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Critical Reviews in Oncology/Hematology 96 (2015) 167–182

Hematology
 Incorporating Geriatric Oncology

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Acute skin toxicity management in head and neck cancer patients treated with radiotherapy and chemotherapy or EGFR inhibitors: Literature review and consensus

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Accepted 4 June 2015

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<http://dx.doi.org/10.1016/j.critrevonc.2015.06.001>

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Abstract

The adverse effects of radiation therapy, often integrated with chemotherapy and/or targeted therapies, on the skin include severe acute and chronic dermatitis associated with pain, discomfort, itching, and burning, and may heavily affect patients' quality of life. The management of these skin adverse effects in head and neck cancer patients (HNCs) are very heterogeneous due to the lack of shared rigorous classification systems and evidence based treatments.

A multidisciplinary group of head and neck cancer specialists from Italy met with the aim of reaching a consensus on a clinical definition and management of dermatitis in HNCs treated with radiotherapy with or without systemic therapies in order to improve skin toxicity management. The Delphi Appropriateness Method was used. External expert reviewers then evaluated the conclusions carefully according to their area of expertise.

This paper offers contains seven clusters of statements about the management of dermatitis in HNCs and a review of recent literature on these topics.

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Keywords: Skin toxicity; Radiotherapy; Cetuximab; Chemotherapy; Head and neck cancer; Biodermatitis; EGFRi

1. Introduction

The improvements in head and neck cancer (HNC) treatment have led to an increase in the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) [1].

Unfortunately, the use of radiation therapy, often integrated with chemotherapy and/or targeted therapies, must deal with severe acute and chronic skin toxicity often associated with pain, discomfort, itching, and burning, heavily affecting patients' quality of life [2–4].

Significant acute skin toxicity may affect up to 95% of these patients, which sometimes impacts negatively on the proper adherence to the treatment protocol [5].

Contemporary radiation technologies allow the skin to receive only a fraction of the total dose that is delivered to the target, but in the case of HNC the skin is so near target volumes that radio-dermatitis cannot be avoided.

Furthermore, the association of radio-sensitizing systemic therapies (e.g. 5-fluorouracil, Cetuximab, etc.)

increases this toxicity [3,6–8] and may modify the timing and clinical aspects of radio-dermatitis effects. For instance, radio-induced dry desquamation may be aggravated and its timing shortened by the Cetuximab-induced xerosis [9]. Similarly, radio-induced moist desquamation may be complicated by chemotherapy or epidermal growth factor receptor inhibitors that predispose HNCs to systemic inflammation response [10] and to infection [11].

The management of these skin adverse effects in HNCs is very heterogeneous because of the lack of shared rigorous classification systems and evidence based treatments. A recent study from Belgium [12] showed that the disclosure and implementation of a skin protocol enhanced standardization in Flanders improved adherence to evidence-based guidelines and led to the disappearance of out-dated ritualistic practices.

For all these reasons Italian medical oncologists, radiation oncologists and nurses met with the aim of reaching a consensus on a clinical definition and management of acute

radiation dermatitis in HNCPs, particularly in regard to those statements with limited evidence.

The results of the literature review and the statements that obtained a consensus are reported and discussed in this paper.

2. Materials and methods

The Delphi Appropriateness method was used for this Consensus [13].

The panel, a group of 32 multidisciplinary experts (medical oncologists, radiation oncologists, dermatologists, nutritionists, and nurses), met in Milan on February 17th–18th, 2013 and appointed a facilitator board of six expert members, from different clinical settings (three radiation oncologists, 1 medical oncologist, and two nurses). The facilitator board performed a systematic review of the literature on skin toxicity.

The MEDLINE database was searched for studies published from 1990 to March 2013 containing the terms skin toxicity, skin reaction, actinic dermatitis, head and neck cancer, chemotherapy, Cetuximab and radiotherapy (RT). The literature search was limited to articles in Italian, English and French about human cancers treated with RT.

Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO) and the European Society of Medical Oncology (ESMO) were also 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; and (e) consensus guidelines. Furthermore, the electronic search results were supplemented by manual examination of reference lists from selected articles.

On the basis of this literature review, the facilitators identified a number of key statements.

All the experts rated these statements through a two-round process. A scale of four steps was used, where 1 was defined as “high consensus”, two was defined as “low consensus”, three was defined as “no consensus”, and four was chosen by panellists when they felt unable to express an opinion.

A web meeting was held before the second rating, where statements were discussed. The statements that received a weak or no approval (less than 75% of votes) were redefined according to the observations of panellists. The second ratings were analyzed to identify the statements that reached a consensus.

Each expert (including facilitators) was equally weighted in scoring the statements.

