Epidermal Growth Factor Receptor Inhibitors and Radiation Therapy in Head and Neck Cancer: Potential Management Strategies for Skin Reactions

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Abstract

Head and neck cancer remains a formidable disease entity. Many of the patients with this tumor type present with locally advanced disease, and although treatment options have increased significantly, improving survival, patients with head and neck cancer often relapse or develop recurrent disease. Thus, interest in improving treatment of this patient population is significant. The mainstay of treatment has been radiation therapy. Recently, chemotherapy has been added to radiation to improve responsiveness. One of the most intriguing therapeutic options for this disease integrates the use of an epidermal growth factor receptor inhibiting (EGFRI) agent, cetuximab, with radiation therapy. In the pivotal trials studying this combination, radiation dermatitis was not significantly increased with the addition of this EGFRI agent. However, subsequent postmarketing reports and analyses have demonstrated different outcomes, with some patients experiencing enhanced skin toxicity with the combination of cetuximab and radiation therapy. This article will discuss the interaction of EGFRI therapy with radiation therapy in patients with head and neck cancer and current reports of increased skin toxicity. A case study format will illustrate patient outcomes and management strategies. Recommended guidelines for management of skin toxicity associated with radiation and EGFRI agents will be discussed.

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Epidermal growth factor receptor inhibiting (EGFRI) agents have played an important role in ushering in the era of targeted therapy. These agents focus on the epidermal growth factor receptor (EGFR), which is overexpressed in many epithelial tumors, including those of the lungs, kidneys, colon, and others (Lynch et al., 2007). EGFR also plays an important role in head and neck cancers (HNC), and newer therapies have been designed to target this receptor in treatment of HNC as well. Compared with traditional chemotherapy, EGFRI agents work very differently. Although they are not commonly implicated in toxicities seen with chemotherapy (e.g., myelosuppression), the toxicity profile for EGFRI agents does carry significant side effects. These side effects may include skin and hair abnormalities (e.g., rash), electrolyte disturbances, gastrointestinal effects

(e.g., diarrhea), and infusion reactions. Oncology nurses and other professionals caring for patients receiving EGFRI agents must be well versed in management of EGFRI-associated side effects and have steadily gained experience in the care of patients with various cancers receiving these agents.

As the use of EGFRI agents increases in the treatment of patients with HNC, assessment and management strategies for cutaneous side effects must be refined. Although the initial trials examining the use of cetuximab (Erbitux) and radiation therapy in the treatment of patients with HNC showed no increase in radiation dermatitis and skin toxicity, subsequent case reports have suggested enhanced patient toxicity. Additionally, information on the management of rash associated with EGFRI agents and radiation is limited. Care strategies may differ from those used in patients who have colorectal cancers and experience EGFRI-associated rash.

This article examines current care strategies for EGFRI-associated rash and radiation therapy in patients with HNC. Recent care guidelines will be discussed. A case report will be used to illustrate symptom management challenges for this patient population.

Scope of the Problem

Epidermal growth factor receptor inhibitor agents target the EGFR. This receptor is physiologically important in cellular growth and differentiation and plays a critical role in the growth and development of specific tumors (Lacouture, 2006). The unique side-effect profile of these agents includes cutaneous reactions. For most patients, the appearance of the characteristic papular-pustular rash indicates probable response, and therefore the rash is desired (Dragovich & Campen, 2009). The rash occurs in over half of all patients receiving these agents, and in some patient populations, this figure is much higher, with rash occurring in 75% to 100% of patients with colorectal cancer (Burtness, Goldwasser, Flood, Mattar, & Forastiere, 2005; Hu, Sadeghi, Pinter-Brown, Yashar, & Chiu, 2007; Segaert & Van Cutsem, 2005).

Rash was noted to occur in many of the patients receiving cetuximab in clinical trials for HNC. Although clinicians expressed concern that the rash could increase or magnify skin toxicity associated with radiation therapy in the treatment field, this was not seen in the original trials. However, sporadic case reports and a retrospective review of the literature have confirmed that increased toxicity has been seen in select patients receiving concomitant radiation with cetuximab therapy, heightening the need to have specific guidelines for management of patients on combination therapy.

