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Review

Management of radiodermatitis associated with cetuximab in squamous cell carcinomas of the head and neck

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Abstract

The objective of this review is to report to the medical community the most recent knowledge on prevention and management of dermatitis with the use of cetuximab simultaneously with radiotherapy in the treatment of squamous cell carcinomas of the head and neck. A review was conducted in PubMed of English language publications between 2010 and 2015. The search employed the terms 'skin toxicity', 'radiodermatitis', 'cetuximab', 'radiotherapy', and 'head and neck cancer'. Data related to the classification and management of dermatitis, associated with cetuximab with concomitant radiotherapy (n = 22), were critically reviewed. We conclude that dermatitis associated with bioradiotherapy is a predictable, treatable, and reversible event that does not affect administration of therapy or its clinical outcome when treated appropriately.

Introduction

Radiotherapy (RT) concomitant with targeted therapies in the treatment of squamous cell carcinomas of the head and neck (SCCHN) induces skin toxicity. It is frequently associated with pain, pruritus, burning, and discomfort, which affects the patient's quality of life (QOL) and negatively affects treatment adherence.

RT causes a complex wound, interfering with epidermal basal cell layer and hair-follicle maturation, proliferation, and regrowth; also, the number of dermal fibroblasts and vessels are affected. This generates immediate damage to the DNA, as well as recruitment of inflammatory cells, leading to direct tissue damage, thus disturbing the healing process.

Radiation administered repeatedly inhibits adequate cellular proliferation, while dose fractionation favors faster regrowth of the more radiosensitive germinal cells. In addition, epidermal growth factor (EGF) and adhesion molecules are overregulated, which improves repair and changes the epidermal barrier function that, associated with Langerhans cell depletion, produces immunologic alterations, leading to colonization, superinfection, and production of superantigens.[1]

The epithelial growth factor receptor (EGFR) plays an important role in epidermal development and maintenance as well as in inflammatory and immune response. Anti-EGFR target therapies inhibit cell survival, migration, and proliferation. Therefore, perifollicular inflammation and the production of antimicrobial peptides are observed due to alteration of toll-like receptors (TLR), promoting microbial colonization and infection.[2]

Methodology

We searched the MEDLINE database for studies published from January 2010 to December 2015 that included the terms 'skin toxicity', 'radiodermatitis', 'cetuximab', 'radiotherapy', and 'head and neck cancer'. The search was limited to articles written in English about human head and neck cancers treated with radiotherapy. Potentially relevant abstracts presented at annual meetings of the American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and American Society for Radiation Oncology (ASTRO) were examined. The study selection included the following: (i) observational and prospective studies about radio dermatitis

assessment and treatment; (ii) randomized, double blind, placebo-controlled, or open label studies; (iii) retrospective and open label studies; (iv) systematic reviews and meta-analyses; and (v) consensus guidelines. Furthermore, electronic search results were supplemented by manual examination of reference lists from selected articles and were periodically updated until December 2015.

Mechanism of action of cetuximab

Cetuximab (CTX) is an anti-EGFR, Immunoglobulin G1 (IgG1), chimeric monoclonal antibody. The binding of the antibody to the receptor G1, blocks the binding of the endogenous ligands (epiregulin, amphiregulin, betacellulin, transforming growth factor [TGF], and epidermal growth factor [EGF]), and promotes receptor internalization, leading to deregulation of the EGFR signaling cascade. The blockade inhibits cellular proliferation, angiogenesis, and metastasis, and restores apoptosis. At the extracellular level, it promotes the attack of cytotoxic cells on tumor cells expressing EGFR, due to fragment crystallizable (Fc) region recognition of IgG1 by natural killer cells. RT-associated CTX inhibits DNA repair and tumor angiogenesis, while at the same time promotes apoptosis, sensitizes G1-phase cells to radiation, and reduces radioresistance of S-phase cells.[3–5]

Bioradiodermatitis

Anti-EGFR antibodies increase the sensitivity of tumor cells to radiation.[5] Concomitant with RT, the effects synergize and generate xerosis (with greater intensity, frequency, and shorter time of appearance), which can lead to skin necrosis. Simultaneously, they produce more inflammatory exudate, with the subsequent formation of crusts that cause micro traumas, aggravate inflammation, and favor pain, bleeding, and increased risk of infection.