Then, external radiation oncologists (JAL, R-JB), a medical oncologist (CP), and a dermatologist (GG) reviewed the statements.

The panellists had a second meeting in Milan on 5 May 2014 in order to approve the final version of the statements.

3. Results

Consensus-reached statements are listed in [Table 1](#)

4. Comments

4.1. General statements

1. The most commonly-used RTOG/EORTC and CTCAE v.3-4.3 grading systems do not capture the symptoms or impact due to RT-associated systemic therapies on radiation dermatitis.
2. When it is necessary to capture symptoms, other scales, such as RISRAS or Skindex-16, could be used additionally [2,4,14–16].

The use of a common, sensitive, specific, and easy tool is fundamental for the classification and the management of all possible skin toxicities.

Some commonly used grading tools for the assessment and documentation of radio-dermatitis include the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) toxicity criteria [17], the Common Terminology Criteria for Adverse Events, version 3 and 4.03 (CTCAE) [18,19], the Skin Toxicity Assessment Tool [20], the Radiation-Induced Skin Reaction Assessment Scale [2,15], and the Skindex-16 scale [16].

Most of the tools are observer assessments that do not capture the symptoms or the skin-reaction impacts on Activities of Daily Living (ADL) or on the clinical management. On the contrary, the recent classification of CTCAE v. 4 published in May 2009 evaluates the impact of the Adverse Events on the patient’s ADL and on the clinical management [21] (see [Table 2](#)).

3. When it is necessary to capture the impact of systemic biological therapy on radiation dermatitis, it is advisable to use the in-field bio-radiation skin-toxicity grading score.

Radiation dermatitis developing in patients receiving Cetuximab concomitantly with RT for locally advanced squamous cell HNC is now recognized as having different pathophysiological and clinical characteristics with respect to the radiation dermatitis due to RT alone [22,23].

While version 4 of the NCI “Cancer Therapy Evaluation Program” (CTCAE v.4) graded new systemic dermatological toxicities (e.g. “Rash acneiform” hierarchically grouped into the “Skin and subcutaneous tissue disorders” (System Organ Class), which are more appropriate for grading systemic EGFR-inhibitor (EGFRi) toxicities than previous versions [24,25], there has not yet been any grading system which

Table 1
Consensus-reached statements.

Cluster Phase	Description	Whom is it in charge of?
1 Before CRT	<p>1. General statements</p> <p>1. The most commonly-used RTOG/EORTC and CTCAE v.3-4.3 grading systems do not capture the symptoms or impact due to RT-associated systemic therapies on radiation dermatitis.</p> <p>2. When it is necessary to capture symptoms, other scales, such as RISRAS or Skindex-16, could be used additionally.</p> <p>3. When it is necessary to capture the impact of systemic biological therapy on radiation dermatitis, it is advisable to use the in-field bio-radiation skin-toxicity grading score</p>	Oncology Physician–Nurse
2 Before CRT	<p>1. Risk factors (factors that place patients at increased risk of severe skin toxicity, and that should be considered at the baseline skin assessment)</p> <p>1.1. Host factors:</p> <p>1. Personal factors such as skin friction, nutritional status, age, race and ethnicity, sun exposure, smoking and pre-existing skin disease (such as atopic eczema or psoriasis, or autoimmune bullous diseases).</p> <p>2. Co-morbidities (such as rheumatoid arthritis, lupus erythematosus, or scleroderma, etc.)</p> <p>3. Diagnosis of gene repair disorders (for example Xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anaemia, Nijmegen syndrome, etc.)</p> <p>1.2. Treatment-related factors:</p> <p>1. Skin total dose, Fraction size, type and energy of radiation and the use of bolus.</p> <p>2. Chemotherapy or other medical photosensitizing concomitant therapies</p>	Oncology Physician–Nurse–Patient
3 Baseline evaluation	<p>2. Baseline assessment (successively, during CRT, at least weekly) and preventive recommendations</p> <p>2.1. General recommendations:</p> <p>1. A detailed medical history relating to personal and family risk factors should be carefully collected.</p> <p>2. It is important to establish a proper technique to minimize the dose delivered to the skin.</p> <p>3. Avoid radio-sensitizing drugs during radiation treatment, if clinically indicated: when chemotherapy is not concurrent (paclitaxel, docetaxel), a period of almost seven days has to be respected (see point 2b2).</p> <p>4. Caution must be used with non-necessary common photosensitizing drugs and sun exposure during chemo-radiation (see point 2b2).</p> <p>5. Patients must avoid smoking.</p> <p>2.2. Preventive hygiene recommendations:</p> <p>1. Washing with lukewarm water and a mild soap (pH-neutral or non-alkaline soap) can be used as routine care for all patients receiving radiation therapy.</p> <p>2. Shaving with a sharp, disposable multi-blade wet razor or with a non-traumatizing electric razor.</p> <p>3. Avoid micro-traumas in irradiated area or tapes and adhesives.</p> <p>4. Preventive non-steroidal treatments: A moisturizing cream based on urea or anionic polar phospholipid is advised. Trolamine and Aloe Vera are not recommended.</p> <p>5. It is not advisable to use cream or other skin products from 1 to 4 h before treatment so as to avoid “build-up” effects.</p> <p>2.3. Recommendations if risk factors are present.</p> <p>1. Maintain an optimal control of co-morbidities as diabetes and nutritional status; a close collaboration with the diabetologist and the dietician is needed.</p> <p>2. If active signs/symptoms of rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, or scleroderma are diagnosed, consider using conventional fractionation, reducing total dose where possible, keeping treatment volumes as small as possible and keeping a high level of caution with multimodality treatments, especially when RT is associated to concurrent chemotherapy or biological anticancer treatments. A close liaison with the rheumatologist and dermatologist is needed.</p> <p>3. If gene repair disorders are diagnosed (for example Xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anaemia, Nijmegen syndrome, etc.) consider avoiding RT.</p>	Oncology Physician–Nurse–Patient

