dose isotretinoin for refractory grade II/III acneiform rash, use of topical steroid-sparing agents like topical pimecrolimus in the maintenance phase and use of doxycycline in either 100 or 200 mg per day as prophylactic treatment. Interestingly, experts did not recommend topical antibiotics, neither for prevention, nor for treatment. Consensus failure in 3/84 objects is mostly related to the lack of robust data on these topics.

For affiliations refer to page 738.

Conclusion: This consensus offers crucial insights often overlooked by radiotherapists, general practitioners, dermatologists and oncologists, and it is expected to improve the management of oncologic patients treated with EGFRi in different settings and continents.

INTRODUCTION

The human epidermal growth factor receptors (HER) belong to a family of tyrosine kinases with a pivotal role in signalling pathways.[1,2] Due to their essential biological roles, these receptors have been targeted for the development of dual/pan HER or more specific HER 1 inhibitors (EGFRi), which play a central role in the treatment of a large range of solid cancers. Two primary classes of EGFRi exist: reversible and irreversible small-molecule inhibitors, binding to the active site of EGFR kinases (tyrosine kinase inhibitors [TKIs]) and monoclonal antibodies (mAbs) against the extracellular domain, respectively. EGFRi are categorized by their chemical structures, pharmacological uses and cytotoxicity potency.[3–5]

Acneiform rash is the most common EGFRi-induced cutaneous toxicity, observed in up to 90% of patients exposed. It appears more frequently with mAbs (cetuximab and panitumumab) than with TKIs (e.g. erlotinib and gefitinib).[6,7] Similar acneiform lesions can also develop with other targeted therapies such as MEK inhibitors and to a lesser extend mTOR and JAK inhibitors. Risk factors contributing to increased severity and higher-grade toxicity include secondary skin infections, sun exposure and radiation therapy.[8,9]

The significant impact of skin toxicity on patients' quality of life (QoL) and the frequency of subsequent treatment disruptions underscore the need for early and appropriate intervention.[10–13] Numerous studies highlight the role of adequate management of EGFRi-associated dermatologic AEs, whilst ESMO (European Society Medical Oncology) guidelines committee has incorporated practical recommendations for the management of acneiform rash in specific guidelines.[14–16]

With regard to available treatments, topical corticosteroids have shown efficacy in managing low-grade acneiform eruption, whilst more severe toxicity demands combination of systemic and topical regimens.[17–19] Taking into account the high incidence of cutaneous toxicity emerging from EGFRi, pre-emptive therapeutic approach is also recommended.[20,21] However, many oncologists are still reluctant towards pre-emptive treatment, mostly considering that cutaneous reactions may serve as indicators of response to treatment, with higher response rates and increased survival observed in patients undergoing specific treatment.[22,23]

Despite the extensive use of EGFRi in oncologic treatment during the last two decades, certain aspects of managing EGFRi-induced acneiform rash, such as precise dosing and potency of topical steroids in the pre-emptive and reactive context, remain vague. There are several systemic drugs used in the setting of EGFRi-induced acneiform rash in the daily practice, but their use is not always supported by robust evidence and remains mostly empirical, including oral tetracyclines.[21,24–28] The scarcity of well-conducted studies and unified widely accepted guidelines often result in confusion in many aspects of management, including diagnosis, grading of severity, type of intervention and treatment duration.[29–34]

Why was the study undertaken?

The main research target of the study was to resolve ambiguities regarding management of EGFRi-induced acneiform rash and establish unified guidance for its treatment.

What does this study add?

Based on a Delphi consensus process among experts, the document provides unified guidelines for the diagnosis and treatment of EGFR-inhibitor papulopustular rash in oncology patients.

What are the implications of this study for disease understanding and/or clinical care?

The article makes a valuable contribution as it allows dermatology to lead a position paper on a common cutaneous adverse effect derived from EGFR inhibitors. The consensus emphasizes the importance of early, accurate diagnosis and grading, appropriate use of prophylactic, pre-emptive and reactive treatment, and the importance of tailoring treatment to each specific individual.

To resolve ambiguities regarding management of EGFRi-induced acneiform rash and establish unified guidance for its treatment, we organized a survey-based, Delphi consensus study, assembling European, American and Asian experts in supportive oncodermatology.

