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Symptom Management and Supportive Care

Management of Skin Toxicity Associated with Cetuximab Treatment in Combination with Chemotherapy or Radiotherapy

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ABSTRACT

Background. **Cetuximab was demonstrated by clinical trials to improve response rate and survival of patients with metastatic and nonresectable colorectal cancer or carcinoma of the head and neck. Appropriate management of skin toxicity associated with epidermal growth factor receptor inhibitor (EGFR-i) therapy is necessary to allow adequate drug administration and to improve quality of life and outcomes.**

Methods. **A group of Italian Experts produced recommendations for skin toxicity management using the RAND/UCLA Appropriateness Method. Statements were generated on the basis of a systematic revision of the literature and voted twice by a panel of 40 expert physicians; the second vote was preceded by a meeting of the panelists.**

Results. **Skin toxicity included skin rash, skin dryness, pruritus, paronychia, hair abnormality, and mucositis. Recommendations for prophylaxis and therapeutic interventions for each type of toxicity were proposed.**

Conclusions. **Interventions that were considered appropriate to improve compliance and outcomes of cancer patients treated with EGFR-i were identified.** ***The Oncologist*** 2011;16:228–238

INTRODUCTION

Cetuximab (Erbitux; Merck-Serono, Darmstadt, Germany) is a human-murine chimeric monoclonal antibody directed to the epidermal growth factor receptor (EGFR) binding site [1–4]. Clinical trials on metastatic and nonresectable colorectal cancer and on carcinoma of the head and neck demonstrated improvement of response rate and survival after cetuximab treatment [5–14].

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The major side effect associated with cetuximab treatment is skin toxicity, including skin rash, dry skin, hair growth disorders, pruritus, and nail changes [15, 16]. Cutaneous toxicity can severely impact patients' physical, psychological, and social well-being and can lead to treatment discontinuation and dose reduction. Therefore, appropriate management is necessary to allow adequate drug administration and to improve health-related quality of life and outcomes.

Interest in rash has recently increased because it was suggested to have a possible relationship with clinical outcomes [2, 13, 14, 17–27]. However, skin rash is not a useful criterion to distinguish patients with a better outcome because it is a very frequent adverse event with EGFR-targeting antibodies, and it occurs only after the exposure to these agents.

The agreement between oncologists and dermatologists in labelling and grading cutaneous lesions is poor, and interobserver inconsistencies are frequent [28]. As a consequence, the current terminology remains variable, and even the clinical features corresponding to the same terms, such as rash or acneiform rash or acnelike rash, are probably different across the trials.

Medical oncologists, radiation oncologists, and dermatologists from Italy had a meeting in Rome on December 17–18, 2009, with the aim of reaching a consensus on clinical definition and management of cetuximab skin toxicity. In the absence of definitive evidence from clinical trials, they proposed recommendations on the basis of expert opinions developed by RAND Corporation/UCLA Appropriateness Method [29].

Consensus Method

The RAND/UCLA Appropriateness method was used for this Consensus [29].

A group of expert clinicians (Advisory Board) performed a systematic review of the literature on cutaneous toxicity associated with EGFR inhibitor (EGFR-i) treatment of cancer patients. Considered issues included assessment of toxicity and benefits of different interventions in metastatic head and neck and colorectal cancer settings [30–43]. The MEDLINE database was searched for English-language studies that were published from 2005 to October 2009 and that contained the terms EGFR inhibitors, cetuximab, skin toxicity, skin rash, and/or radiation dermatitis in the title or abstract. Potentially relevant abstracts that were presented at annual meetings or gastrointestinal symposia of the American Society of Clinical Oncology and the European Society of Medical Oncology were examined. The study selection included the following: (a) observational and prospective studies about assessment and treatment; (b) randomized, double-blind, placebo-controlled, or uncontrolled studies; (c) retrospective and uncontrolled studies; (d) systematic reviews and meta-analyses; (e) consensus guidelines; and (f) available data for drugs tested in phase III studies (including abstracts).

On the basis of this literature review, the Board chose a number of key variables and generated clinical scenarios with permutations of these key variables. A wider group of panelists rated the appropriateness of treatment for each scenario through a two-round process. A meeting was held before the second rating, where statements were discussed. The final ratings were analyzed to identify aspects of skin toxicity for which the treatment was considered appropriate or inappropriate.