Some studies show that the addition of CTX does not significantly increase the adverse effects associated with RT[6,7]; however, others report greater frequency of skin reactions than those observed in RT.[8-13] In a phase III study, a 5% increase in the incidence of grade 3 and 4 radiodermatitis in the bioradiotherapy (BRT) group was reported[6]; this increase is generally not greater compared with RT.[14,15] Several reasons could explain discrepancies in incidence rates; these can include the use of different toxicity classification systems, bias in the selection of patients, and the use of different techniques and radiation doses. Additionally, observational data suggest that, natural killer although there could be a greater incidence of grade 3 or 4 radiodermatitis in patients with BRT compared with chemoradiotherapy (CRT), CRT adverse effects could exert a greater negative impact on symptomatology severity and therapy compliance.[16]

Risk factors

Risk factors for severe bioradiodermatitis include the following:

Host factors:

Skin integrity, nutritional status, age, race, ethnicity, sun exposure, smoking, and pre-existing skin diseases, such as atopic eczema, psoriasis, or autoimmune diseases.
Comorbidities (rheumatoid arthritis, lupus erythematosus, scleroderma, etc.)
DNA gene repair disorders (xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anemia, Nijmegen syndrome, etc.).

Treatment-related factors:

Skin total dose, dose fractionation (concomitant boost or conventional fractionation), type and energy of radiation, treatment technique (conformational, intensity-modulated RT [IMRT]), and higher surface dose association of chemotherapy (CHT) or other photosensitizing therapies. It should be considered that certain areas are prone to bioradiodermatitis, such as the face and anterior neck, since the skin is very thin and exposed to microtraumas (skin folds, use of scarves or necklaces, as well as of shirt collars or high neck shirts). Weight control is recommended, as well as the nutritional state, in order to have healthy skin prior to radiation and avoiding smoking and exposure to high temperatures.

If rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, or scleroderma are present, it is convenient to consider the use of conventional fractionation or reduction of the total dose, maintaining treatment volume as small as possible. It is important to be cautious with multimodality treatments, especially with CRT or concurrent BRT. Teamwork is required between rheumatologists and dermatologists. In DNA gene repair disorders (e.g., xeroderma pigmentosum, ataxia-telangiectasia, Fanconi anemia, Nijmegen syndrome, etc.), avoidance of RT is recommended.[17,18]

Classification

The most commonly used classification scales for radiodermatitis include Common Terminology Criteria for Adverse Events (CTCAE) version 3.0-4.3 and Radiation Therapy Oncology Group/European Organization for Research and Treatment in Cancer (RTOG/EORTC). However, these do not include symptoms or effects of the associated systemic therapies. Since radiodermatitis associated with anti-EGFR therapies presents different clinical and pathophysiologic characteristics, a specific classification system is required. The absence of a BRT-associated adverse event classification hinders the management of these events, therapy adherence, and efficacy. Recently, efforts

Table 1 Classification of dermatitis associated with Bioradiotherapy (BRT) concomitant with Cetuximab (CTX) (Russi, 2013)