Table 1 (Continued)

Cluster Phase	Description	Whom is it in charge of?
4 During CRT	3. Topical steroidal agents 1. The use of corticosteroid creams for treating itching or irritation should be limited over time as they can cause thinning of the skin and bacterial infections. 2. The use of corticosteroid creams in the prevention of skin reactions is not advisable as they can cause thinning of the skin and bacterial infections	Oncology Physician–Nurse
5 During CRT	4. Dressing and advanced medications 1. Even though there is insufficient evidence to support a recommendation for using dressings or advanced medications, these can be used to protect irradiated skin from trauma or, in the case of wet desquamation, in order to control pain, bleeding, and exudates. 2. Protection of ulcerated parts can be provided with hydrocolloid films after having cleaned the skin. The ultrathin films can be maintained during radiation. This dressing should be removed when it is saturated with exudate. 3. Hydrofibers, calcium alginate dressings, and polyurethane or silicone foams could be used when the exudate is very abundant. No evidence exists to support one product over another. 4. When crusts or crustose exudations are present, the debridement of crusts may help to reduce the risk of super-infection and bleeding and may help with pain management.	Oncology Physician–Nurse
6 During CRT	5. Infection management 1. Consider topical or systemic antimicrobials if positive cultures or documented infections are present. 2. An empirical systemic antibiotic therapy must be used as soon as possible when two altered parameters of Systemic Inflammatory Response Syndrome (SIRS) and/or other signs of systemic inflammatory response to infection (such as inflammatory, haemodynamic, organ dysfunction and tissue perfusion parameters) coexist with a suspected infection	Oncology Physician–Nurse
7 During CRT	6. Serious toxicity and treatment interruption. 6.1. Grade III toxicity ○ In the case of toxicity of grade 3 or less every effort should be made to not stop the radiation treatment. 6.2. Grade IV toxicity 1. Consider interrupting both systemic and radiation treatments. If the patient has been treated with Cetuximab and RT, Cetuximab should be interrupted until the skin reaction has resolved to at least grade II 2. Refer patient for wound care or wound specialist management.	Oncology Physician–Nurse

assesses the severity of Adverse Events (AEs) due to the association of bio-therapies with RT.

In 2011, Bernier et al. proposed a new classification [26] that considers the adverse effects of both radio-dermatitis and Cetuximab on “in-field” skin. The limits of this classification are the fact that it does not take into account the impact of the AEs on the patient’s activities of daily living (ADL) and their impacts on the clinical management as required by CTCAE v.4. Furthermore, it considers only the effects of Cetuximab without considering the possibility that new biological anti-cancer therapies – with different AEs – might be used in the near future.

For this reason, a group of US and European experts [27] proposed a new classification that considers the CTCAE recommendations regarding ADL and that does not limit the grades exclusively to Cetuximab but extend them to the possible effects of new future biotherapies (at the moment non predictable) on the irradiated skin.

Even though the latter scale has not yet been validated [28], the panellists suggested adopting it, in the absence of a more appropriate one.

4.2. Risk factors

The factors that may influence the response of the patient’s skin to RT have been grouped into two categories: host factors depending on the patient’s biological characteristics and treatment-related factors. These factors may place the patient at increased risk of dermatitis and should be considered at the baseline skin assessment.