Consensus Panel

An Advisory Board of 9 expert members, from different clinical settings (6 medical oncologists, 2 radiation oncologists, and 1 dermatologist), was appointed, and a group of 40 panelists was identified. Each panelist and Board component had equal weight in scoring appropriateness of clinical scenarios.

Clinical Scenarios

A list of 107 common scenarios was provided by the Board, based on literature review. The interventions were categorized according to hypothetical situations or clinical scenarios based on combinations of various clinical factors. The clinical scenarios were then rated for each considered option.

First-Round Ratings

The first-round scenarios and the report of the systematic literature review were sent to the panelists. They were instructed to rate, independently, the appropriateness of treatment for each scenario without discussion with the other panelists. A scale of 1–9 was used, where 9 was defined as extremely appropriate (benefits greatly exceed risks), 5 was defined as uncertain (benefits and risks about equal), and 1 was defined as extremely inappropriate (risks greatly exceed benefits).

A treatment was appropriate if the expected health benefit exceeded the expected drawbacks and initiating the treatment was worthwhile. Panelists' ratings of the scenarios were collected online by the research team.

Second-Round Ratings

Panelists and Board discussed available evidence in a 2-day meeting, and then re-rated the appropriateness of the scenarios.

Analysis

Recommendations were scored appropriate for median ratings 7–9 (without disagreement), inappropriate for median ratings 1–3 (without disagreement), and uncertain for median ratings 4–6 or if panelists disagreed. Agreement was met when >1/3 of the scores were in the same range; disagreement was when <1/3 of the scores were in the same range. All other score distributions were defined as intermediate. Dedicated software was developed for statistical analysis of data.

Recommendations for Management during Chemotherapy

Clinical Features and Grading

Skin toxicities include skin rash, skin dryness (xerosis), pruritus, paronychia, hair abnormality, mucositis, and increased growth of the eyelashes or facial hair [15, 44–47].

Skin Rash

The most common toxicity is a papulo-pustular eruption, which affects 60%–80% of patients. It is generally mild to moderate, and it is severe (grades 3–4) in 5%–20% of patients [8, 48]. Incidence and severity are usually dose-related [44]. The rash is reversible, usually with complete resolution within 4 weeks of treatment discontinuation or sometimes during continued treatment; it may relapse or worsen at treatment restart [1, 49]. With long-term treatment, severity of rash may decrease [44].

The papulo-pustular eruption consists of erythematous follicular papules that evolve into pustules. Lesions may coalesce into plaques covered with pustules that dry and form yellow crusts [46]. In some cases, a seborrheic dermatitis-like pattern is seen on the face [1]. Rarely an edematous, warm erythema of the face, sometimes with follicular papulo-pustules and telangiectasia resembling rosacea, is seen. The eruption is acneiform and is usually confined to seborrheic areas; rarely it may involve the extremities, lower back, abdomen, and buttocks [46]. No comedones occur. In contrast to acneiform eruptions caused by other drugs, the rash may be accompanied by pruritus, sometimes severe. Cultures are negative for yeasts and bacteria. However, papulo-pustular lesion may become infected, usually with *Staphylococcus aureus*; then, oozing and yellowish crusts occur.

Skin Xerosis

Skin xerosis is present in up to 35% of patients receiving EGFR-i therapy and more frequent in patients undergoing gefitinib therapy [15, 50–53]. Xerosis develops over time and typically presents as dry, scaly, itchy skin, particularly in areas previously or simultaneously affected with the papulo-pustular eruption. Xerosis is often more widespread than the skin rash [50]. Some patients experience dryness of the vagina and perineum, causing discomfort on urination. The xerosis may evolve to chronic asteatotic eczema, with erythema and worsening of pruritus. Xerosis and eczematous changes at the fingertips, palms, and soles are associated with painful fissures.