Pathophysiology of EGFR Inhibitors

Inhibitors of EGFR carry a specific side-effect profile, which differs from that of conventional chemotherapy. Because EGFRI agents affect basal keratinocytes rich in EGFR expression, rash development is typical in patients receiving these agents (Lacouture, 2006). It is reported that skin reactions occur in over 50% of patients receiving these agents (Segaert & Van Cutsem, 2005). Although there are two types of EGFRIs—monoclonal antibodies (moAbs) and tyrosine kinase inhibitors—the focus of this discussion will be on the moAb cetuximab, as it is the only agent currently approved in combination with radiation therapy for the treatment of patients with HNC.

The EGFRs are members of the erb family and include erb1 (EGFR), erb2 (HER2), erb3 (HER3), and erb4 (HER4; Karar & Maity, 2009; Merlano & Occelli, 2007). These receptors are part of a family of receptor tyrosine kinases that are important in normal cellular physiology and as mediators of cell growth and differentiation (Ng & Zhu, 2008). When overexpressed, EGFR is implicated in the growth and development of several types of cancer, including epithelial tumors and particularly non–small cell lung cancers and HNC (Karar & Maity, 2009). The EGFR pathway is often dysregulated in cancer, including breast, ovarian, lung, colon, and others (Ng & Zhu, 2008).

Activation of EGFR by a growth factor or ligand such as EGF or transforming growth factor (TGF) can switch on the intracellular signaling pathway and subsequent phosphorylation, which activates growth pathways such as the RAS-RAF pathway (Spano, Milano, Vignot, & Khayat, 2008). Once activated, the cell signaling message promotes tumor growth, cellular proliferation and migration, and angiogenesis.

Administration of a moAb such as cetuximab can prevent the intracellular signaling activation when the moAb occupies the receptor site and prevents dimerization, phosphorylation, and subsequent activation of the pathway. Inflammation

is primarily responsible for the characteristic signs and symptoms associated with EGFRI-induced rash; however, the most significant causative event may be the altered EGFR signaling that occurs with administration of these agents (Lacouture, 2006).

Role of EGFR Inhibitors in Radiation Therapy

Although radiation therapy has been the primary mode of therapy for locally advanced, unresectable squamous cell carcinoma of the head and neck, patients often relapse, and the majority of patients die of locoregional disease (Robert et al., 2001). Multiple factors may play a role in this high relapse rate, including repopulation of tumor cells during therapy, tumor hypoxia, and radioresistance, leading to increased efforts to secure improvements in local tumor control and long-term survival (Robert et al., 2001). Therapies to improve outcome have included the use of radiation sensitizers, altered fractionation regimens, and the use of combined-modality treatment with radiation and chemotherapy. Because of the role of EGFR in HNC, targeting the receptor with an inhibitor of EGFR has gained interest, and cetuximab has been studied in multiple trials with this tumor type.

Cetuximab is an IgG1 moAb that specifically targets the EGFR (Ang, 2008). Cetuximab increases the radiosensitivity of HNC cells and was found to inhibit the proliferation of head and neck tumor cells in a study of cell culture media treated with the moAb (Huang, Bock, & Harari, 1999). The drug was also found to amplify radiation-induced apoptosis for both single-dose and fractionated radiation (Huang, et al., 1999).

Cetuximab was found to have activity when combined with radiotherapy in patients with locoregionally advanced HNC. In a phase I study of 16 patients, a standard dose-escalation procedure was used to deliver cetuximab in patients with advanced HNC (Robert et al., 2001). Common adverse events included fever, asthenia, elevation of transaminase levels, nausea, and skin toxicities (grade 1 or 2 in most patients). The authors concluded that cetuximab could be safely administered with radiation therapy and recommended an initial dose of 400 to 500 mg/m^2, with a maintenance weekly dose of 250 mg/m^2 for patients in subsequent phase II/III studies (Robert et al., 2001).