4.2.1. Host factors

1. Personal factors such as skin friction, nutritional status, age, race and ethnicity, sun exposure, smoking and pre-existing skin disease (such as atopic eczema or psoriasis, or autoimmune bullous diseases).

Table 2
In-field adverse events due to radiation therapy with or without biological therapies.

	Grade 1	Grade 2	Grade 3	Grade 4
NCI–CTCAE, v4.03 general criteria	Mild; asymptomatic or mild symptoms; Clinical or diagnostic observations only; intervention not indicated.	Moderate; Minimal, local or non-invasive intervention indicated; Limiting age-appropriate instrumental ADL (refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; Limiting self care AD (refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden	Life-threatening consequences; Urgent intervention indicated
Radiation dermatitis	Faint erythema or dry desquamation.	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; Spontaneous bleeding from involved site; skin graft indicated
Bio-radiation dermatitis [27]	Faint erythema or dry desquamation; and lesions due to bio-treatment (e.g. xerosis, papules, pustules, and other clinical signs), which may or may not be associated with symptoms of pruritus or tenderness. No limiting age-appropriate ADL.	Moderate to brisk erythema; patchy moist desquamation in folds and creases; lesions due to bio-treatment (e.g. crusts, papules, pustules, and other clinical signs) mostly confined to less than 50% of radiated area; bleeding lesions with friction or trauma. Limiting age-appropriate instrumental ADL.	Moist desquamation in areas other than skin folds and creases; extensive (>50% of involved field) confluent lesions due to bio-treatment (e.g. crusts, papules, pustules, and other clinical signs) associated to bleeding by minor trauma or abrasion. Limiting selfcare.	Life-threatening consequences: skin necrosis or ulceration of full thickness dermis; Extensive (>50% of involved field) confluent lesions due to bio-treatment (e.g. crusts, papules, pustules, and other clinical signs) associated to signs of spontaneous bleeding. Systemic inflammation response syndrome (SIRS)

The skin integrity (including the presence of skin atrophy), body site (such as the neck skin where the epidermis is thin and subjected to friction from overlapping skin folds [23]), obesity [29], nutritional status, age, sun exposure, exposure to extreme temperatures, and smoking, are all factors that increase the risk of radiation-induced toxicity [30]. Race and ethnicity are also considered factors that may affect the skin response to RT [31,32].

Pre-existing inflammatory skin disease may favour the development of severe radiation dermatitis, although no formal studies have confirmed this hypothesis. In particular, atopic eczema, which very frequently affects the head and neck area, is associated with skin that is very sensitive to a variety of environmental factors including heat, solar radiation, detergents, and water. In addition, ionizing radiation may elicit or exacerbate autoimmune bullous disease such as pemphigus [33–35].

2. Co-morbidities (such as rheumatoid arthritis, lupus erythematosus, or scleroderma, etc.)

Pre-existing connective tissue or autoimmune diseases, including scleroderma, lupus erythematosus, and perhaps rheumatoid arthritis (RA), unpredictably predispose

patients to the development of severe radiation dermatitis [36–39]. At any rate, the studies that support this statement are retrospective with small numbers of patients and use different scoring scales for complications. As a consequence, these factors may contribute to an overestimation of true radiation-induced morbidity, but the fact that peripheral lymphocytes from patients with lupus erythematosus, RA and systemic sclerosis have significantly greater DNA damage after irradiation than do those from control subjects [40,41]. It is in any case advisable to be prudent in particular when the connective tissue disease is active or associated to an uncontrolled hypertension and type I diabetes [42].

3. Diagnosis of gene repair disorders (for example Xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anaemia, Nijmegen syndrome, etc.)

As ionizing radiation produces DNA damage, patients with impaired cellular DNA repair capabilities are at increased risk. Patients with ataxia-telangiectasia, a rare autosomal-recessive disorder resulting from mutations in both copies of the ATM gene, are predisposed to develop

severe complications after RT. It is hypothesized that some patients who develop serious, unanticipated radiation dermatitis may be heterozygous for this mutated ATM gene (approximately 1% of the general population) [43,44].

Other rare diseases with reduced cellular DNA repair capability, such as hereditary nevoid basal cell carcinoma syndrome (Gorlin syndrome), Fanconi's anaemia, Bloom syndrome, Xeroderma pigmentosum, Nijmegen breakage syndrome [45], familial polyposis, Gardner's syndrome, hereditary malignant melanoma, dysplastic nevus syndrome, and DNA ligase IV deficiency [45–56], may expose patients to severe risks and either RT should be avoided altogether or the skin-doses should be selected with great care.