METHODS

Recruitment of expert panel members

We employed a consensus-based approach, utilizing the survey-based Delphi process. Participants were experts in supportive oncodermatology and belonged to either the European Academy Dermatology Venereology

Task Force of 'Dermatology for cancer patients' or the US Oncodermatology Society. The recruitment process was facilitated by the Chair and co-Chairs of the EADV Task Force (ZA, VS and AF). Participants were selected for diverse country representation and supportive oncodermatology expertise, and were provided with comprehensive study information in advance, outlining the Delphi process's objectives, the estimated timing of their contribution and the potential corresponding scientific benefits.

Delphi process design and development

The Delphi process consisted of two independent rounds of online questionnaires anonymously completed by participants and structured into four sections (diagnosis and grading, prophylactic treatment, pre-emptive pharmaceutical treatment and reactive treatment). A leading group of five experts (ZA, VS, AF-M, DF and PS) developed the statements for the questionnaires, after an extensive literature review and group discussion among the experts. The statements aimed to cover all the problematic areas in this topic. Draft statements were then reviewed by the leading group for appropriateness and clarity. The two parts of the questionnaire were created using the Survey Monkey (Survey Monkey Inc., San Mateo, California, USA) online platform and its functionality was assessed in a pilot test by the project team.

Determining consensus

A 5-point Likert scale was applied for participants to indicate their level of agreement or disagreement in each statement: strongly disagree; disagree; neutral; agree; and strongly agree.[35] Strong positive consensus (in favour of the statement) was reached once ≥75% of respondents 'strongly agreed' or 'agreed' with a statement, whilst strong negative consensus (against the statement) was achieved once ≥75% of contributors 'strongly disagreed' or 'disagreed' with a statement.[36–40]

Moderate consensus was attained when the rate of agreement among the respondents was between 50 and 74%.

Statements not reaching strong consensus in the first round were reviewed and modified, if necessary, by the leading group for inclusion in the second round of Delphi. Statements achieving strong consensus in the first round were excluded from the second one. Participants were given a 2-week deadline for completing both survey rounds.

RESULTS

Thirty-two experts in supportive oncodermatology from Europe,[17] America (United States, $n = 12$; Canada, $n = 1$; Argentina, $n = 1$), Asia (Philippines = 1) and Israel (=1) participated in the two rounds of our Delphi-technique survey. European representation was as follows: France: 2, Greece: 2, Italy: 3, Spain: 2, Switzerland: 1, Germany: 1, the Netherlands: 1, Finland: 1, Albania: 1 and Bulgaria: 1.

Delphi Round 1

The first-round questionnaire included 80 statements, with strong positive or negative consensus achieved in 36/80 (45%) of them. The statements included in the first round of the Delphi survey are listed in Table 1.

Delphi Round 2

To enhance agreement levels in the second round, the leading group reviewed and modified 44 statements, in which there was a lack of consensus in the first round. Thirty-six of forty-four statements were merged, resulting in a total of 26 statements. In addition, four new statements were introduced in the second round, to better clarify the panel of discussed issues. The second round featured a total of 30 statements (26 from the first round and 4 additional items that are listed in Table 2). In this second round, a strong consensus in 21 out of 30 statements (70.0%) and moderate consensus in six statements (20.0%) was achieved, whilst three statements (10.0%) failed to obtain either strong or moderate positive/negative consensus (Figure 1).

Diagnosis and grading

The results indicated a high level of consensus among participants in the vast majority of statements included in the section of diagnosis and grading (Table 1; Table S1). The diagnosis of acneiform rash is primarily determined by the morphology and distribution of the rash, along with a recent history of EGFRi initiation, a consensus agreed upon by 96.88% of respondents, whilst 87.50% recognize the importance of distinguishing EGFRi acneiform rash from corticosteroid-induced acneiform rash. Biopsy for diagnostic purposes is not recommended (84.37%) and should be only performed if signs and symptoms persist, despite appropriate treatment (83.88%). Furthermore, strong consensus was achieved on the necessity of performing bacterial swab cultures in cases of clinical signs and/or symptoms of skin superinfection, or in cases of treatment resistance (not responding after 1 week of treatment), both at approximately 90.0% level of agreement. The systematic detection and treatment of skin superinfection also appears necessary, as recommended by more than 90% of experts in the case of severe or resistant forms (Table 2). This is in strict correlation with the available data on the risk of staphylococcus aureus superinfection in nearly 30% of cases.[41–43]

Considering the proposal to align grading with oncologists, using the Common Terminology Criteria for Adverse

TABLE 1 Selected statements of the Delphi process, for which strong consensus was reached from Round 1.