Nail, Periungual, and Hair Toxicity

Nail and periungual toxicity occurs in 10%–20% of patients after several weeks to months of therapy and may present as acute paronychia (swollen and tender lateral nailfold), oozing, bleeding, and formation of granulation tissue leading to pyogenic granuloma-like lesions. Changes of the nails are common and include pitting, discoloration, and onycholysis, with partial or complete loss of nails. Most patients who develop nail or paronychial toxicities also experience follicular eruption. Cultures for bacteria and yeast are usually negative, but secondary infection is common. Nail changes can persist long after discontinuation of the EGFR-i [54]. Hair impairment can occur in up to 50% of patients and usually presents as either excess growth of the eyelashes and/or eyebrows (i.e., trichomegaly) or curly, wavy, fine, and brittle texture of facial hair and scalp hair. Hair toxicity usually occurs 2–5 months after the start of treatment and may resolve in weeks to months after treatment discontinuation [15].

Predictive Factors

Predictive factors for EGFR-i skin toxicity were not investigated. A retrospective study (published exclusively in abstract form) on a limited number of patients treated with erlotinib showed that a darker skin phototype was associated with reduced frequency and severity of skin toxicity [55].

Grading System

The most commonly used grading system for skin toxicity is the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI CTCAE v3.0) [56]. This classification, however, was not specifically designed to classify cutaneous side effects of EGFR-i therapy. Many of the skin signs included (e.g., vesicular eruption, bullae, exfoliation) are not associated with EGFR-i therapy. Moreover, in most patients, the eruption affects <30% of the body surface area (BSA), and the distinction between grades 2 and 3 is based on a 50% BSA involvement, which is very rarely seen if calculated accurately. A new version that distinguishes the diverse drug-related skin manifestations, including

EGFR-i skin toxicity, has been released [56], but it is not widely used yet. Unfortunately, it is very difficult to define the area affected by a follicular eruption. Important factors not yet taken into consideration include the prevalent type (e.g., papular vs. pustular), the density (and thus the total number of lesions), and the infiltration of skin lesions. Local superinfection may not always be a relevant aggravating factor. Eventually, nail-related clinical features described in this grading scale do not reflect those typically seen in response to EGFR-i.

Wollenberg et al. proposed a new composite objective scoring system specific for the acneiform eruption, which considers the type of lesions and emphasizes the facial involvement, taking into account self-related symptoms [57]. Moreover, Lacouture et al. have recently presented a new grading scale specific to EGFR-i cutaneous toxicity. This grading system needs to be validated in future clinical trials [58]. A recent study on 80 patients treated with cetuximab showed that skin rash did not significantly affect some quality of life issues, such as psychological status or social life [59]. A correlation was found with psychological distress but not with social avoidance. Unfortunately, the type of skin rash was not defined. Instead, Joshi et al. reported a quality of life decrease in patients experiencing dermatological toxicities, and particularly rash. Both physical and psychological effects were directly related to skin toxicities. Moreover, patients $<$50 years had significantly lower quality of life than patients $>$50 years [60]**.** Further studies on the impact of skin toxicity to EGFR-i therapy on quality of life are warranted.

Management of Skin Toxicity (General Skin Toxicity)

General Prophylactic Measures

Before the start of cetuximab treatment, medical history and full-body skin evaluation should be performed, with attention to xerosis, atopic dermatitis, and severe acne vulgaris. Some educational and general interventions may be used:

- Using sunscreens;
- Avoiding habits/products that can produce dry skin (e.g., hot water, alcohol-based cosmetics);
- Enhancing skin hydration (bath oils, etc.);
- Using frequently alcohol-free moisturizing creams;
- Using tocopherol oil or gel;
- Avoiding tight shoes; and
- Avoiding excessive beard growth, shaving with regular shaving razor, sharp multiblade; using pre-shaving cream emollients and moisturizing aftershave, not using alcohol and aftershave or using electric shaver.

Strategies for Single Type of Skin Toxicity

Skin Rash (Adapted from NCI-CTC Version 3) [56]. Grade 1: No dose modifications or treatment interruptions are indicated. No specific treatments should be started. Only general interventions are recommended (Fig. 1A and Table 1).