4.2.2. Treatment-related factors

1. Skin total dose, Fraction size, type and energy of radiation and the use of bolus

Treatment-related factors such as skin total dose, fraction size, type and energy of radiation can impact skin reactions: larger treatment volume, larger total dose of radiation, larger fraction size (>2 Gy per fraction), and higher surface dose (bolused or low energy beams) can increase skin toxicity [5,57–60].

2. Chemotherapy or other medical photosensitizing concomitant therapies

Also chemotherapy or other medical radio-sensitizing or photosensitizing concomitant therapies may also increase acute toxicity to the skin [3,7,61–65].

Radio-sensitizers are drugs that given either immediately before/during, or less than 7 days after radiation, cause increased cellular damage and impaired repair [62]. Paclitaxel or docetaxel when used in conjunction with RT produce synergistic cutaneous toxicity that is both schedule- and dose-dependent [61].

Photosensitizers are drugs that are activated by UVA, UVB, and visible range beams and their photo-activated compounds damage the surrounding cutaneous tissue [65].

4.3. Baseline assessment (successively, during CRT, at least weekly) and preventive recommendations

4.3.1. General recommendations

1. A detailed medical history relating to personal and family risk factors should be carefully collected.
2. It is important to establish a proper technique to minimize the dose delivered to the skin [57,66–68].

In head and neck IMRT plans, high skin dose [67] is consequent to multiple tangential-to-skin beams and to the bolus effect of immobilization devices. Some Authors suggest excluding the skin over uninvolved neck nodes from target volumes in order to reduce the dose to the skin by 6–7% [57,69].

At any rate, every effort must be taken to avoid high doses to the skin. The use of advanced technologies for evaluating the skin dose might be considered [70,71].

3. Avoid radio-sensitizing drugs during radiation treatment, if clinically indicated: when chemotherapy is not concurrent (paclitaxel, docetaxel), a period of almost seven days has to be respected (see point 2b2).
4. Caution must be used with non-necessary common photosensitizing drugs and sun exposure during chemoradiation (see point 2b2).
5. Patients must avoid smoking [72].

The dangerous effects of tobacco on irradiated skin [72], immune response [73], and repairing capacity of the tissue [74] are well known.

4.3.2. Preventive hygienic recommendations

1. Washing with lukewarm water and a mild soap (pH-neutral or non-alkaline soap) can be used as routine care for all patients receiving radiation therapy.

Washing with lukewarm water and a mild pH-neutral or non-alkaline soap should not be restricted as routine care for patients receiving radiation therapy [75–78].

2. Shaving with a sharp, disposable multi-blade wet razor or with a non-traumatizing electric razor.

It is advisable to shave with a sharp, disinfected wet razor or with a non-traumatizing electric razor [26].

3. Avoid micro-traumas in irradiated area or tapes and adhesives.

Physical traumas, for example due to clothes, exposure to direct sunlight or exposure to extreme temperatures and the use of skin irritants such as alcohol-based lotions and perfumes should be avoided. This recommendation is particularly important if epidermal growth-factor receptor inhibitors are used [26].

4. Preventive non-steroidal treatments: A moisturizing cream based on urea or anionic polar phospholipid is advised. Trolamine and Aloe Vera are not recommended.

Many non-steroidal topical treatments or oral systemic therapies have been used in radio-dermatitis prevention. They have been used especially on breast skin, but it is generally believed that these results can be reported also for head-and-neck skin.

Oral preventive treatment

Oral systemic therapies such as zinc supplements [79], pentoxifylline [80], and Wobe-Mugos E (i.e. proteolytic enzymes containing 100 mg papain, 40 mg trypsin, and 40 mg chymotrypsin that should provide anti-inflammatory and analgesic effects) [81–83] are not sufficiently supported by the literature results in radio-dermatitis prophylaxis [84].

Non-steroidal preventive topical treatments

Lipiderm [85], vitamin C solution [86], chamomile cream [87], almond ointment [87], petroleum based ointment (Aquaphor) [88–90], hyaluronic acid [90–95], sucalfate and its derivatives [93,96–98], glutathione and anthocyanin (Raygel) [99], LED (light-emitting diode lasers) [100], Theta cream [101], and Dexpanthenol (a

provitamin of B5) [91,101,102] did not demonstrate a sufficient benefit in terms of dermatitis prevention.

On the contrary, aloe vera [103–106] and trolamine [85,88–90,107,108] are not recommended [84]. In particular aloe vera is not a moisturizer [109], thus it may be contraindicated in the case of xerosis.

Calendula is likely to be effective [107,110] but it is difficult to apply [107] [84].