A combination of cetuximab and cisplatin was also studied in patients with recurrent squamous cell carcinoma of the head and neck, showing a high percentage of saturation of EGFR in tumor tissue, with 67% of the nine evaluable patients achieving major responses and 22%, complete responses (Shin et al., 2001).

In the pivotal trial leading to US Food and Drug Administration approval of cetuximab in the treatment of this disease, patients with locoregionally advanced HNC were randomly assigned to therapy with high-dose radiation alone (n = 213) versus high-dose radiation plus weekly cetuximab (n = 211; Bonner et al., 2006). Cetuximab was given in an initial loading dose of 400 mg/m^2, followed by 250 mg/m^2 weekly for the duration of the planned radiation therapy. The results showed a median duration of locoregional tumor control of 24.4 months for the cetuximab/radiation therapy group versus 14.9 months for the patients receiving radiation therapy alone (p = .005). The median duration of overall survival was 40 months for the combined-modality group versus 29.3 months for radiation alone (p = .03). Although the group receiving cetuximab had a higher incidence of infusion reactions and acneiform rash, as would be expected, the incidence of grade 3 or greater toxic effects such as radiation dermatitis and mucositis was not significantly different between the study groups.

Recently published follow-up data show that the 5-year overall survival rate continues to be higher for patients who received the combined-modality therapy than for those who received radiation alone (45.6% vs. 36.4%, respectively; Bonner et al., 2009). The follow-up data also showed that patients who received cetuximab and had an acneiform rash of at least grade 2 had a significantly improved overall survival compared with patients who experienced no rash or grade 1 rash (HR = 0.49; 95% CI, 0.34–0.72; p = .002).

Cetuximab is currently approved for the treatment of locoregionally advanced squamous cell carcinoma of the head and neck in combination with radiation therapy and as a single agent for patients who have received prior platinum-based therapy and have relapsed disease. Vermorken and colleagues (2008) also reported on the effectiveness of cetuximab in combination with fluorouracil and cisplatin chemotherapy versus fluorouracil and cisplatin alone in a randomized study of 442 patients with untreated recurrent or

Table 1. National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.02 selected toxicity data

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acneiform rash				
Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Radiation dermatitis				
Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

Note: BSA = body surface area; ADL = activities of daily living. Reprinted from the National Cancer Institute Common Terminology Criteria (CTC) version 4.02

metastatic squamous cell carcinoma of the head and neck. The results showed that combination chemotherapy/cetuximab recipients experienced a significantly prolonged median overall survival of 10.1 months as compared with 7.4 months for the chemotherapy-alone group, with a 9% incidence of grade 3 skin reactions in the EGFRI group (Vermorken et al., 2008).

Other chemotherapy agents are also being studied in combination with cetuximab therapy in this patient population, but results have yet to be published.

Pathophysiology of Radiodermatitis

Layers of the skin normally undergo a shedding process by which cells replace themselves by proliferation and differentiation. The basal layer of the epidermis contains stem cells, which divide and push new cells into the higher layers to continually replace the outer cells that are lost. The superficial cells are shed through normal desquamation from wear and tear throughout the day and normally take 2 to 4 weeks to turn over (Hogle, 2010).

Radiation hastens this shedding process, and the cells at the basal layer may or may not be able to be produced fast enough to replace the lost cells. Changes in vasculature, effects of fibroblasts, and varying levels of regulatory growth factors result in the potential for altered wound healing when radiation is given (McQuestion, 2006). Ionizing radiation essentially damages the mitotic ability of stem cells within the basal layer, thus preventing the process of repopulation and weakening the integrity of the skin. Repeated radiation impairs the cell division within the basal layer, and so the degree to which a skin reaction develops is dependent on the survival of actively proliferating basal cells in the epidermis. Typically, skin reactions manifest as erythema or redness in 10 to 14 days because of the transit time for new skin cells to migrate to the surface (McQuestion, 2010). Skin reactions are dose dependent, and the severity often peaks at the completion of therapy, with recovery typically occurring by the 1-month follow-up visit (see Table 1).