Grade 2: No dose modification or treatment interruptions are indicated. Topical antibiotic treatment with clindamycin 1% gel, erythromycin 3% gel/cream, or metronidazole 0.75%–1% cream/gel can be used 2 times per day until improvement to grade 1. Benzoyl peroxide should be avoided. For lesions of the scalp, erythromycin 2% lotion can be applied. When papules prevail (grade 2A), no systemic therapy is recommended. For pustule prevalent type (grade 2B), oral semisynthetic tetracycline (minocycline 100 mg/day, doxycicline 100 mg/day) can be used for $\geq$4 weeks and until the rash is symptomatic (Fig. 1B and Table 2).

Grade 3: Interrupt treatment for $\leq$21 days, until improvement to grade $\leq$2. At improvement, if response to cetuximab had been obtained, continue EGFR-i therapy at full dose of 250 mg/m^2. If no improvement occurs, discontinue therapy. For a second or third recurrence of skin rash, follow the dose modifications listed in Table 3. For a fourth recurrence, discontinue the treatment definitively. Topical treatment as for grade 2 can be used together with systemic therapy with oral semisynthetic tetracycline (minocycline, doxycicline) for $\geq$4 weeks and until the rash is asymptomatic, and oral corticosteroids (methylprednisolone 0.4 mg/kg, prednisone 0.5 mg/kg) for up to 10 days. For grade 3 highly symptomatic/nonresponsive patients, treatment with oral retinoids (isotretinoin 0.3–0.5 mg/kg), intravenous corticosteroids (methylprednisolone, dexamethasone), intramuscular/intravenous antihistamines (clorfenamine), intravenous antibiotics (amoxicillin/clavulanic acid, gentamicin), or hydration can be considered (Fig. 1C and Table 3).

Grade 4: Interrupt EGFR-i treatment immediately and definitively. Provide topical treatment as indicated for grades 2 and 3. Consider systemic management with oral retinoids (isotretinoin 0.3–0.5 mg/kg), intravenous corticosteroids (methylprednisolone, dexamethasone), intramuscular/intravenous antihistamines (clorfenamine), intravenous antibiotics (amoxicillin/clavulanic acid, gentamicin), and intravenous hydration (Fig. 1D and Table 4).