	Grade I	Grade II	Grade III	Grade IV
Bioradiation-associated dermatitis	Mild erythema or dry scaling; biotherapy-associated lesions (*e.g.,* xerosis, papules, pustules, and other clinical signs), associated or not with pruritus or sensitivity	Moderate-to-intense erythema, irregular moist scaling, limited to body folds, biotherapy-associated lesions (*e.g.,* scabs/crusts, papules, pustules, and clinical signs), signs limited to at least 50% of the irradiated area; signs associated with bleeding caused by friction or trauma	Moist scaling in different areas in body folds, signs present in 50% or more of the irradiated area; confluent lesions associated with bioradiotherapy (BRT) (*e.g.,* scabs/crusts, papules, pustules, and other clinical signs), and signs associated with bleeding caused by trauma or minor abrasions	Consequences that place life at risk: skin necrosis or ulceration of the dermis; signs present in 50% or more of the irradiated area; confluent lesions associated with bioradiotherapy (BRT) (*e.g.,* scabs/crusts, papules, pustules, and other clinical signs), signs associated with spontaneous bleeding. Systemic Inflammatory Response Syndrome (SIRS)
Activities of Daily Living (ADL)	Not limited to age appropriate ADL	Limits the instrument to age appropriate ADL	Limits ADL associated with self-care	
Action	Topical therapy (moisturizers, corticosteroids, antibiotics)	Topical and oral therapy	Topical and oral therapy. Indication for care of lesions and dressings	

have been done to propose and validate a specific classification. As a result of these efforts, it is possible to recognize that BRT-related skin reactions are different from those observed with RT,[2] and an impact is noted on activities of daily living[8a] (Table 1 and Fig. 1). These proposals are expert recommendations and require validation with randomized prospective trials.

Management of bioradiodermatitis

Effective treatment of radiodermatitis in patients with CTX and RT should ensure therapy adherence. The multidisciplinary approach group (medical oncologist, radiation oncologist, dermatologist, and nurse) should bear in mind the epidermal damage, inflammation, and risk of infection to optimize clinical outcome.

General management includes pain control, prevention of infections, general skin care, and education of the patient on hygiene and self-care measures. Despite the existence of some protocols designed to prevent radiodermatitis, at present, to our knowledge, there is not any validated.[19–21] However, intervention at early stages is crucial for effective treatment.

The treatment guidelines proposed by Bernier et al[2] suggest that management of grade 1 and 2 patients should be outpatient, and to check progress weekly, or twice weekly if erythema intensifies. Patients who develop early intense erythema should be examined more frequent throughout treatment. In the case of grade 3 or 4 dermatitis, a multidisciplinary group (headed by a dermatologist) should evaluate the need for visiting the patient daily, in case this is not possible, or at weekends, then patients should be trained about actions to follow if the reaction increases.[22–24] Treatment continuity with CTX depends on the grade. If treated correctly, skin toxicity does not require suspension or dose reduction of CTX. Weekly administration of CTX is recommended in patients with grade 1, 2, and 3 dermatitis, and

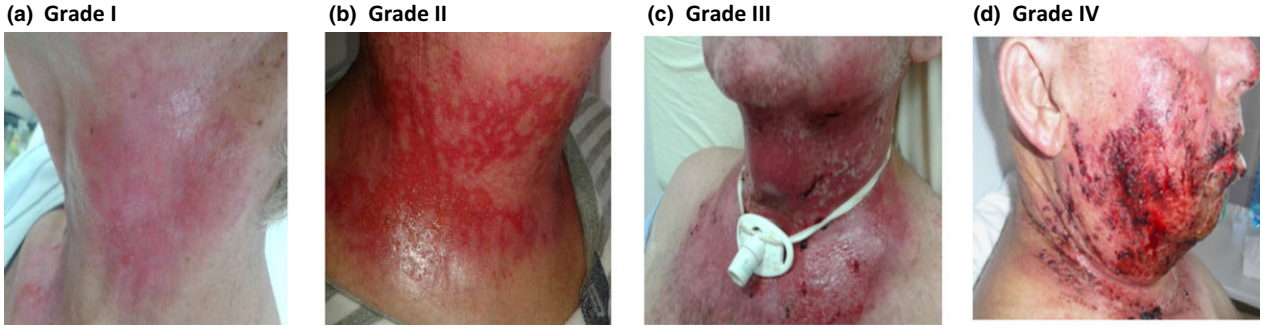

Figure 1 Radiodermatitis grades associated with CTX, (a) grade 1, (b) grade 2, (c) grade 3, and (d) grade 4. Photographs courtesy of Esther Vilajosana (Institut Català d'Oncologia)