Statement	Agreement/vote	Strong consensus
Diagnosis and grading		
Diagnosis of papulopustular rash is mostly based upon the morphology and distribution of the rash and history of recent EGFRi initiation	96.88% in favour	Yes
Differentiation of EGFRi papulopustular rash from acneiform rash attributed to corticosteroids is important and it is mostly based on patients' history, morphology and distribution of rash (corticosteroid-induced acne typically presents with a monomorphous inflammatory papular or pustular rash usually involving the upper trunk and arms and in a lesser degree the face)	87.5% in favour	Yes
Biopsy for diagnostic purposes is usually not recommended	84.37% in favour	Yes
Cultures from exudate or scale should be performed (bacterial, viral, fungal) if clinical signs and/or symptoms of superinfection are present (crusts, pain, exudate)	90.32% in favour	Yes
Cultures from exudate or scale should be performed (bacterial, viral, fungal) in resistant-to-treatment cases	90.62% in favour	Yes
Grading based on CTCAE should be recommended to align with oncologists.	78.12% in favour	Yes
BSA alone is not an adequate tool for grading	90.63% in favour	Yes
Patient-oriented outcomes (DLQI, Pruritus NRS) and specific scales, such as FACT EGFRi 18, should be considered for grading and subsequent EGFRi modification	75.00% in favour	Yes
Prophylactic treatment		
All patients under EGFRi treatment should be advised to use a topical emollient on a daily basis	100% in favour	Yes
All patients under EGFRi treatment should be advised to use a sunscreen (SPF > 30)	93.54% in favour	Yes
The patients under EGFRi should be advised to avoid irritative products, such as those containing salicylic acid, retinoids and other regimens usually used for acne vulgaris	90.63% in favour	Yes
Pre-emptive pharmaceutical treatment		
Pre-emptive treatment should be offered to all individuals scheduled to receive EGFRi	76.25% in favour	Yes
Mild-potency topical steroids once-daily, should be used as a pre-emptive treatment (e.g. hydrocortisone 1%)	Strongly disagree (3.12%), Disagree (40.62%), Neutral (31.25%), Agree (25.00%), Strongly agree (0%)	No
Medium-potency topical steroid twice-daily should be used as a pre-emptive treatment (e.g. methylprednisolone aceponate 0.1%)	75.00% in favour	Yes
High-potency topical steroid once-daily should be used as a pre-emptive treatment (e.g. betamethasone)	84.37% against	Yes
High-potency topical steroid twice-daily should be used as a pre-emptive treatment (e.g. betamethasone)	93.75% against	Yes
Very high-potency topical steroid once-daily should be used as a pre-emptive treatment (e.g. clobetasol propionate)	84.37% against	Yes
Very high-potency topical steroid twice-daily should be used as a pre-emptive treatment (e.g. clobetasol propionate)	87.50% against	Yes
Pre-emptive treatment should continue for at least 6 weeks after EGFRi initiation	75.13% in favour	Yes
Minocycline should be offered (instead of doxycycline) in patients with history of photosensitivity or in geographic areas or during seasons with high levels of UV index	75% in favour	Yes
Standard dose of systemic isotretinoin is useful as a pre-emptive treatment	78.12% against	Yes
Reactive treatment		
Management should be individualized for each case, based upon the severity, and extension of the acneiform rash	100% in favour	Yes
Mild-potency steroids should be used for face and anatomic folds	84.37% in favour	Yes
Doxycycline (200 mg/d) should be used as a reactive treatment for grade II/III rash	81.25% in favour	Yes
Low doses of systemic isotretinoin should be offered as a first-line treatment in grade I rash	90.63% against	Yes
Standard doses of systemic isotretinoin should be offered as a first-line treatment in grade II/III rash	84.37% against	Yes
Systemic acitretin should be offered as a first-line treatment in grade II/III rash	84.38% against	Yes

TABLE 1 (Continued)

