Support Care Cancer (2012) 20:1395–1404
DOI 10.1007/s00520-012-1451-6

REVIEW ARTICLE

Management of cutaneous adverse events induced by anti-EGFR (epidermal growth factor receptor): a French interdisciplinary therapeutic algorithm

Z. Reguiai · J. B. Bachet · C. Bachmeyer · L. Peuvrel · M. Beylot-Barry · M. Bezier · E. Boucher · C. Chevelle · P. Colin · R. Guimbaud · L. Mineur · M. A. Richard · P. Artru · P. Dufour · J. M. Gornet · E. Samalin · R. J. Bensadoun · M. Ychou · T. André · B. Dreno · O. Bouché

Received: 7 December 2011 / Accepted: 26 March 2012 / Published online: 27 April 2012

Abstract
Purpose Cutaneous adverse events induced by epidermal growth factor receptor (EGFR) inhibitors can hamper the patients' quality of life. The aim of our work was to draft an algorithm for the optimised management of this skin toxicity.

Methods This algorithm was built in three steps under the responsibility of a steering committee. *Step I*: a systematic literature analysis (SLA) has been performed. *Step II*: the collection of information about practices was performed through a questionnaire.These questions were asked during regional meetings to which oncologists, gastro-enterologists,

B. Dreno For equal work of the last author.

Z. Reguiai (✉)
Department of Dermatology, CHU Reims, Hôpital Robert Debré,
avenue du Général Koenig,
51092 Reims, France
e-mail: zreguiai@chu-reims.fr

J. B. Bachet
Department of Hepato-Gastro-Enterology, Groupe Hospitalier
Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris,
Paris, France

C. Bachmeyer
Department of Internal Medicine, Hôpital Tenon, Assistance
Publique-Hôpitaux de Paris,
Paris, France

L. Peuvrel · B. Dreno
Department of Dermatology-Oncology, CHU Hôtel Dieu,
Nantes, France

M. Beylot-Barry
Department of Dermatology, Hôpital du Haut Lévêque,
CHU Bordeaux,
Pessac, France

M. Bezier
Department of Dermatology-Venerology, Hôpital Saint Louis,
Paris, France

E. Boucher
Department of Medical Oncology, Centre Régional de Lutte contre
le Cancer Eugène Marquis,
Rennes, France

C. Chevelle
Department of Radiotherapy, Clinique Pasteur,
Toulouse, France

P. Colin
Department of Oncology Radiotherapy, Polyclinique Courlancy,
Reims, France

R. Guimbaud
Department of Gastro-Enterology, Hôpital de Rangueil,
Toulouse, France

L. Mineur
Department of Oncology Radiotherapy, Institut Sainte Catherine,
Avignon, France

radiotherapists, and dermatologists were invited. *Step III*: a final meeting was organised involving the bibliography group and the steering committee and regional scientific committees for proposing a final algorithm.
Results Step I: 14 publications were selected to evaluate the use of cyclines as curative or prophylactic treatment of the folliculitis induced by EGFR inhibitors. Nineteen publications were retained for the topical treatment of the folliculitis. Forty-six articles were selected for the management of the cutaneous lesions in link with appendages and 12 for xerosis and pruritus. *Step II*: 96 delegates attended the seven regional meetings and 67 questionnaires were analysed. *Step III*: a final algorithm was proposed on the basis of the conclusions of the first two steps and expert opinions present at this final meeting. The different propositions were unanimously approved by the 14 experts who voted.
Conclusions This multidisciplinary study summarising published data and current practices produced a therapeutic algorithm, which should facilitate the standardised, optimised management of skin toxicity associated with EGFR inhibitors in France.

Keywords Epidermal growth factor receptor inhibitors · Cetuximab · Panitumumab · Erlotinib · Gefitinib · Drug eruption · Paronychia · Pruritus

Introduction

Epidermal growth factor receptor (EGFR) inhibitors have proven their efficacy in the management of advanced colorectal, lung cancers and squamous cell cancers of the head and neck by improving the survival rate of treated patients. This efficacy is, however, often associated with essentially dermatological side effects, which can significantly impact a patient's quality of life and thus hamper continued treatment. A greater understanding of these side effects and appropriate treatment regimens for this toxicity should optimise treatment acceptance and improve compliance.

A number of recommendations have recently been published in an attempt to specify the ways in which these skin-related side effects can be managed [1–15]. Nevertheless, management strategy is empirical and is usually based on personal prescription patterns. The aim of our work was to draft a therapeutic algorithm to manage EGFR inhibitor-induced skin lesions, thus creating a structured management framework and harmonised practices.