An anti-inflammatory drug from Chinese medicine (Lian Bai liquid) in a non-blinded trial of 126 participants [111] reported the effectiveness in preventing and treating radio-induced dermatitis. This drug needs confirming in further multicentre trials.

Silver sulfadiazine cream was shown to be active in preventing radio-dermatitis [112,113], but its use as prophylactic management is not recommended because of concerns about sensitivity or resistance with overuse [109,114].

Finally, urea lotion [115,116], and anionic phospholipid-based cream [117] were shown to be more effective than the control arms that used conventional dry skin care and aloe vera gel respectively. Urea cream should be used only with a urea concentration of 5–10%.

Preventive dressing: barrier films

Barrier films have been used in order to reduce trauma and retain moisture in the maintenance of intact skin during RT.

In a breast cancer study by Graham et al. [118], a spray-on no-sting barrier was evaluated as a prophylactic treatment in the prevention of moist desquamation (vs. glycerine cream) and it was associated with a lower total skin toxicity score ($p=0.005$) and a lower prevalence of pruritus ($p=0.01$). Successively, the same Authors, testing a moisturizing alcohol-free barrier film (MDBC), did not find any advantages vs. glycerine cream [119]. Dermofilm (a micro-thin emollient skin protector, containing hydrophilic and lipophilic agents) also was used and, although a symptomatic improvement occurred, a larger trial was advocated but never performed [120].

Safetac-based silicon dressings (Mepilex-Lite® dressings) provide mechanical protection from trauma, similarly to no-sting barriers, and showed a significant 30–40% decrease in skin reaction severity in breast cancer patients [121–123]. However, Mepilex-Lite dressings did not affect moist desquamation rates when used to manage existing skin reactions [123]. This failure was attributed by the Authors to the necessity to remove Mepilex-Lite dressings during radiation delivery because of their thickness and their bolus effect [122]. Thus, the same Authors used Mepitel Film (a thinner Safetac-based dressing) with a clinically insignificant bolus effect of 0.12 mm [124]. This film could be safely left on during radiation delivery and it was shown that it prevented the occurrence of radiation-induced moist desquamation and decreased the extent of skin reaction severity by 92%. These dressings

have never been used as a preventive tool in HNCPs where the irregularity of skin surface makes these devices difficult to be left in site (in the personal experience of one of the authors: R.E.).

Silver dressing (a non-adherent rayon and polyester material coated with nano-crystalline silver) does not seem to be useful as a preventive treatment [125].

5. It is not advisable to use cream or other skin products from 1 to 4 h before treatment so as to avoid “build-up” effects.

While the practice of avoiding the use of products on the skin from 1 to 4 h before treatment may have a theoretical foundation in order to avoid the so called “build-up” effect, no evidence exists to support this practice [126].

Topical Vitamin K1 in prophylactic or reactive treatment may reduce the incidence of grade-3 toxicity and improve Cetuximab compliance. Indeed, Vitamin K activates EGFR signalling. Preclinical studies have shown that vitamin K3 completely abrogated EGFR inhibition in vitro and was associated with up-regulation of phosphorylated EGFRs in the skin when used in topically-applied cream [127,128]. Some clinical evidence has been presented on the beneficial effect of vitamin K1 cream on patients experiencing a severe anti-EGFR-induced acne-like rash [129–132]. Yet, the panellists retain there is not sufficient evidence to recommend it in HNCPs and future prospective multicentre randomized trials are needed.

4.3.3. Recommendations if risk factors are present.

1. Maintain an optimal control of co-morbidities as diabetes and nutritional status; a close collaboration with the diabetologist and the dietician is needed.
2. If active signs/symptoms of rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, or scleroderma are diagnosed, consider using conventional fractionation, reducing total dose where possible, keeping treatment volumes as small as possible and keeping a high level of caution with multimodality treatments, especially when RT is associated to concurrent chemotherapy or biological anticancer treatments. A close liaison with the rheumatologist and dermatologist is needed.
3. If gene repair disorders are diagnosed (for example Xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anaemia, Nijmegen syndrome, etc.) consider avoiding RT.

Particular attention is needed for those patients with active connective tissue disease and/or a combination of uncontrolled hypertension with type I diabetes [42].

Apparently healthy HNCPs, carrying heterozygote diseases with a reduced DNA-repairing capability in their family history, should be treated with prudently selected doses or, when possible, with a non-radiation oncological approach.

RT must be avoided in patients with Ataxia-telangiectasia or suffering from those diseases with a reduced cellular DNA repair capability (see point 2a3).

It is essential to evaluate the HNCP’s skin prior to any treatment, especially those areas that will be irradiated.

Every pre-existing skin disease, such as atopic eczema, acne, rosacea, ichthyosis, and psoriasis, must be documented, especially if using EGFRis [22].