Statement	Agreement/vote	Strong consensus
Topical retinoids should be offered as a reactive treatment (e.g. adapalene, tazarotene)	77.42 against	Yes
EGFRi modification/discontinuation should be based on grade of the rash	75% in favour	Yes
EGFRi modification/discontinuation should be considered only in life-threatening situations, or if patients QoL is severely impaired	96.87% in favour	Yes
Discontinuation of EGFR-inhibitor therapy due to skin rash, must involve the patient preferences, and the oncologist and dermatologist opinion	100% in favour	Yes
EGFRi re-challenge should be attempted when severity is < grade III	87.50% in favour	Yes
If pruritus is present, oral H1 antihistamines, including sedating or not sedating may be useful	75% in favour	Yes
Skin superinfection should be detected in more severe cases or resistant to treatment	96.88% in favour	Yes
Skin superinfection (if detected) should be treated in an appropriate way, based on the antibiogram	96.87% in favour	Yes
Reassessment of the rash after 1–2 weeks of treatment is recommended	93.76% in favour	Yes
Topical pimecrolimus/tacrolimus can be used as steroid-sparing agents, for long-term maintenance of the treatment outcome after topical steroid cessation	75% in favour	Yes

Note: Selected statements included in Round 1 of the Delphi process.

Events (CTCAE), there was an agreement of 78.12%. Additionally, there is strong consensus (90.63%) against the adequacy of relying solely on body surface area (BSA) for grading. A considerable percentage (74.19%) recommends utilization of patient-oriented outcomes and specific scales for grading and subsequent modification of EGFRi treatment.[44]

Prophylactic treatment

The results in Table 1 revealed unanimous agreement, with 100% consensus, on the recommendation that all patients undergoing EGFRi treatment should be counselled to use a topical emollient daily. Furthermore, there is a high level of consensus, reaching 93.54%, that patients receiving EGFRi treatment should be advised to apply sunscreen with a sun protection factor (SPF) of 30 or higher. Another significant consensus, supported by 90.63% agreement, is the recommendation to increase awareness among patients undergoing EGFRi treatment against the use of irritative topical products, including those containing salicylic acid, retinoids and other regimens typically employed for acne vulgaris.

Pre-emptive medical treatment

Seventy-six per cent (strong consensus) of the experts agreed from the first round that pre-emptive treatment should be offered to all individuals scheduled to receive EGFRi.

Despite the high level of agreement towards administration of pre-emptive treatment, there was no agreement with regard to the precise dose of doxycycline (100 mg or 200 mg per day). For this reason, the initial two statements (Table 1) were modified and merged into one, which was included in the second round (Table S1). The latter change resulted in a consensus favouring doxycycline use, either in 100 or 200 mg per day, in the pre-emptive context.

Diversity was also recorded concerning the type and dosing of topical corticosteroids that should be offered as a pre-emptive measure. A notable disagreement was evident regarding the prophylactic application of high-potency topical steroids (e.g. fluocinonide), with 84.37% opposing their application once-daily and an even higher percentage (93.75%), for twice-daily use. A parallel trend was observed for very high-potency topical steroids (e.g. clobetasol propionate), with 84.37% and 87.50% disagreeing with once-daily or twice-daily application, respectively. However, consensus regarding the use of medium-potency topical steroids (e.g. betamethasone valerate) twice-daily as a pre-emptive treatment, gathered 75.0% concurrence.

Of note, 81.25% advocated for discontinuation of pre-emptive treatment with oral antibiotics after 6–8 weeks of EGFRi introduction if no papulopastular rash developed. A strong positive consensus (75.0%) was achieved for the use of minocycline as an alternative to doxycycline, under specific circumstances, such as a history of photosensitivity or during periods with a high UV index. Lastly, a majority of experts voted against low or standard dose of systemic isotretinoin as a pre-emptive treatment (Table 1; Table S1).

Reactive treatment (upon the development of the acneiform rash)

As indicated in Table 1, a unanimous 100% of panellists advocated for a personalized approach in managing each

TABLE 2 Consensus recommendations on EGFRi acneiform rash management.