If chemotherapy is administered concurrently, it only intensifies the peak, or the peak occurs earlier. Basal cell loss begins once the radiation dose reaches 20 to 25 Gy, and the maximum depletion of basal cells occurs when the patient has received a dose of 50 Gy (McQuestion, 2010). In clinical practice, this means that skin reactions tend to become visible around the second to third week of radiation therapy, reaching a peak at the end of or within 1 week of completion of treatment (see Figures 1 and 2). Adding EGFRI agents to therapy quickens the reaction.

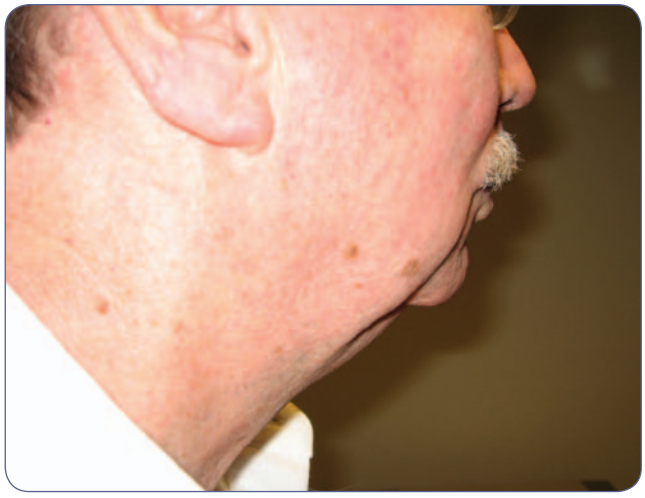

Figure 1. Grade 1 radiation dermatitis reaction.

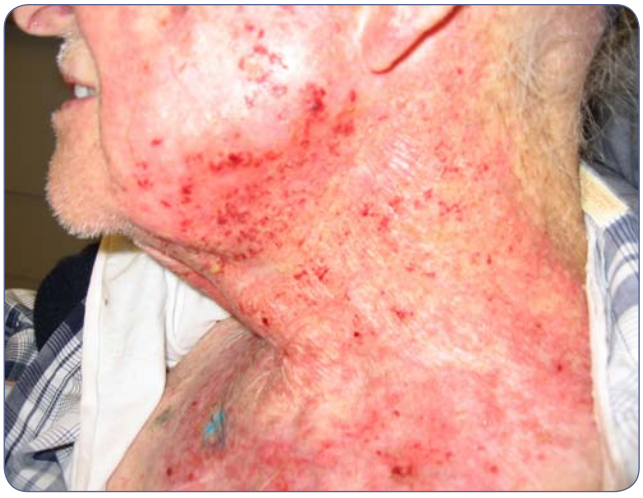

Figure 2. Grade 3 radiation dermatitis reaction with a grade 3 acneiform rash.

EGFRI-Associated Rash, Radiation Dermatitis, and Increased Toxicity

Radiation therapy produces characteristic changes to the involved skin in the treatment area. Radiation dermatitis and radiation-induced acute mucositis can be serious dose-limiting side effects for patients with HNC receiving this therapy (Hong et al., 2009). Of interest, areas of previously irradiated skin have been shown in some patients to be free of the commonly seen papular-pustular rash associated with EFGRI agents (Mitra & Simcock, 2006). This phenomenon may be related to chronic effects from previously administered radiation developed over months to years, possibly linked to an absence of hair follicles and sebaceous glands along with fibrosis in the previously irradiated area (Lacouture, Hwang, Marymont, & Patel, 2007).