Method

Our work began in May 2010 with the creation of a multidisciplinary steering committee comprising two gastrointestinal oncologists, one radiotherapist and one dermatologist (chairman). This committee defined the methodology with three steps permitting to reach a final algorithm based both on evidence-based medicine and clinical experience of both oncologists and dermatologists.

Step I

A bibliographical study group composed by three dermatologists and one oncologist initially carried out a systematic review of relevant published data. This systematic literature

M. A. Richard
Department of Dermatology, CHU Timone, Assistance Publique des Hopitaux de Marseille,
Marseille, France

P. Artru
Department of Internal Medicine—Oncology, Hôpital Privé Jean Mermoz,
Lyon, France

P. Dufour
Centre Régional de Lutte Contre le Cancer, Centre Paul Strauss,
Strasbourg, France

J. M. Gornet
Department of Hepato-Gastro-Enterology, Hôpital Saint Louis,
Paris, France

E. Samalin
Centre Régional de Lutte contre le Cancer Val d'Aurelle,
Montpellier, France

R. J. Bensadoun
Radiation Oncology Department,
Poitiers University Hospital and Faculty of Medicine,
2 rue de la Milétrie, BP 577, 86021 Poitiers Cedex, France

M. Ychou
Centre Régional de Lutte Contre le Cancer Val d'Aurelle,
Montpellier, France

T. André
Department of Medical Oncology, Hôpital St. Antoine, Assistance Publique—Hôpitaux de Paris,
Paris, France

O. Bouché
Department of Hepato-Gastro-Enterology and Gastro-Intestinal Oncology, CHU Reimsn,
Reims, France

analysis (SLA) was carried out in accordance with the Cochrane Collaboration Guidelines [16].

The search strategy was compiled with the help of an experienced librarian. Three electronic databases, Pubmed, Embase and Cochrane (central register of randomised controlled trials), were searched simultaneously in November 2010. The clinical questions to be assessed by the systematic review were defined on the basis of the types of skin lesions caused by EGFR inhibitors, starting from the anatomical structures of the skin which were involved: (1) the pilo-sebaceous follicle for folliculitis; (2) the skin barrier for xerosis and fissures, and eczema; and (3) the cutaneous appendages: nails and hairs. The searches were structured in the form of key words relating to EGFR inhibitor treatments and their cutaneous adverse events ("EGFR inhibitor", "anti-epidermal growth factor", "cetuximab", "panitumumab", "erlotinib" and "gefitinib") and skin toxicity study ("skin toxicity", "rash", ""acne", "acneiform", "nail", "paronychia", "hair", "alopecia", "hirsutism", "hypertrichosis", "trichomegaly", "xerosis", "pruritus" and "itch"). On completion of this electronic search, a manual search using the references quoted in the articles allowed additional publications to be extracted. Only articles written in English and French were selected. The literature reviews, recommendations or consensus conference and the series of clinical cases for which the treatment or clinical course was unclear were not included in our analysis. The methodological quality of the selected articles was subjected to an evidence-based analysis, as defined by the Oxford Centre for Evidence-Based Medicine [17].

Step II

The collection of information about practices was performed through a questionnaire of 31 questions compiled by the steering committee, and the questions referred to the management of ten current clinical situations put forward in the context of prescribing an EGFR inhibitor (prevention, slight folliculitis, severe folliculitis, superinfected folliculitis, xerosis and skin fissures, paronychia, trichomegaly, scalp lesions and associated radiodermatitis). These questions were asked during regional meetings to which oncologists, gastro-enterologists, radiotherapists and dermatologists were invited. Regional meetings were held between November 2010 and January 2011 in seven French towns/cities (Paris, Reims, Strasbourg, Lyon, Rennes, Toulouse and Aix-en-Provence). A regional scientific committee (RSC) comprising three to five local experts, each one representing the medical specialty involved, chaired these meetings. The questionnaires, completed outside discussions, highlighted the prescription patterns of the 79 practitioners who attended. The answers given in the questionnaires were assessed by descriptive analysis taking the objective into account for those participants who were not dermatologists. The dermatologists were only involved in the post-questionnaire discussion of the clinical cases.

Step III

In May 2011, a national meeting was held over 1.5 days. The aim of this meeting was to build an algorithm for the management of cutaneous adverse event-induced EGFR inhibitors according to their severity, taking into account both the literature (systematic review performed by the bibliographic study group) and the clinical experience (collected during regional meetings). The 20 members of this meeting were the steering committee, chairs of the regional meetings and bibliographic study group. After 1 day of discussions between the experts, the final algorithm was proposed by the steering committee trying to respect the

Table 1 Prevention of EGFR inhibitor-induced skin lesions or procedure to adopt when introducing EGFR inhibitor treatment