Table 2 Management strategies for radiodermatitis in patients receiving CTX plus RT (adapted from Bernier *et al.*)[2]

	Grade 2	Grade 3	Grade 4
Frequency of follow-up/treatment continuity	Twice weekly for rapid change. Continue treatment.	Evaluate the need for daily follow-up. Frequent monitoring in search of signs of local or systemic infection. For reactions occurring at <50 Gy, consider a brief treatment interruption.	CTX should be interrupted until skin reaction has resolved to at least grade 2
Management	1. Dry desquamation without crusts: Consider glucocorticosteroid creams or ointments for a limited period (1-2 weeks) In the presence of any signs of infection, use topical antiseptics and antibiotics. Consider the use of topical antiseptics and antibiotics for prevention of more severe reactions 2. Moist desquamation in skin folds: Topical antiseptic Consider daily application of glucocorticosteroid lotion to reduce inflammation for a limited period (1-2 weeks) Topical antibiotics against Staphylococcus *aureus* under the sign of infection. Consider systemic antibiotics in the case of more severe infection Eosin or zinc topical preparations in skin folds 3. Dry desquamation with isolated nonhemorrhagic crusts: Topical antiseptics Consider daily application of glucocorticosteroid lotion for reducing inflammation for a limited period (1-2 weeks) Topical antibiotics against *Staphylococcus aureus* under sign of infection. Consider systemic antibiotics in the case of more severe infection Topical eosin or soft zinc preparations in the skin folds Hydrogels can be used to keep crusts flexible Consider debridement using hydrogels	1. Confluent moist desquamation without crusts: Topical antiseptic Consider daily application of glucocorticosteroid lotion to reduce inflammation for a limited period (1-2 weeks) Topical antibiotics against *Staphylococcus aureus* under any sign of infection. If infection becomes more severe, Consider the use of IV antibiotics if unresponsive to oral therapy. Eosin or zinc preparations in skin folds 2. Confluent moist desquamation with crust: Topical antiseptic If infection become more severe, consider the use of IV antibiotics if unresponsive to oral therapy. Consider debridement using hydrogels If protective hydrochloride dressings are used, the thickness of the dressing should be considered in the RT dosimetry.	In the case of severe infection, consider the use of IV antibiotics if unresponsive to oral therapy. Hospitalize the patient

in the latter when patients are at care centers with experienced staff in the management of this skin reaction, all efforts shall be done not to stop radiotherapy or delay RT. In patients with severe grade 3 dermatitis, consider a brief treatment interruption. In grade 4 toxicity, systemic treatment and radiation should be interrupted. If the patient has been treated with CTX and

Table 3 Selection of some agents for management of radiodermatitis in patients receiving CTX plus RT (adapted from Bernier *et al.*)[2]

Type of intervention	Examples
Moisturizing lotions and creams	Unscented or uncolored cream (Nivea)
Topical antiseptics	Chlorhexidine 0.5–1.0% (nonirritated skin)
	Sulfadiazine silver
	dressings with nanocrystalline silver
	Calcium alginate
Glucocorticosteroid cream	Hydrocortisone butyrate 0.1% (face)
	Clobetasol
	Methylprednisolone aceponate
	Mometasone furoate
Glucocorticosteroid ointment	Methylprednisolone aceponate
	Mometasone furoate
Glucocorticosteroid lotion	Betamethasone
	Methylprednisolone aceponate
Glucocorticosteroids with antibiotic	Betamethasone 0.1% with fusidic acid 2%
Topical antibiotics for superinfections (active against *Staphylococcus aureus*)	Ciprofloxacin
	Clindamycin
	Mupirocin
	Fusidic acid
	Retapamulin
	Nadifloxacin
Systemic antibiotics for superinfections (active against *Staphylococcus aureus*)	Amoxicillin/clavulanic acid
	Ciprofloxacin
	Clindamycin
	Doxycycline
	Flucloxacillin
Hydrogels for debridement	DuoDERM, IntraSite, Normigel, UN-GEL, Purilon