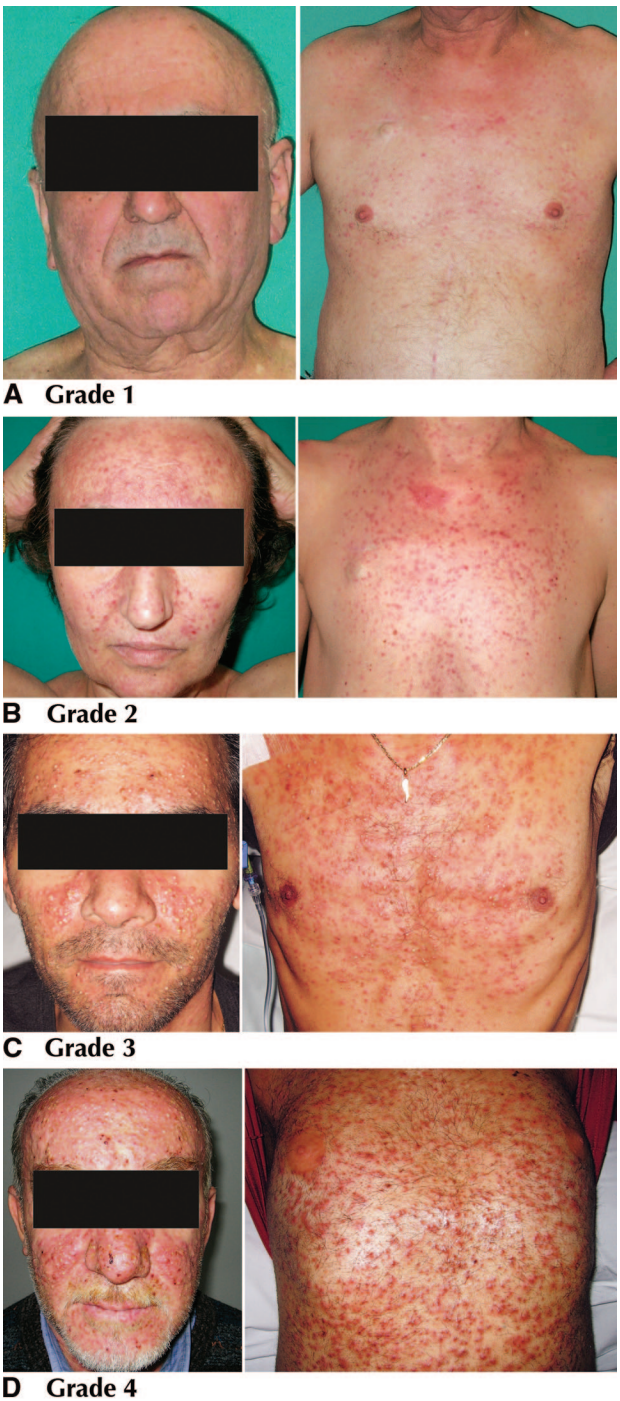

Figure 1. Skin rash grades 1–4.

Xerosis, Fissures, and Eczema. General educational and prophylactic measures are important. The regular use of emollient ointments, almond oil, preparations of polyethylene glycol, is recommended. For eczema, topical treatment with medium-potency corticosteroids for 1–2 weeks can be used: betamethasone dipropionate 0.05%–0.1% cream, clobetasone 0.05% cream, ointment fluocinolone acetonide, or hydrocortisone butyrate 0.1% cream. Simple or occlusive dressing can be considered for the extremities. Topical antibiotic is recommended for superinfection: fusidic acid 2% cream, bacitracin cream, or mupirocin 2% cream.

Table 1. Management of grade 1 skin rash

Skin lesions and symptoms	Papules, pustules, or symptom-free erythema
Cetuximab dose modifications	No
Topical treatment	No
Systemic treatment	No
Intervention	General educational and prophylactic measures

Paronychia. As a preventive intervention, it is necessary to avoid friction and pressure on the nail fold (avoid tight shoes). If paronychia develops, the following are suggested:

- Washing with antiseptics: diluted hydrochloric acid solution or boric acid solution 3%;
- Using creams containing corticosteroids and antiseptics: betamethasone 0.05% plus cliochinol 3% ointment, betamethasone 0.1% plus gentamicin 0.05% cream, betamethasone 0.1% plus gentamycin 0.1% cream, betamethasone valerate 0.1% plus fusidic 2% acid cream, triamcinolone acetonide 3% plus chlortetracycline 0.1% ointment, or triamcinolone benetonide 2% plus fusidic acid 0.03% cream;
- Using oral antibiotics for superinfection: amoxicillin/clavulanic tablets, cefalexin tablets, or clindamycin capsules;
- Using analgesic drugs (NSAIDs) per os.

Recommendations for Management during Radiotherapy

Management of Skin Toxicity (Radiation Dermatitis)

The recommendations for the management of general skin toxicity (different from radiation dermatitis) are the same as reported in the previous paragraph. Radiation dermatitis is modified by the introduction of EGFR-i in combination with radiotherapy. Leading principles according to the NCI CTCAE (version 3) grading of radiation dermatitis (Table 5) are as follows:

- Skin toxicity, if well managed, does not necessitate discontinuation or dose reduction of EGFR-i therapy.
- Treatment should be adapted to type of lesions, depending on time, patient condition, and location.

Table 2. Management of grade 2 skin rash

Skin lesions and symptoms	Eruption with papules (grade 2A) or pustules (grade 2B) covering <50% of body surface, with moderate symptoms, and that does not interfere with daily activities
Cetuximab dose modifications	No
Topical treatment	Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75%–1% cream/gel, twice/day until regression to grade 1 (avoid benzoyl peroxide products). Lesions of the scalp: erythromycin 2% lotion
Systemic treatment	Prevalence of papules (grade 2A): No Prevalence of pustules (grade 2B): Antibiotics: minocycline 100 mg per os once/day, doxycycline 100 mg per os once/day for ≥4 weeks and until the rash is symptomatic