	Prevention
Systemic treatment	Cyclines (mg/day)[a]:
	—Doxycycline 200 mg, in 2 divided doses (level II)
	Alternatives (EO):
	In once a day
	—Doxycycline 100 mg
	—Lymecycline 300 mg
	—Minocycline 100 mg
	Duration of treatment: at least 6 weeks
Local treatment	Not indicated
Accompanying skin care products (cosmetology)	Recommend:(EO)
	—Emollient, moisturising cream
	—Perfume-free cleanser with a pH close to that of the skin (pH 5.5): liquid or solid syndet, dermatological soap
	—Conventional photoprotection (not reinforced, opt for photoprotection by clothing, SPF≥15, anti-UVA efficacy)
	—Cut the nails straight but not too short
	—Non-aggressive shaving, with caution
	Avoid:(EO)
	—Harsh manicure and/or pedicure
	—Ordinary soap (basic PH), aggressive washing, alcohol-based fragrances and lotions, and any irritation due to physical factors (hot, cold, etc.)
	—Local traumas (tightly fitting shoes and/or high heels, washing up, DIY, etc.)
Dermatological consultation	No, unless accompanied by advancing skin lesion(s) or history of dermatitis

[a] No randomised dose-finding study

Table 2 Procedure to adopt in the case of EGFR inhibitor-induced folliculitis, according to grade

	Grade 1 Papules and/or pustules covering less than 10 % of the body surface area± associated with pruritus or pain	Grade 2 Papules and/or pustules covering 10 to 30 % of the body surface area±associated with pruritus or pain. Psychosocial impact: limited daily routine	Grade 3 Papules and/or pustules covering more than 30 % of the body surface area±associated with pruritus or pain. Limited personal activities. Combined with local superinfection with indication for oral antibiotherapy
Local treatment (EO)	*Topical steroids*: apply only in the evening (class II) *if functional signs are present* (*pruritus*, *burns*)	*Topical steroids*: apply only in the evening (classes II to III), *in the absence of superinfection*	*Topical steroids*: apply only in the evening (classes III, IV[a]) *in the absence of documented superinfection*
	No other local treatment recommended	No other local treatment recommended	No local antibiotherapy (even in the event of an infection
Systemic treatment (EO)	Continuation of cyclines prescribed as preventive treatment at the same dosage and *at least until the symptoms disappear*	Continuation of cyclines prescribed as preventive treatment at the same dosage and *at least until the symptoms disappear*	Continuation of cyclines prescribed as preventive treatment at the same dosage and *at least until symptoms disappear* If secondary infection is suspected: —Bacteriological and/or viral swab. *If secondary bacterial infection is confirmed*: —Suspension of cyclines —Systemic antibiotherapy: penicillin M, synergistine (pristinamycin), or macrolides *In the case of secondary viral infection*: ⇒ Aciclovir/valaciclovir
Accompanying skin care products (cosmetology) (EO)	—Emollient, moisturising cream —Perfume-free cleanser with a pH close to that of the skin (5.5): liquid or solid syndet, foaming cleanser —Photoprotection notreinforced, conventional (SPF 30, effective anti-UVA, opt for photoprotection by clothing) —Non-aggressive shaving, with caution —*Therapeutic make-up* *Avoid*: —Ordinary soap, aggressive washing, alcohol-based fragrances and lotions, and any irritation due to physical factors (hot, cold, etc.)	Same accompanying skin care products as grade 1	Same accompanying skin care products as grades 1 and 2 To adapt to skin tolerance
Position vis-à-vis EGFR inhibitors (EO)	Treatment continued at the same dosage	Treatment continued at the same dosage. *Temporary discontinuation of treatment is possible if major psychosocial impact is present and depending ononcological therapeutic objective*	*Temporary discontinuation until symptoms improve* Package inserts for every drug have their own set of recommendations for dose modifications[b]
Dermatological consultation (EO)	If associated with progressive dermatological lesions	Desirable	Recommended

EO Experts' opinion

[a] Apart from the face

[b] Package inserts for every drug when the initial reaction has resolved to grade 2

Panitumumab: Initial occurrence: continuing infusion at 100 % of original dose. At the second occurrence: continuing infusion at 80 % of original dose. At the third occurrence: continuing infusion at 60 % of original dose. At the fourth occurrence: discontinue

Cetuximab: Initial occurrence: treatment may be resumed without any change in dose level (250 mg/m^2). Treatment may be resumed at a lower dose level (200 mg/m^2 after the second occurrence and 150 mg/m^2 after the third occurrence). If severe skin reactions occur a fourth time or do not resolve to grade 2 during interruption of treatment, permanent discontinuation of cetuximab treatment is required

Erlotinib: When dose adjustment is necessary, the dose should be reduced in 50 mg steps

Gefitinib: Patients with poorly tolerated skin adverse reactions may be successfully managed by providing a brief (up to 14 days) therapy interruption followed by reinstatement of the 250 mg dose. For patients unable to tolerate treatment after a therapy interruption, Gefitinib should be discontinued and an alternative treatment should be considered

most independent and objective approach, making a distinction between what constituted scientific proof, general facts and empirical practice. The algorithm was, therefore, put forward for presentation the next day to all experts and assessed using a democratic voting system. Their approval was measured on a scale ranging from 1 (no approval whatsoever) to 10 (full approval given).