Prophylactic skincare recommendations
• Use of a daily topical emollient
• Sun protection with SPF > 30 regularly
• Avoidance of irritative products, (i.e. salicylic acid)
Pre-emptive pharmaceutical recommendations
• Use medium-potency topical steroid twice-daily (i.e. methylprednisolone aceponate 0.1%)
• Use of 100 or 200 mg/d of doxycycline
• Administer pre-emptive treatment with oral antibiotics for at least 6 weeks following the initiation of EGFRi
• Do not consider topical antibiotics as a pre-emptive or curative modality
Management individualization
• Management should be individualized based on the severity and extension of the rash
Topical rash management
• Medium-potency steroids should be used for acneiform rash on the trunk and extremities
• Mild-potency steroids should be used for the face and anatomic folds
Systemic antibiotics
• Doxycycline as Pre-Emptive Treatment should be offered at a dose of 100 mg or 200 mg/d
• Minocycline should be used over doxycycline in patients with a history of photosensitivity or in regions with high UV index
• Doxycycline (200 mg/d) is recommended as a reactive treatment for grade 2/3 rash, but not for grade 1
• Topical Antibiotics should not be offered as reactive treatments
Duration of antibiotic treatment
• Discontinuation of pre-emptive treatment with oral antibiotics after 6–8 weeks if no clinical signs of acneiform rash develop
• Continuation of systemic antibiotics for more than 8 weeks if acneiform rash develops
Skin superinfection
• In severe or resistant cases, treat skin superinfections (most common Staphylococcus aureus) based on the antibiogram
Systemic retinoids
• Systemic isotretinoin or acitretin are not recommended as a first-line treatment for grades 1 to 3 rash
• Consideration for low dose of oral isotretinoin (0.3 mg/kg) is suggested as a second line in grade 2/3 cases not responding to or contraindicated for doxycycline/minocycline
Pruritus management
• Oral H1 antihistamines
EGFRi therapy modifications/discontinuation
• EGFRi modifications or discontinuation should be guided by the severity of the rash
• EGFRi modification/discontinuation should be considered only in life-threatening situations, or when the patient's quality of life is significantly impacted
• EGFRi re-challenge should be attempted when the severity is less than grade 3
• EGFRi discontinuation involves patient and oncologist/dermatologist preferences
• EGFRi rash should be reassessed after 1–2 weeks of treatment

Note: Consensus guidelines on EGFRi acneiform rash management.

case, tailoring it according to the severity and extent of the acneiform rash. The consensus, at 76.87%, supported the use of mild/medium-potency steroids once or twice-daily, specifically for the face and anatomical folds (84.37%). Additionally, 81.25% favoured prescribing doxycycline (200 mg/d) as a reactive treatment for grade II/III rash only.

A majority of experts agreed or strongly agreed with using oral antibiotics (grade 2/3) and topical corticosteroids (all grades) as reactive treatments. Even if the optimal duration of treatment is not defined, all experts suggest adapting management to each case (Table 1), which may include a gradual reduction in prescribed doses and screening for secondary skin superinfection. Likewise, management should also consider the limited duration of the rash over time, generally lasting a few weeks. Finally, the use of low-dose isotretinoin should be reserved for refractory and severe forms and limited to a shorter duration because of potential adverse events.

However, opinions diverged on the administration of systemic isotretinoin. Analytically, there was no consensus on the use of standard isotretinoin as a first- or second-line treatment, regardless severity of clinical grading. In addition, a resounding 90.63% strongly disagreed with offering low doses as the primary treatment for grade I rash. Similarly, 84.38% did not recommend systemic acitretin as a primary treatment for grade II/III rash. On the contrary, experts agreed that low doses of systemic isotretinoin should be offered as a second-line treatment in grade II/III rash not responding or contraindicated in doxycycline/minocycline. However, its use must be limited to refractory and severe forms, over a probably even more limited period.

A large majority of experts disagreed with prescribing skin-directive therapy including topical antibiotics (erythromycin, clindamycin, metronidazole and chloramphenicol, Table S1, round 2) or topical retinoids (e.g. adapalene and tazarotene) as a reactive treatment (strong negative consensus of 78.13% and 77.42%, respectively). A clear consensus against the use of topical vitamin K1 and K3 was also observed.

Respondents agreed (75%) that modifying or discontinuing EGFRi should be based on the rash's grade, and 96.87% supported disruption/discontinuation only in life-threatening situations, or when the patient's QoL is severely impaired. EGFRi discontinuation must consider patient and oncologist/dermatologist preference (100% positive consensus). Respondents also expressed a strong positive consensus (87.5%) for attempting EGFRi re-challenge when the grade of severity is <3. Regarding pruritus management, 75% supported the potential usefulness of oral H1 antihistamines.