Table 3. Management of grade 3 skin rash

Skin lesions and symptoms	Eruption with papules (grade 3A) or pustules (grade 3B) covering >50% of body surface; severe symptoms that interfere with daily activities
Cetuximab dose modifications	First occurrence: delay cetuximab infusion for ≤21 days until the skin rash improves to grade ≤ 2. If there is an improvement, continue at 250 mg/m^2. If there is no improvement, discontinue therapy. Second occurrence: delay cetuximab infusion for ≤21 days until the skin rash improves to grade ≤ 2. If there is an improvement, continue at reduced dose of 200 mg/m^2. If there is no improvement, discontinue therapy. Third occurrence: delay cetuximab infusion for ≤21 days until the skin rash improves to grade ≤ 2. If there is improvement, continue at reduced dose of 150 mg/m^2. If there is no improvement, discontinue therapy. Fourth occurrence: discontinue therapy definitively
Topical treatment	Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75–1% cream/gel, twice/day until regression to grade 1 (avoid benzoyl peroxide products). Lesions of the scalp: erythromycin 2% lotion
Systemic treatment	Antibiotics: minocycline 100 mg per os once/day, doxycycline 100 mg per os once/day for ≥4 weeks and until the rash is symptomatic Corticosteroids: methylprednisolone 0.4 mg/kg per os, prednisone 0.5 mg/kg per os, for up to 10 days
Systemic treatment in highly symptomatic/nonresponsive patients	Retinoids: isotretinoin 0.3–0.5 mg/kg per os Corticosteroids: methylprednisolone or dexamethasone i.v. Antihistamines: clorfenamine i.m./i.v. Antibiotics: amoxicillin/clavulanic acid, gentamicin i.v. Intravenous hydration

- General recommendations for prophylaxis are similar to those for acnelike rash of nonirradiated skin [15, 43].
- Cutaneous hydration should be achieved with creams or grease, with moisturizing factors (urea, lactic acid, and so on). Creams should be preferred to avoid greasy macerating effect in sweaty areas. Occlusive dressing (polyurethane with safetac) can be used to protect skin from microtrauma [61].
- Debridement of crusts should be achieved with hydrogels [33, 62, 63].
- Protect the desquamated areas with occlusive dressing (polyuretane) or burn dressing (hydrocolloids or hydrofibers). Hydrocolloids and hydrofibers contain carboxymethylcellulose (a gel-forming agent), inserted in an adhesive polymeric matrix. This agent absorbs exudates changing into gel and improves symptoms of intertriginous areas [35, 62, 63]. It manages pain very well but can favor maceration and delay healing.
- Topical moisturizers, gels, emulsions, and dressings should not be applied shortly before radiation treat-

Table 4. Management of grade 4 skin rash

Skin lesions and symptoms	Generalized rash; severe symptoms that require emergency treatment
Cetuximab dose modifications	Discontinue therapy immediately and definitively
Topical treatment	Antibiotics: clindamycin 1% gel, erythromycin 3% gel/cream, metronidazole 0.75%–1% cream/gel, 2 times daily until regression to grade 1 (avoid benzoyl peroxide products). Lesions of the scalp: erythromycin 2% lotion
Systemic treatment	Retinoids: isotretinoin 0.3–0.5 mg/kg per os
	Corticosteroids: methylprednisolone, dexamethasone i.v.
	Antihistamines: clorfenamine i.m./i.v.
	Antibiotics: amoxicillin/clavulanic acid, gentamicin i.v.
	Intravenous hydration
	Hospitalization

Table 5. Grade-specific management of skin toxicity (radiation dermatitis) from radiotherapy and cetuximab

Grade	**1**	**2–3**	**3**	**4**
Radiotherapy	Continue	Continue	Continue	Discontinue and verify that radiation dose and distribution are correct
Cetuximab	Continue	Continue	Reduce the dosage	Discontinue
Maintain hygiene with soft detergent	Yes	Yes	Keep the irradiated area clean even when ulcerated	Multispecialist evaluation: radiation oncologist, oncologist, dermatologist and nurse
Topical moisturizers	Yes	Yes (limited to not abraded skin)	Yes (limited to not abraded skin)	
Normal saline solution (+/− not aggressive disinfectants: sodium hypochlorite 1%–3%)	No	Yes (on abraded skin)	Yes (on abraded skin)	
Occlusive wound dressing (polyurethane with safetac)	No	Useful in cases of crusty exudates; if it is thin, it is not removed before radiation treatment.		
Hydrogel wound dressing and burn dressing	No	Yes in case of xerosis as a lenitive treatment; it helps debridement in case of crusty exudates	Debridement of crusty exudates	
Hydrocolloids, hydrofibers	No	No	Use to cover and protect moist desquamated area; if they are ultrathin, it is not necessary to remove before radiation treatment	
Topical antibiotics	Should not be used prophylactically		Use on suspected area after swabbing (if possible)	
Antibiotics	In the presence of SIRS[a] with suspected infection. When feasible, culture data should always be obtained prior to initiating antibiotic therapy. Empiric antibiotic therapy should be guided by available practice guidelines and knowledge of the local antibiogram			