Results

Step I: review of the literature

Folliculitis

Forty-three publications were screened to evaluate the use of cyclines as curative or prophylactic treatment of the folliculitis induced by the EGFR inhibitors. Amongst these, 29 were excluded (guidelines, unclear outcome…). Fourteen publications were definitely selected. Four randomised trials [18–21] evaluated the use of cyclines for the prevention of the onset of folliculitis. Only one study (STEPP) [18] was positive in terms of its primary objective, which was to reduce the incidence of grades 2–3 folliculitis during the first 6 weeks of treatment. The level of evidence of these studies is II.

No randomised study investigated the efficacy of cyclines as curative treatment for folliculitis; seven publications of one to four clinical cases and three non-randomised, prospective series of 11 to 24 patients reported the results of curative treatment with minocycline, doxycycline or tetracycline in conjunction with different local topical agents to varying degrees [22–25]. Cycline treatment with or without topical treatment was reported to be effective and associated with a reduction in the grade of folliculitis. The level of evidence of these articles is IV.

Regarding other topical treatments (corticoids, tazarotene, pimecrolimus, antibiotics…), 43 publications were initially selected. Twenty-four were excluded (insufficient data, unclear outcome…). Nineteen publications were finally retained: three randomised studies [18, 21, 26] and numerous case series with extremely heterogeneous management strategies combining local treatments or local and systemic treatments. Topical corticosteroids are considered efficient as curative treatment. There is no solid data evaluating the interest of hydrocortisone or any other local topical corticosteroids alone for the prevention of cutaneous adverse events induced by EGFR inhibitors. Randomised trials showed tazarotene [21] and pimecrolimus [26] to be ineffective for the treatment of the folliculitis.

Table 3 Procedure to adopt in the case of EGFR inhibitor-induced paronychia

	Asymptomatic paronychia	Moderate and symptomatic paronychia	Severe paronychia impacting upon daily life
Local treatment (EO)	Class IV topical steroids	*In the absence of superinfection*, class IV topical steroids with occlusion	*In the absence of superinfection*, class IV topical steroids with occlusion
Systemic treatment (EO)	Continuation of cyclines prescribed as preventive treatment at the same dosage and *at least until the symptoms disappear* (EO)	Continuation of cyclines prescribed as preventive treatment at the same dosage and *at least until the symptoms disappear* (EO)	Continuation of cyclines prescribed as preventive treatment at the same dose and *at least until the symptoms disappear* (EO) *If secondary infection is suspected*: —Bacteriological swab *If secondary bacterial infection is confirmed*: —Suspension of cyclines —Systemic antibiotherapy: penicillin M, synergistine (pristinamycin), or macrolides
Accompanying skin care products (cosmetology) (EO)	Do not cut the nails too short or too straight *Avoid*: —Harsh pedicure and/or manicure —Local traumas (tightly fitting shoes and/or high heels, washing up, DIY, etc.)	Same asymptomatic form + *Pedicure and/or manicure solely on dermatological advice*	Same asymptomatic form + *Pedicure and/or manicure solely on dermatological advice*
Position vis-à-vis EGFR inhibitors (EO)	No change	No change	No change unless in the event of major psychosocial impact depending on oncological therapeutic objective Temporary discontinuation possible
Dermatological consultation (EO)	No	No	—If secondary infection is suspected (release of pus around the nail) —In the event of pyogenic granuloma

EO Experts' opinion

Cutaneous lesions in link with appendages

In the case of paronychia and pyogenic granulomas: 24 articles were selected. Only the STEPP study [18] focused on the efficacy of prophylactic treatment. Its aim was to assess a treatment combining emollients, 1 % hydrocortisone applied to the hands and feet once a day, and advice on preventing irritation using an audiovisual document and doxycycline at the dose of 2×100 mg/day. At 6 weeks, the onset of paronychia was observed in 17 % of patients in this treated group versus 36 % in the second group, the difference being statistically significant. Amongst the 23 articles focusing on the curative efficacy of treatment, we did not find any randomised study. The cases presented were small, open-label, prospective or retrospective observational studies including only one to six cases of paronychia and one microbiological study including 29 patients [27].