There was almost unanimous consensus for the detection and treatment of skin superinfection (96.88% and 96.87%, respectively) in more severe cases or those resistant to treatment, based on the results of the bacterial sensitivities. Re-evaluation of the rash was recommended after 1–2 weeks of treatment (93.76%). Finally, 75% expressed a positive vote for using topical pimecrolimus/tacrolimus as steroid-sparing

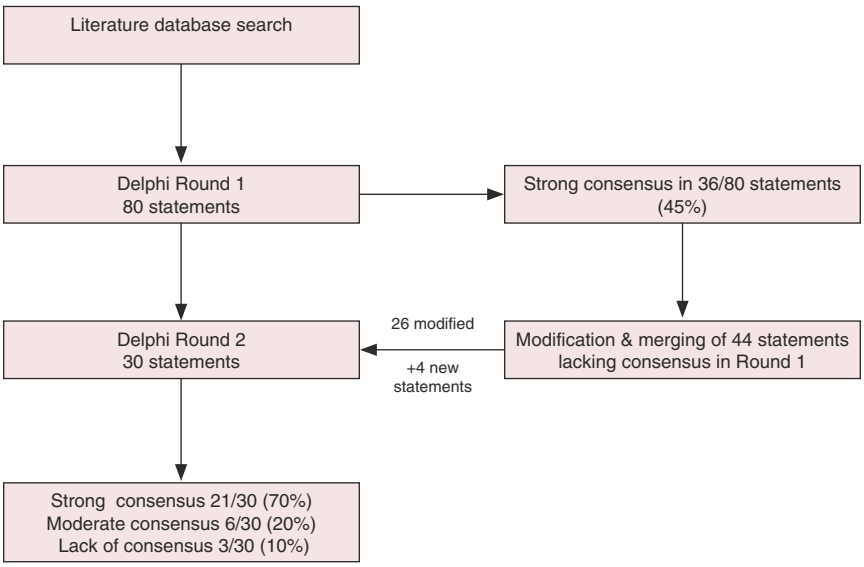

FIGURE 1 Flowchart of the modified Delphi process.

agents for the long-term maintenance of treatment outcomes after topical steroid cessation.

Items with lack of consensus (round 2)

The three items that failed strong or moderate consensus were related to (i) the use of topical pimecrolimus/tacrolimus as a first-line treatment in acneiform rash, instead of topical steroids (Strongly disagree [16.13%], Disagree [25.81%], Neutral [9.68%], Agree [45.16%], Strongly agree [3.23%]) the first one, (ii) to the use of systemic acitretin as a second-line treatment in grade II/III rash not responding or contraindicated to doxycycline/minocycline/isotretinoin (Strongly disagree [3.12%], Disagree [43.75%], Neutral [6.25%], Agree [43.75%], Strongly agree [3.12%]) the second one and (iii) to the need of evaluating serum zinc levels in individuals with EGFR-I induced acneiform rash (Strongly disagree [3.12%], Disagree [43.75%], Neutral [21.88%], Agree [28.12%], Strongly agree [3.12%]) the third one (Figure 1).

With regard to the use of topical calcineurin inhibitors as first-line options, in EGFRi-induced acneiform rash there are conflicting data in the literature. The majority of the existing studies conclude that these regimens fail to show a beneficial effect.[45,46] However, in daily practice topical calcineurin inhibitors are still used as first-line therapy by certain physicians, especially in body sites prone to develop corticosteroids-related AEs, for example flexular areas and neck.[45]

Considering the use of systemic acitretin as a second-line treatment in grade II/III rash, literature data are scarce, potentially resulting in the lack of consensus.[47,48] In the same way, there is a lack of clear evidence regarding the role of zinc deficiency and zinc supplementation in the context of EGFRi acneiform rash, resulting in lack of clear guidance.[49]

Proposed comprehensive guidelines following Delphi consensus

A comprehensive guide based on the consensus and recommendations for managing acneiform rash associated with EGFRi are illustrated in Figure 2. Prophylactic skincare measures include daily use of topical emollients, SPF > 30 sun protection and avoidance of irritative products. Pre-emptive skin-directed therapy may involve application of a medium-potency topical steroid, such as methylprednisolone aceponate 0.1%. Management must be individualized based on rash severity. Steroid-sparing agents like topical pimecrolimus/tacrolimus can be used as an alternative to topical corticosteroids for long-term maintenance. The use of oral antibiotics, such as doxycycline or minocycline, vary based on factors like photosensitivity, dose and rash severity. Systemic retinoids are not recommended as first-line, but low-dose isotretinoin may be considered as a second-line option in grade II/III. Pruritus should be managed with oral H1 antihistamines. EGFRi dose adjustment or discontinuation should be guided by rash severity, with re-challenge attempts for severity ≤ Grade II, and discontinuation based on patient and oncologist/dermatologist preferences in life-threatening situations or significant QoL impairment. Regular reassessment of the EGFRi rash is recommended after 1–2 weeks of treatment.

An algorithm of practical guidelines of EGFRi acneiform rash based on our Delphi consensus is illustrated in Figure 2.