[a]SIRS, Systemic Inflammatory Response Syndrome. It is defined as 2 or more of the following variables: fever >38°C or <36°C, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or $PaCO_2$ level <32 mmHg, abnormal white blood cell count (>12,000 per μL or <4,000 per μL or >10% bands).

ment to prevent a possible bolus effect, artificially increasing the radiation dose to the epidermis. Toward the end of the radiotherapy, if there are ulcerations, a thin burn dressing (hydrocolloid or hydrofibers) can be

used during the treatment to avoid infections and trauma. A very thin dressing is recommended to avoid the bolus effect and permit the repositioning of the immobilizer mask.
- Corticosteroids can be used in radiation dermatitis, but it is suggested that the overall treatment time be limited to <12 weeks [35].
- Attention should be paid to pain relief.
- When systemic impairment is suspected, monitor the presence of Systemic Inflammatory Response Syndrome (SIRS) [64]. If SIRS is present and infection is suspected, culture should always be obtained before antibiotic therapy.

Recommendations for Clinical Organization

The Italian Experts agreed that a multidisciplinary management could minimize skin toxicities, limit the incidence of severe symptoms, improve patient compliance, avoid modification of prescribed therapies (radiotherapy and/or EGFR-i), and optimize outcomes [38]. No agreement was found about the composition of the multidisciplinary team that should deal with the issue.

Nonsevere skin reactions can be managed by trained nurses. Accordingly, in the Consensus Guidelines for management of radiation skin toxicity in head and neck cancer, the role of the nurse is essential for low-grade cases [30]. Referral to the dermatologist is recommended for grades 3–4 toxicity (in a survey, only 8% of patients obtained a dermatology consult [65]).

The presence of a wound specialist or a psychologist in the multidisciplinary team is recommended only for selected cases. Skin rash was not found to impact on patients' psychological status or social life, according to FACT-C (Functional Assessment of Cancer Therapy–Colorectal) and PDI (Psychological Distress Inventory), in patients with advanced colorectal cancer and treated with cetuximab-based therapy [59]. It was speculated that skin rash is considered as part of the suffering caused by cancer, and that patients are encouraged by oncologists to continue treatment because the skin rash is indicative of a therapy response.

A summary of Italian Experts recommendations is as follows:

- A multidisciplinary approach is necessary.
- A medical and a radiation oncologist should be in the team dealing with rash management when radiotherapy is used.
- Trained nurses can manage low-grade skin toxicity.
- Referral to the dermatologist is necessary when severe toxicity (grades 3–4) is present.
- A wound specialist or a psychological consult are needed only in selected cases.

Conclusions

The introduction of cetuximab in colorectal and head-neck cancer therapy had a significant impact on outcomes. A strategic approach to the management of skin toxicity will allow one to limit the incidence of skin rash, to improve patients' compliance, and to optimize outcomes.

Nowadays, new topical agents are in development as potential therapy for rash: vitamin K, and in particular vitamin K1 (fillochinone) and K3 (menadione). Interesting evidence has been presented on the beneficial effect of vitamin K1 cream on patients experiencing severe acnelike rash, anti-EGFr induced [16,42,66–68].

The Expert Opinions reported in this article represent the Italian consensus derived from best clinical practices and the scientific literature available on the treatment of anti-EGFR skin toxicity. The large and increasing use of cetuximab in cancer treatment and the lack of specific clinical trials call for the development of medical research to hone a more accurate evaluation/grading and evidence-based treatment of skin toxicity.

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