Concerning hair abnormalities, 22 articles about hypertrichosis and trichomegaly and six focusing on alopecia were selected. They were isolated clinical cases. Specific prophylactic treatment was never proposed for any of these undesirable effects. The treatment of hirsutism, hypertrichosis and trichomegaly was symptomatic [28, 29]. No curative treatment of alopecia was mentioned.

Cutaneous lesions in link with the skin barrier and pruritus

No study has been carried out to assess the efficacy and interest of the treatments proposed in the management of skin xerosis or pruritus. Twelve articles were selected and analysed. The clinical cases published involved between 16 and 33 patients. Emollient are generally recommended. Recently, Vincenzi et al. [30] reported a possible interest in the use outside MA indications of the anti-emetic aprepitant in erlotinib-induced pruritus. The level of evidence of this literature is low, IV.

Step II: collection of information about current practices in daily practice

Ninety-six delegates, including 12 dermatologists, attended the seven regional meetings. Sixty-seven questionnaires, completed by 33 oncologists, 31 gastroenterologist and three radiotherapists, were analysed. In

Table 4 Procedure to adopt in the case of EGFR inhibitor-induced xerosis (EO)

	Grade 1	Grade 2	Grade 3
	Slight, <10 % of the body surface area without related erythema or pruritus	Moderate, >10 % and <30 % of the body surface area with related erythema or pruritus and limiting key daily routine activities (food preparation, using the telephone, etc.)	Severe, affecting over 30 % of the body surface area with related erythema or pruritus and limiting key daily routine activities in the specific management of the patient (washing oneself, feeding oneself, taking medication, etc.)
Accompanying skin care products (cosmetology)	—*Emollient*: *moisturising cream*	—*Emollient*: *cream or ointment*	—*Emollient*: *ointment*
	—Bath oil	—Bath oil	* Cerat de Galien
	Continuation of accompanying preventive measures	Continuation of accompanying preventive measures	* Cold cream
			* Vaseline
			* Ointment/salve
			—Bath oil
			In the event of fissures:
			—Occlusive dressing (hydrocolloid)
			—Ethyl-cyanoacrylate skin adhesive
Other local treatment	Topical steroids not indicated	Topical steroids not indicated	Topical steroids not indicated
Systemic treatment	Efficacy of H1 anti-histamines not demonstrated	Efficacy of H1 anti-histamines not demonstrated	Efficacy of H1 anti-histamines not demonstrated
Position vis-à-vis EGFR inhibitors	No change	No change	No change unless major psychosocial impact and according to the oncological therapeutic objective
			Temporary discontinuation possible
Dermatological consultation	No	No	In the event of debilitating eczema or pruritus

preventive treatment, moisturising and cyclines were recommended by the majority of practitioners (63 % and 62 %, respectively). In curative treatment, a consensus approach was adopted, especially for uncomplicated cases of folliculitis. Differences mainly appeared in the treatment of less typical cases. The referral to a dermatologist is low. It was not envisaged at the moment of introduction of EGFR inhibitors. Once lesion appeared, only 43.3 % of practitioners proposed a dermatology visit motivated by a significant psychological or functional impact and 40.3 % because a secondary infection was either present or suspected. The behaviour concerning the interruption or continuation of EGFR inhibitors was uniform for mild lesions (grade I); conversely, for the more severe cases of folliculitis (grades II and III) or specific cases combined with radiodermatitis, the approach was less clear-cut.

Step III: therapeutic algorithm

The algorithm is composed of five parts summarised in five tables: prevention treatment (Table 1), then three parts for the treatment of cutaneous lesions in link with either pilo-sebaceous follicle, or appendages or skin barrier and finally in the fifth part is given the treatment of cutaneous lesions after combined therapy with anti-EGFR and radiotherapy. Except for prevention, the treatment proposed took into account of the severity of cutaneous lesions according to three grades based on the classification currently used in clinical trials, The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [31]. Regarding paronychia, the expert panel deemed that this classification was inappropriate and proposed a more suitable segmentation.

All of our recommendations are level IV in terms of expert opinion (EO) apart from the recommendation regarding doxycyclines on introducing EGFR inhibitor treatment, which constitutes level II. The different propositions were unanimously approved by the 14 experts who voted. The level of acceptance was very high, ranging from 9.10 to 9.85.

Preventive measures recommended on introduction of EGFR inhibitors (Table 1)

Based on literature it is recommended, simultaneously to the introduction of EGFR inhibitors, to prescribe cyclines at 200 mg/day and a daily use of moisturing cream. Many accompanying care including measures that are not recommended and should be avoided are summarised in Table 1; they were mainly based on expert opinion.