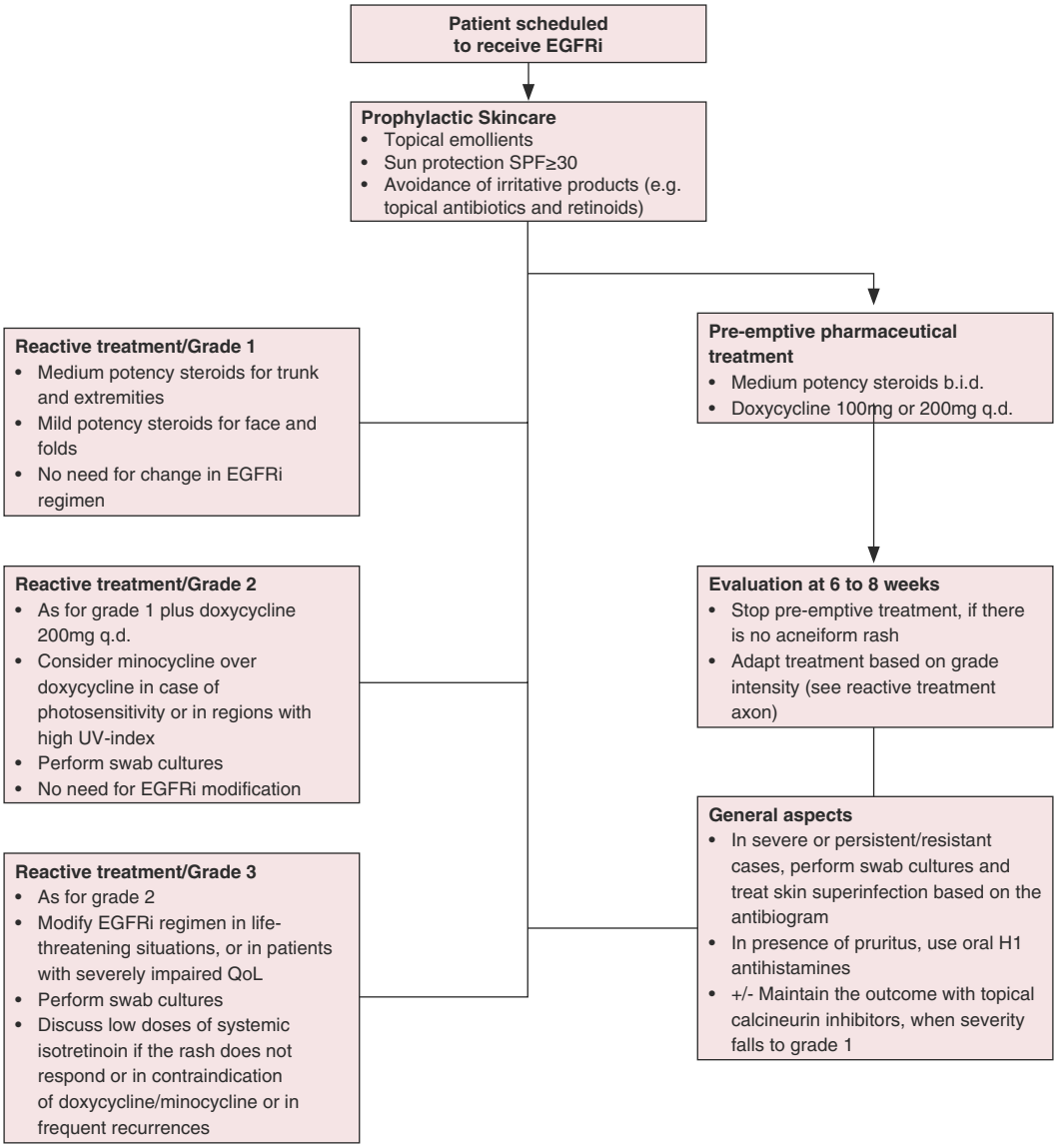

FIGURE 2 Algorithm of practical guidelines of EGFRi acneiform rash based on Delphi consensus.

DISCUSSION

There is a plethora of data in the literature, and a few consensus statements, providing comprehensive guidelines for managing EGFRi-related dermatologic AE.[9,19,24,27,28,41–44] The latter often emerge from contradictory or unconsolidated data from experts who manage patients on a daily basis.