Table 4 Some considerations in the education of the patients receiving CTX plus RT

Education of the patient
Prior to BRT
• Wash hands no more than twice a day (morning and night), use warm water and pH neutral soap or nonalkaline soap
• Shave with a previously disinfected, moist shaver, with an electric shaver recommended
• Utilize unscented, uncolored moisturizing cream daily on the entire skin surface
• Do not use synthetic fibers, high necks, scarves, or jewelry
• Avoid the use of lotions or perfumes
During BRT
In addition to the recommendations prior to BRT:
• Do not manipulate skin of the affected area, except for routine hygiene and daily treatment, wash hands before the procedure
• Carry out gentle manipulations, with special consideration of the affected zone
• Apply treatment products after RT or at night, according to the case, never prior to RT
• Avoid exposure to the sun
• Avoid smoking
• It is recommended to ingest abundant liquids (when there is no contraindication)
• Do not apply any skin product without medical recommendation
• Avoid hair tints during treatment
• Avoid scratching or rubbing the skin surface, especially in the injured zone
• Avoid removing crusts and scales
• Consult the specialist if skin reactions persist or worsen.
After BRT
In addition to recommendations prior to BRT:
• Avoid sun exposure for a minimum of 3 months after finalizing treatment. Use sun protection
• Avoid hair dye until 2 months after treatment.

RT, CTX should be ceased until the reaction downgrades at least to grade 2.[17]

Bernier et al.[2] suggested grade-specific treatment strategies for patients who develop radiodermatitis during treatment with CTX plus RT (Table 2). Some examples of recommended agents are present in Table 3. Recommendations for daily skin care should start as soon as possible, 1 week prior to treatment. It is important to keep in mind that body surface area is not always related with degree of disease extent; thus, for example, affection can be observed in a small area with greater severity, or conversely.

General measures include registration of personal and familial risk factors, establish a suitable technique to minimize the dose delivered to the skin, and avoidance of radiosensitizing drugs during treatment if clinically indicated. When CHT is not concurrent (paclitaxel, docetaxel), a 7-day period without drug is suggested. Similarly, keep away from sun exposure and smoking.

Hygiene advice includes: wash with warm water and gentle soap (with a pH neutral or a nonalkaline soap) or soap substitutes, shaving with a moist blade, multiple blade razor, or electric shaver following the direction of the hair growth, avoid microtraumas, tapes, and adhesives in the irradiated zone. Trolamine and aloe vera are not recommended, nor scented or colored creams and body lotions. It is not advisable to use cream or other products 1–4 hours prior to treatment to avoid 'build-up' effects.[17]

The use of topical steroid creams for itching or irritation should be limited to 1–2 weeks, because they can cause skin atrophy and promote bacterial infections. The prophylactic use of steroid creams to prevent skin reactions is not indicated.[17] Although there is not enough evidence to support the use of advanced-care wound dressings (hydrocolloid films, hydrofibers, calcium alginate films, polyurethane or silicone foams), these can be used to protect the irradiated skin from trauma or, in the case of moist desquamation, to control pain, bleeding, and exudates. Ulcerated zones can be covered with hydrocolloids after their cleansing. Ultrathin films can be used during radiation, and can be removed when they saturate with exudate. In case of