4.4. Topical steroidal agents

1. 4.4a. The use of corticosteroid creams for treating itching or irritation should be limited over time as they can cause thinning of the skin and bacterial infections.
2. 4.4b. The use of corticosteroid creams in the prevention of skin reactions is not advisable as they can cause thinning of the skin and bacterial infections.

Corticosteroids have potent anti-inflammatory effects (such as vasoconstriction, reduced capillary permeability, and inhibition of leucocyte migration [133,134]) in many dermatological conditions, thus they have often been prescribed in both the prevention and management of radiation skin reactions.

The use of corticosteroid creams in the management or prevention of skin reactions has provided contrasting results [102,135–140]. However, this use must be limited over time because it can cause thinning of the skin and favour bacterial infections [77,78,141,142]. Current evidence is insufficient to support or refute this practice.

While topical glucocorticosteroid can help in the treatment of xerosis and reduce water loss from the skin in patients receiving panitumumab [143], there is no consensus regarding the efficacy of these agents on irradiated skin [102,139]. Moreover, some authors suggest that topical glucocorticoids may increase the cutaneous toxicity of EGFRis [127]. In any case, it is prudently advisable to limit the use of glucocorticosteroids to short periods of time (1–2 weeks) [22,26].

4.5. Dressings and advanced medications

1. Even though there is insufficient evidence to support a recommendation for using dressings or advanced medications, these can be used to protect irradiated skin from trauma or, in the case of wet desquamation, in order to control pain, bleeding, and exudates.
2. Protection of ulcerated parts can be provided with hydrocolloid films after having cleaned the skin. The ultrathin films can be maintained during radiation. This dressing should be removed when it is saturated with exudate.
3. Hydrofibers, calcium alginate dressings, and polyurethane or silicone foams could be used when the exudate is very abundant. No evidence exists to support one product over another.
4. When crusts or crustose exudations are present, the debridement of crusts may help to reduce the risk of super-infection and bleeding and may help with pain management

The use of hydrogel and hydrocolloid dressings has been reported in the case of moist desquamation. Hydrogel

lacks supporting evidence of superior efficacy when tested against either gentian violet [144] or drying dressings [145]. Although hydrocolloid dressings do not seem to be advantageous in terms of healing time, they appear to be useful in terms of pain control in severe Cetuximab/RT dermal toxicity [4,9].

Finally, in a small study, a silver-leaf dressing (effective for the prevention of radio-dermatitis in anal or gynaecological cancer patients [146]) was used on HNCP skin: no differences between the dressing and silver sulfadiazine cream in terms of severity of skin toxicity or healing was obtained, but pain control was improved using silver-leaf dressing [112].

4.6. Infection management

1. 4.6a. Consider topical or systemic antimicrobials if positive cultures or documented infections are present.
2. 4.6b. An empirical systemic antibiotic therapy must be used as soon as possible when two altered parameters of Systemic Inflammatory Response Syndrome (SIRS) and/or other signs of systemic inflammatory response to infection (such as inflammatory, haemodynamic, organ dysfunction and tissue perfusion parameters [147,148]) coexist with a suspected infection.

SIRS parameters need monitoring. Indeed, even if two positive SIRS parameters are not specific of sepsis [148–150], they may help physicians to graduate the urgency of intervention, to promptly activate the search for infection and for other signs of systemic inflammatory response to infection (such as inflammatory, haemodynamic, organ dysfunction and tissue perfusion parameters [147,148]), in order to shorten the time to start antibiotic administration [151].

In cases of dermatitis of grade 2/3, when a super-infection is suspected without systemic-inflammatory-response involvement, antiseptics and/or topical antibiotics (such as clindamycin and erythromycin) may be helpful, but it might be useful to obtain an antibiogram of exudative lesions.

If serious toxicity is associated to a systemic inflammatory response, culture data should be obtained before starting any empirical antibiotic treatment [151].

4.7. Serious toxicity and treatment interruption

4.7.1. Grade III toxicity

- In the case of toxicity of grade III or less, every effort should be made in order not to avoid interrupting the radiation treatment.

4.7.2. Grade IV toxicity

1. Consider interrupting both systemic and radiation treatments. If the patient has been treated with Cetuximab and RT, Cetuximab should be interrupted until the skin reaction has resolved to at least grade II.
2. Refer patient for wound care or wound specialist management.

Any interruption of radiation therapy may result in a decreased risk of local oncological control. Thus, in the presence of grade three toxicity the panel suggests continuing RT because the advantages consequent to local-toxicity recovering might be annulled by the negative effects of tumour re-growth [152,153]. Of course, the symptoms of local toxicity must be monitored/controlled and the panel suggests that HNCPs might be hospitalized in order that the specific antineoplastic treatments can continue safely by limiting interruption as much as possible.