This Delphi consensus was obtained after evaluation by recognized experts in the field, with extensive experience in the management of these dermatological toxicities in Europe, Canada, Argentina, the United States, Israel and Asia. Existing literature was reviewed, including preventive strategies, therapeutic interventions and guidelines/recommendations related to the management of EGFRi-related acneiform rash, and a total of 84 statements were included in this survey-based Delphi consensus process.[50–52]

We addressed aspects such as diagnosis, grading of severity, prophylactic measures, pre-emptive and reactive interventions, and issues related to the impact on patients' QoL and team management. The findings presented in Table 1 provide valuable insights into the agreements and divergences. Results in Table S1 underscore the importance of achieving consensus on proactive measures for managing dermatologic AEs linked to EGFRi therapy. This emphasizes the essential requirement for a standardized approach to prophylactic care in order to enhance the overall management of this AEs.

Systemic antibiotics, notably tetracyclines, have been tested in both, pre-emptive and therapeutic context, of EGFRi-related skin toxicity, and are the regimens mostly used in the daily practice.[21,24–26,29–33] Prophylactic, topical therapies, such as dapsone and tazarotene have been also assessed with promising results.[53,54] Adapalene and clindamycin phosphate

with benzoyl peroxide gels have also demonstrated efficacy, but their use is limited by the irritation they may provoke.[55,56] Nadifloxacin cream and prednicarbate cream showed improvement in a specific patient subset.[57] Whilst pre-emptive treatment with systemic antibiotic typically involves the use of doxycycline 200 mg per day,[16] in our study consensus was reached for the use of oral doxycycline, either in 100 or 200 mg per day, as a pre-emptive strategy. Conversely, we observed a consensus against the use of topical antibiotics in a curative approach.

Conflicting results also exist in the literature in regards with the use of prophylactic and reactive treatment approaches including topical pimecrolimus and vitamins K1 and K3.[46,58–61] Based on our results, topical vitamin K1 and K3 should not be considered, neither as prophylactic, nor as reactive treatment. Efficacy of topical chloramphenicol cream has been also investigated, but the evidence is poor.[62]

Research has been conducted regarding the role of preventive application of topical or oral retinoids and their effectiveness in averting acneiform eruptions. Despite the substantial evidence concerning usefulness of topical and oral retinoids in EGFRi-induced acneiform rash, their utilization in daily practice is not widely accepted mostly due to safety and tolerability issues.[14,29,48,63] Our consensus is against the use of topical or oral retinoids, as pre-emptive or reactive modalities. However, the experts favoured administration of low doses of systemic isotretinoin, as a second-line treatment in grade II/III rash not responding or contraindicated in doxycycline/minocycline.

Aligned with existing literature, outcomes from the Delphi process illustrate the diverse viewpoints regarding the optimal pre-emptive management strategies and reactive treatment of EGFRi-associated acneiform rash. These results bring to light the intricacies and nuances inherent in clinical decision-making.

In conclusion, this consensus sheds light on critical aspects often overlooked by medical professionals managing EGFRi-induced acneiform rash, such as the precise dose of doxycycline in the pre-emptive and therapeutic context, the potential benefits of low-dose isotretinoin in grade II/III acneiform rash, the potency of topical steroids depending on grade of severity and the utility of steroid-sparing agents like pimecrolimus, as a maintenance treatment. Our findings provide vital information that is often unknown to radiotherapists, general practitioners and oncologists, who remain the main target for education and a foundation for clinicians to make informed decisions in the management acneiform rash.

AUTHOR CONTRIBUTIONS

Development of statements: ZA, VS, AF-M, DF and PS. Literature review: KG, AO-B, VN, SD, SB, AG, NK, MB-B, CL, CI, JS, IT, RD-G, MS, CC, BK, MW, NL, PR, MS, VM, JR, JH, ABP, CMR-H, LK, MK, MF, JH and ML. Original draft preparation: ZA. Writing—editing: KG, AFM and SV. Visualization: KG. All authors reviewed, read and agreed to the published version of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

Ethics approval was not required, since the paper did not involve research with human participants.

ETHICAL STATEMENT

This material is the authors' own original work and has not been previously published or is under consideration for publication elsewhere. The paper reflects the authors' own research and analysis in a truthful and complete manner. The paper properly credits the meaningful contributions of co-authors and co-researchers. The results are appropriately placed in the context of prior and existing research. All sources used are properly disclosed (correct citation). Literally copying of text must be indicated as such by using quotation marks and giving proper reference. All authors have been personally and actively involved in substantial work leading to the paper and will take public responsibility for its content.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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