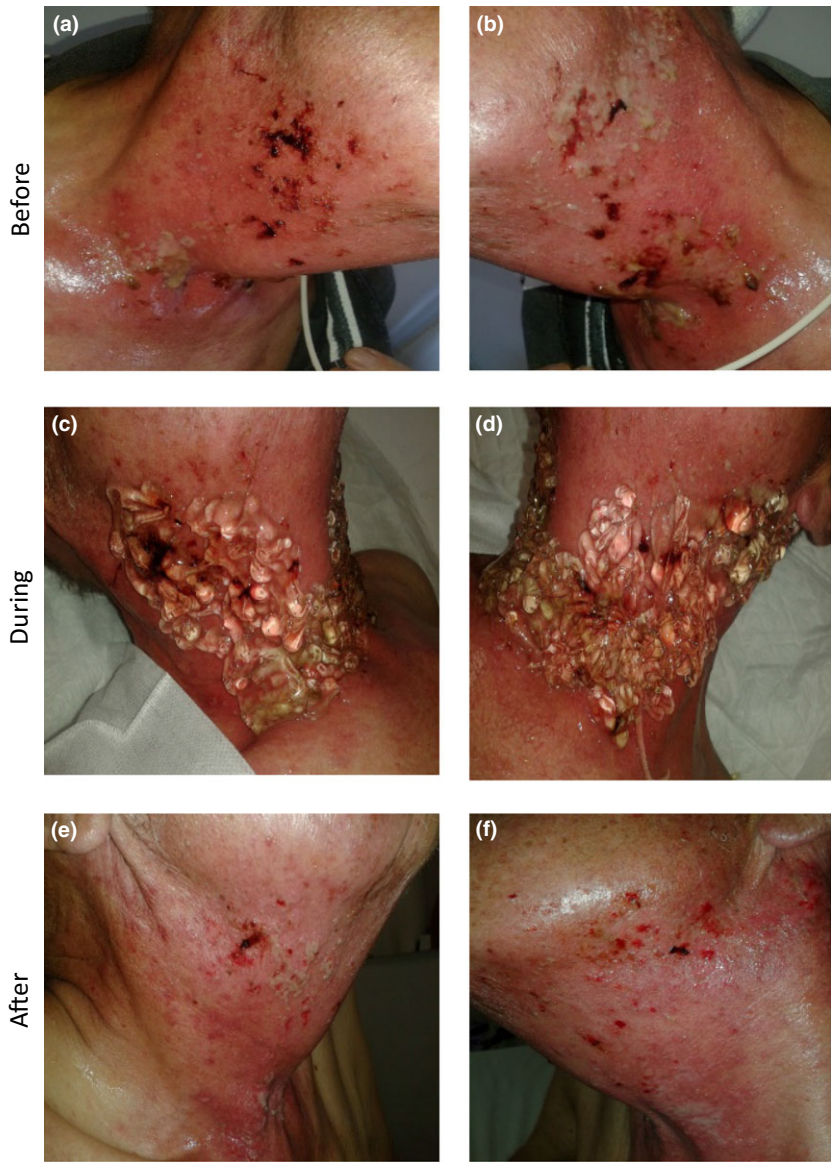

Figure 2 Effect of debridement with hydrogels in patients receiving CTX plus RT. Before debridement, right side (a) and left side of the neck (b); during debridement, right side (c) and left side (d); after debridement, right side (e) and left side (f). Photographs courtesy of Esther Vilajosana (Institut Català d'Oncologia)

abundant exudate, hydrofibers, calcium alginate dressings, polyurethane, or silicone foams are indicated. There is no evidence, to our knowledge, to support one product or another.[17] The educational measures offered to the patient before, during, and after BRT are summarized in Table 4.

When crusts are present, debridement can reduce the risk of superinfection and bleeding and can aid in pain control. To reduce pain and trauma during the debridement process, hydrogels are recommended and, after the debridement process, emollients. An example of debridement process consists of covering the entire lesion with a hydrogel layer of approximately 1 cm width, maintain this during 1 hour, and remove the layer by dragging it with a moistened gauze with saline solution (Fig. 2).