Table 5 Procedure to adopt in the case of radiodermatitis associated with EGFR inhibitor-induced folliculitis (EO)

	Folliculitis grade 1 Papules and/or pustules covering less than 10 % of the body surface area±associated with pruritus or pain	Folliculitis grade 2 Papules and/or pustules covering 10 to 30 % of the body surface area±associated with pruritus or pain Psychosocial impact: Restricted daily routine	Folliculitis grade 3 Papules and/or pustules covering over30% of the body surface area±associated with pruritus or pain Restricted personal activities Combined with local superinfection with indication of oral anti-biotherapy[a]
Grade I radiodermatitis Follicular or moderate erythema, hair removal, dry desquamation or less sweating	Emollient	Emollient, classes II to III topical steroids	Emollient, classes II to III topical steroids *Temporary withdrawal of radiotherapy and EGFR inhibitor*
Grade II radiodermatitis (*exudative lesions*) Shiny, bright red erythema or weeping, non-confluent desquamation in the skin folds or grooves or moderate oedema	Drying, non-alcoholic solution	Drying, non-alcoholic solution *Temporary discontinuation of EGFR inhibitor*	Drying, non-alcoholic solution *Temporary discontinuation of radiotherapy and EGFR inhibitor*
Grade III radiodermatitis Weeping desquamation outside skin folds or pitting oedema, or bleeding caused by minor trauma or abrasion	*Temporary discontinuation of radiotherapy*	*Temporary discontinuation of radiotherapy and EGFR inhibitor*	*Temporary discontinuation of radiotherapy and EGFR inhibitor*

Radiodermatitis grading is derived from CTCAE scoring system, with grouping so as to simplify our recommendations

[a] If secondary infection is suspected: a bacteriological swab is recommended. If the bacterial secondary infection is confirmed, systemic antibiotics can be given (there is no true radiosensitivity to antibiotics)

Cutaneous lesions in link with pilo-sebaceous follicle (Table 2)

On the basis of the SLA and expert opinion, it is recommended to treat folliculitis by keeping cyclines at the same dosage as prescribed in prophylactic therapy until symptoms disappear. Minocycline is proposed as the second line on an expert consensus based on the experience of dermatologists at a dosage similar to acne: 100 mg/day.

Amongst the other dermatological treatments, only topical steroids were selected, based on expert consensus. The strength of the corticoid should be adapted depending on the degree of severity of the folliculitis. Thus, class III (strong) and class IV (very strong) corticoids are reserved solely for grade 3. The facial application of a class IV corticoid is contraindicated.

Cutaneous lesions in link with appendages (Table 3)

The paronychia was classified by the steering committee according to three grades (asymptomatic, moderate, severe and affecting daily routine), depending on the extent to which they impact a person's lifestyle. For the three grades, class IV (very strong) topical steroids are proposed in the absence of secondary infection, combined with systemic antibiotic therapy with cyclines, which is continued until symptoms disappear (expert consensus). In severe form, grade 3, with secondary infection confirmed with a swab, considers a consultation with a dermatologist.

In the case of pyogenic granuloma, a treatment initiated by dermatologists as silver nitrate, electrocoagulation and intralesional corticoid injections under local anaesthesia and CO_2 laser at his/her fingertips is recommended. In the case of hirsutism-related problems, symptomatic treatment is considered in the event of excessive problematic hair coverage: bleaching, hair removal using a non-aggressive method (tweezers, laser, LED and avoiding wax) or topical eflornithine (expert consensus). In the case of trichomegaly of the lashes, cautious cutting with a pair of scissors is recommended (expert consensus).

Cutaneous lesions in link with the skin barrier—xerosis (Table 4)

The treatment proposed is based on dermo-cosmetic with a foaming soap respecting the acid pH of the skin and a moisturizing cream. Preference is given to greasy emollients for the treatment of more severe forms of xerosis.

Radiodermatitis associated with folliculitis (Table 5)

The approach to adopt for the management of radiodermatitis in the presence of EGFR inhibitor-induced folliculitis differs from that used for conventional radiodermatitis. In this case, it is recommended to take the grade of the folliculitis lesion into account in addition to that of the radiodermatitis so as to adjust anti-cancer treatment, EGFR inhibitor chemotherapy and radiotherapy, in particular. The experts recommended a strategy for cancer treatment

Table 6 Main existing recommendations regarding the management of EGFR inhibitor-induced side effects in the skin