In the case of Grade IV toxicity, the main cause of life-threatening consequences is due to the systemic inflammation response to infection. Thus, the presence of grade IV and/or sepsis should induce the interruption of all systemic (CT or EGFRi) and local (RT) antineoplastic treatments.

5. Considerations for the future

Some novelties are coming out from the genetic and epigenetic research area. Patient populations having a genetic predisposition to radiation dermatitis could be identified [154,155]. Indeed, the object of on-going researches is some gene-clusters, not associated with other genetic diseases/abnormalities [156–158]. These gene-clusters may be present in “healthy” patients (meaning patients who are otherwise healthy beyond having a malignancy) and they might predict sensitivity to radiation. This area should deserve more attention because this strategy might have a big impact in the next future such as in other radiation toxicities (e.g. oral mucositis [159], skin toxicity [154,157]).

Furthermore, the “in-field” toxicity assessment tools need to be refined (CTCAE v 4.0 and bioradiation dermatitis) in light of the next imminent version of CTCAE.

On this purpose, the scientific community should wonder about the concern that the incorporation of ADL components in the scoring scales might result in more of a subjective assessment. This fact might result in a significant drift from the previous scoring scales that were based more on physical appearances of skin lesions. Indeed, the ADL components might further complicate the process of establishing effective treatments for dermatitis. In fact, the addition of the ADL may also be incorporating symptoms arising from more than one radiation toxicity. For example, when a patient is unable to get dressed it might be in consequence of the fact that either he could be physically limited in range of motion or it may be due to pain or to fatigue or to other standalone toxicities. All of these causes might be separate from the effects of dermatitis. These confounding problems could make it difficult to assess treatments for the dermatitis toxicity, specifically. Furthermore, pre-clinical research models, used to screen potential compounds, are designed to mirror clinical scoring scales. Consequently, ADL components could be beyond the physical appearances of dermatitis and this fact could make it more difficult to determine an efficacy signal for providing the appropriate treatment.

Finally, the biodermatitis scale, proposed by European experts and suggested in this consensus, needs validating in a clinical trial. The on-going Gortec 2014-02 trial (Personal communication) is a multinational project that has been prospectively evaluating the rate of severe dermatitis in patients receiving radiation plus Cetuximab for unresectable head and neck cancer. This prospective trial has also the aim to validate the bio-radiation dermatitis scale by comparing it to the assessment scale of NCI-CTC v 4.3.

6. Conclusions

Skin toxicity is a very common occurrence in integrated treatments for HNCPs, and it may result in pain, discomfort, irritation, itching and finally delays or interruptions of antineoplastic treatments, influencing the prognosis of potentially curable tumours. Many studies have been conducted, but there are many uncertainties. As a consequence, clinical management varies from centre to centre.

Our review aimed to obtain some indications for the management of skin toxicity in those situations where evidence is poor and it further tried to draw up recommendations/suggestions for HNCPs based on the consensus among multidisciplinary health professionals. The adopted Delphi strategy provides a highly structured and transparent process to obtain anonymous feedback. The authors believe that this approach, with the support of external experts in this field, allowed participants to give recommendations more safely in those situation where it is necessary to act without the support of strong evidence.

The main aim is to standardize diagnostic and treatment behaviour among centres participating in multicentre trials.

Clearly, the main limit of this study is the fact that part of the evidence is obtained from non-HNCP literature, and many studies are small and/or retrospective.

In the future, an increased understanding of the mechanisms of cellular damage may lead to a better prevention of this toxicity.

Acute in-field skin toxicity management in head and neck cancer patients treated with radiotherapy and chemotherapy or EGFR inhibitors: literature review and consensus

Conflict of interest

The Authors have no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

Funding

This study was partly supported by Lega Tumori sezione di Cuneo.

Acknowledgments

Alterio Daniela (Milan), Azzarello Giuseppe (Padova), Bolner Andrea (Trento), Ciotti Ombretta (Varese), Corvò Renzo (Genova), Fiscella Michela (Milan), Gavazzi Cecilia (Milan), Grisanti Salvatore (Brescia), Mario Grosso (Turin), Magrini Stefano (Brescia), Maurizi Enrici Riccardo (Rome), Orlandi Ester (Milano), Paiar Fabiola (Firenze), Pavanato Giovanni (Rovigo), Pizzorni Nicole (Milano), Ripamonti Carla (Milan), Salgarello Stefano (Brescia), Giuseppe Sanguineti (Rome).

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