Empirical therapy with systemic antibiotic must be administered as soon as possible, when two systemic inflammatory response syndrome (SIRS) parameters are present (body temperature greater than 38 °C or less than 36 °C, heart rate >90 beats/min, respiratory rate >20 breaths/min, white blood cell count >12000/μl or < 4000/μl), and/or when other signs of systemic inflammation response coexist with suspected infection[2,17,25]

Conclusions

Although dermatitis intensity is greater in patients treated with BRT and appears earlier compared to patients with RT alone, resolution time is comparable to radiodermatitis alone, treatment adherence rates equal to radiotherapy alone, and generally skin sequelae, such as scars, are rarely present because grade IV BRT is less frequent than the other three reactions. To date, the information available allows us to conclude that BRT-

associated dermatitis is a predictable, treatable, and reversible event. Moreover, the right treatment does not affect the continuity of the therapy nor the clinical outcome.

Questions (answers provided after references)

1 The radiotherapy cell damage is seen on:
(a) Melanocytes
(b) Adipocytes
(c) Corneocytes
(d) Epidermal germinal cell
(e) Upper layer keratinocytes

2 The anti-EGFR
(a) Inhibits cell migration
(b) Stimulates cell survival
(c) Stimulates cell migration
(d) Stimulates cell proliferation
(e) Inhibits antimicrobial peptides

3 Bioradiodermatitis is
(a) The use of PUVA therapy + anti-EGFR
(b) The use of radiotherpy + anti-EGFR
(c) The use of PUVA therapy + radiotherapy
(d) The use of radiotherapy + chemotherapy
(e) The use of radiotherapy + immunosuppressors

4 Risk Factors include
(a) Atopic eczema, type of cancer, and nutritional state
(b) Single RT dose, Fanconi anemia, and chemotherapy
(c) Recent diagnosis, conformational RT, and scleroderma
(d) Xeroderma pigmentosum, lupus erythematosus, and RT dose
(e) Rt dose, radiation of the extremities, and xeroderma pigmentosum

5 Prevention of radiodermatitis
(a) Cannot be prevented
(b) Needs use of moisturizers
(c) Needs use of topical steroids
(d) Needs antibiotic before treatment
(e) Needs antibiotic during treatment

6 If Bioradiodermatitis is present, you need to
(a) Adjust doses of RT
(b) Control erythema and scaling
(c) Stop use of anti-EGFR
(d) Control pain and prevent infection
(e) Use moisturizers exclusively

7 Grade 4 bioradiodermatitis consists of
(a) Pustules, crusts, and bleeding in 50% of the area
(b) Skin necrosis, ulceration, and bleeding in 50% of the area
(c) Moist desquamation, crust, and pustules in 50% of the area
(d) Moderate erythema and moist desquamation in 30% of the area
(e) Intense erythema, skin necrosis, and ulceration in 10% of the area

8 Treatment of bioradiodermatitis grade 3 includes
(a) Systemic steroids and topical antibiotics
(b) Brief interruption of RT and topical corticosteroids
(c) Permanent interruption of RT and oral corticosteroids
(d) IV antibiotics, hospitalization, and treatment interruption
(e) Brief interruption of anti-EGFR and topical corticosteroids

9 Which is the adequate dressing to control abundant exudate?
(a) Ultrathin hydrogel
(b) Calcium alginate
(c) Ultrathin hydrocolloid
(d) Nonadherent gauze
(e) Impregnated Vaseline gauze

10 Education of patient during treatment includes.
(a) Use of aloe vera, avoid cleansers and perfumes
(b) Avoid shaving, skin cleansers, and moisturizers
(c) Use of trolamine, scarves to cover damaged skin
(d) Use of skin cleansers, avoidance of perfumes and smoking
(e) Use of coverage cosmetics, moisturizers, and skin cleansers

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Answers to questions:

1 d, 2 a, 3 b, 4 d, 5 a, 6 d, 7 b, 8 b, 9 b, 10 d