References	Year	Zone	Specialists involved	Methodology and description
Segaert [2]	2004	Europe	Dermatologists and gastro-enterologists	European consensus conference
Lacouture [6]	2007	US	Haematologists, oncologists, ophthalmologists and dermatologists	Therapeutic approach—clinical cases per proprietary product
Eaby [4]	2007	US	Oncologists, nurses, pharmacists and dermatologists	Created following a multidisciplinary forum—classification in 3 grades
Bernier [8] *Support Merck*	2007	7 countries representing Europe and the US	Medical oncology experts, oncologists, radiotherapists and dermatologists	Discussion of panel comprising 11 experts based on the management of radiodermatitis associated with EGFR inhibitor-induced skin reactions in neck and head cancers
Melosky [3] *Support Amgen*	2008	Canada	Oncologists and dermatologists	Algorithm based on 3 grades of severity of skin rash related to EGFR inhibition AC
Bouché [15]	2009	France	Gastrointestinal oncologists and dermatologists	Expert consensus based on the most relevant publications
Potthoff [13] *Support Amgen*	2010	Germany	Oncologists, dermatologists and pharmacologists	Created following 2 consensus meetings with an expert panel
Lacouture [7]	2011	Multinational	Oncologists, radiotherapists and dermatologists	Expert consensus based on the most relevant publications

(radiotherapy and EGFR inhibitors) driven by the severity of both radiodermitis and folliculitis.

Discussion

Previously published recommendations were approved by national and international learned societies and mostly multidisciplinary expert groups. Their methodology varied, but they were mostly based on expert opinions relying, in turn, on published data (Table 6).

On the one hand, our methodology differed from the expert opinion since an SLA was carried out for folliculitis-, xerosis- and appendage-related problems. On the other hand, an upstream evaluation of current French practices was initiated. Based on our knowledge, it's the first time that such a practice survey has been performed in order to build an algorithm. The SLA allowed numerous publications to be selected and analysed, but it should be noted that the evidence base is generally very poor: only a few randomised trials assessed the management of skin lesions.

Finally, our methodology has allowed more specialists to be involved, since regional meetings brought together 96 practitioners. A total of 20 were able to participate in the summary meeting and in drafting final recommendations with a focus on the practical management of anti-EGFR-induced skin toxicity including medical treatment and cosmetic dermatology procedures.

Few data are actually available regarding the approach vis-à-vis EGFR inhibitors in the case of skin toxicity in clinical trials: dose reduction, even treatment withdrawal. A dose reduction is mentioned in less than 5 % of trials reporting this fact; however, a practical survey on EGFR inhibitor-induced skin toxicity reported much higher figures of 60 % and 32 % in relation to dose reduction and treatment withdrawal, respectively [32]. No published data has evaluated the impact of a reduction in EGFR inhibitor dose levels on the clinical course of an induced skin lesion. Data requiring further investigation should, therefore, be specified in future trials.

A multidisciplinary approach is recognised as essential by most of the teams involved in the recommendations. According to the data collated for French practices, it seems that dermatology consultations are far from routine. The absence of any structure allowing straightforward access to a specialist consultation could account for this low percentage. At the same time, increasing numbers of oncologists now feel that they have sufficient feedback to manage these lesions independently. Some semiological or progressive factors must motivate patients to seek a dermatological consultation. The list is not exhaustive but the main reasons are as follows: lack of improvement after 1 to 2 weeks of appropriate treatment, severe clinical signs (necrosis, blisters, purpura, etc.), secondary infection, atypical clinical signs that could be indicative of dermatitis not related to EGFR inhibitor treatment (differential diagnosis) and severe nail diseases such as pyogenic granuloma, which may warrant specific treatments.

Conclusion

This is the first therapeutic algorithm for the cutaneous adverse events of anti EGFR, which is the result of a consensus between the evidence-based medicine with the SLA and current clinical practice, finally, validated by a vote. It is also interesting that it is the result of a discussion between both oncologists and dermatologists. It is based on a practical severity and combined recommendations not only for drugs but also for cosmetic. They are geared primarily towards the introduction of clearly defined products for the optimised, standardised management of patients receiving EGFR inhibitors by all practitioners involved. The SLA has clearly highlighted the lack of randomised studies for the clear-cut evaluation of the various curative treatments prescribed for induced skin lesions.

Acknowledgments This project and the authors were supported by a grant from Amgen France. We are grateful to the members of Laboratoires Amgen France for their support and to the experts whose knowledge and experience were crucial to the development of these recommendations. Thanks to the Regional experts groups “PROCUR” E. Achille, C. Borel, C. de la Fouchardière, P. Giraud, C. Lebbe, M.T. Leccia, L. Mortier, G. Reuter, J.P. Wagner.

References

1. Segaert S, Tabernero J, Chosidow O et al (2005) The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. J Dtsch Dermatol Ges 3:599–606
2. Segaert S, Van Cutsem E (2007) Clinical management of EGFRI dermatologic toxicities: the European perspective. Oncology (Williston Park) 21:S22–S26
3. Melosky B, Burkes R, Rayson D et al (2009) Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol 16:14–24
4. Eaby B, Culkin A, Lacouture ME (2008) An interdisciplinary consensus on managing skin reactions associated with human epidermal growth factor receptor inhibitors. Clin J Oncol Nurs 12:283–290
5. Lacouture ME, Maitland ML, Segaert S et al (2010) A proposed EGFR inhibitor dermatologic adverse event-specific grading scale from the MASCC skin toxicity study group. Support Care Cancer 18:509–522
6. Lacouture ME, Cotliar J, Mitchell EP (2007) Clinical management of EGFRI dermatologic toxicities: US perspective. Oncology (Williston Park) 21(11 Suppl 5):17–21
7. Lacouture ME, Anadkat MJ, Bensadoun R-J, Bryce J, Chan A, Epstein JB, Eaby-Sandy B, Murphy BA (2011) Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-

associated dermatologic toxicities. Support Care Cancer 19:1079–1095
8. Duvic M (2008) EGFR inhibitor-associated acneiform folliculitis: assessment and management. Am J Clin Dermatol 9:285–294
9. Bernier J, Bonner J, Vermoken JB et al (2008) Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. Ann Oncol 19:142–149
10. Fox LP (2006) Pathology and management of dermatologic toxicities associated with anti-EGFR therapy. Oncology (Williston Park) 20:26–34
11. Gridelli C, Maione P, Amoroso D et al (2008) Clinical significance and treatment of skin rash from erlotinib in non-small cell lung cancer patients: results of an Experts Panel Meeting. Crit Rev Hematol 66:156–162
12. Hu JC, Sadeghi P, Pinter-Brown LC et al (2007) Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. J Am Acad Dermatol 56:317–326
13. Potthoff K, Hofheinz R, Hassel JC et al (2011) Interdisciplinary management of EGFR-inhibitor-induced skin reactions: a German expert opinion. Ann Oncol 22:524–535
14. Oishi KJ, Garey JS, Burke BJ et al (2006) Managing cutaneous side effects associated with erlotinib in head and neck cancer and non small lung cancer patient. J Clin Oncol 24:18s (abstract 18538)
15. Bouché O, Scaglia E, Reguiaï Z et al (2009) Biothérapies ciblées en cancérologie digestive: prise en charge de leurs effets secondaires. Gastroenterol Clin Biol 33:306–322
16. van Tulder M, Furlan A, Bombardier C et al (2003) Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. Spine 28:1290–1299
17. CEBM—http://www.cebm.net/index.aspx?o=1025
18. Lacouture ME, Mitchell EP, Piperdi B et al (2010) Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 28:1351–1357
19. Jatoi A, Rowland K, Sloan JA et al (2008) Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). Cancer 13:847–853
20. Deplanque G, Chavaillon J, Vergnenegre A et al (2010) CYTAR: A randomized clinical trial evaluating the preventive effect of doxycycline on erlotinib-induced folliculitis in non-small cell lung cancer patients. J Clin Oncol 28(No 15_suppl):A9019
21. Scope A, Agero AL, Dusza SW et al (2007) Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. J Clin Oncol 25:5390–5396
22. Wacker B, Nagrani T, Weinberg J et al (2007) Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res 13:3913–3921
23. Matheis P, Socinski MA, Burkhart C et al (2006) Treatment of gefitinib-associated folliculitis. J Am Acad Dermatol 55:710–713
24. Molinari E, De Quatrebarbes J, André T et al (2005) Cetuximab-induced acne. Dermatology 211:330–333
25. de Noronha e Menezes NM, Lima R et al (2009) Description and management of cutaneous side effects during erlotinib and cetuximab treatment in lung and colorectal cancer patients: a prospective and descriptive study of 19 patients. Eur J Dermatol 19:248–251
26. Scope A, Lieb JA, Dusza SW et al (2009) A prospective randomized trial of topical pimecrolimus for cetuximab-associated acne-like eruption. J Am Acad Dermatol 61:614–620
27. Amitay-Laish I, David M, Stemmer SM (2010) *Staphylococcus* coagulase-positive skin inflammation associated with epidermal growth factor receptor-targeted therapy: an early and a late phase of papulopustular eruptions. Oncologist 15:1002–1008
28. Vergou T, Stratigos AJ, Karapanagiotou EM et al (2010) Facial hypertrichosis and trichomegaly developing in patients treated with the epidermal growth factor receptor inhibitor erlotinib. J Am Acad Dermatol 63:e56–e58
29. Bouché O, Brixi-Benmansour H, Bertin A et al (2005) Trichomegaly of the eyelashes following treatment with cetuximab. Ann Oncol 16:1711–1712
30. Vincenzi B, Tonini G, Santini D (2010) Aprepitant for erlotinib-induced pruritus. N Engl J Med 363:397–398
31. NCI Common Terminology Criteria for Adverse Events (CTCAE) v4. ctep.cancer.gov/reporting/ctc.html
32. Boone SL, Rademaker A, Liu D et al (2007) Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. Oncology 72:152–159