In the pivotal clinical trial studying the effects of radiation therapy combined with cetuximab, radiation dermatitis and mucositis were not notably increased in the combined-modality group. However, subsequent reports have noted an increase in skin reactions and mucositis in selected patients (see Table 2). Possible reasons for these increased skin reactions could be enhanced inflammatory responses due to inhibition of EGFR signaling, producing severe inflammatory cutaneous effects with combined-modality therapy (Budach, Bolke, & Horney, 2007). A survey of European Organisation for Research and Treatment of Cancer (EORTC) institutes showed a 49% incidence of grade 3/4 radiation dermatitis with the combination of cetuximab and radiation therapy in 71 HNC patients (Giro et al., 2009). Enhanced toxicity was also seen in a small prospective trial of 13 patients, with 77% of the study participants developing grade 3/4 skin reactions and grade 3/4 mucositis; 46% required hospital admission and 31% needed a treatment break (Pryor et al., 2009).

Tejwani and colleagues (2009) conducted a review of dermatologic toxicity data from abstracts presented at the American Society of Clinical Oncology (ASCO) Annual Meetings and other databases. They noted that the summary incidence of high-grade radiation dermatitis was 31.3% in patients receiving combined-modality treatment with radiation and an EGFRI agent, with rash in 16.1% and mucositis in 52.7%. When the data were compared with those of radiation therapy alone, an increased risk of dermatologic toxicities was suggested for the combined-modality group, prompting the authors to conclude that although increased rash is an expected side effect when using EGFRI agents, the incidence of in-field dermatitis and mucositis is a real safety concern that had gone unrecognized in the earlier trials. Better management strategies are needed to optimally care for this group of patients (Tejwani et al., 2009).

Guidelines for Management of EGFRI-Associated Rash and Radiation Dermatitis

The use of cetuximab in combination with radiation therapy is relatively new. Therefore, lim-

Table 2. Selected trials/reports demonstrating skin toxicity with concurrent radiation and cetuximab treatment

Study author	Study design	Study results	Recommendations
Tejwani et al., 2009	Dermatologic toxicity data analyzed from meeting abstracts and other databases with data from collaborative group, phase III, randomized radiotherapy and chemoradiation trials as controls	Summary incidence of high-grade radiation dermatitis in patients who received radiation plus EGFRI was 31.3% (95% CI, 17.7%–49.1%). Combination radiotherapy plus EGFRI compared to radiation alone showed a risk ratio of 2.38 for radiation dermatitis, 3.01 for rash, and 1.76 for mucositis, suggesting an increased risk of dermatologic toxicities with the combined regimen.	Increased rash is expected with EGFRI; in-field dermatitis and mucositis represent new safety concerns, with need for improved reporting and management strategies to improve patient care.
Giro et al., 2009	EORTC survey of 111 institutions; 28 responses reported on a total of 125 patients, with skin reaction information available from 71 patients with head and neck cancer	Of 71 patients, 36 had no grade 3/4 adverse reactions in the radiation therapy field, 15 had grade 3, and 20 had grade 4 radiation dermatitis. The results show an incidence of 49% grade III/IV radiation dermatitis in head and neck cancer patients treated with cetuximab and concurrent radiotherapy.	A systematic clinical monitoring of cutaneous side effects during radiation therapy and cetuximab treatment is recommended to ensure the safety of this combination.
Pryor et al., 2009	Prospective data collected between August 2007 and May 2008 with 13 consecutive patients with head and neck cancer	Of 13 patients, 10 (77%) had grade 3/4 skin reactions and 10 (77%) had grade 3/4 mucositis; 46% needed admission for management of skin toxicity or mucositis and 31% required a treatment break. Only 31% of patients finished their planned 8 cycles of cetuximab.	The trial demonstrated a higher rate of toxicity compared with the previously reported randomized trial, which impacted treatment compliance and caused delays in radiation therapy.
Koutcher, Wolden, & Lee, 2009	Retrospective review of 115 head and neck cancer patients treated with cetuximab and radiation therapy	Among 115 patients, serious radiation dermatitis was noted in 26 (33%), with 22 patients developing grade 3 dermatitis and 4 patients developing grade 4 dermatitis. Toxicities developed during the fifth week of therapy.	Serious skin toxicities develop with concomitant cetuximab and radiation therapy compared with radiation therapy and cisplatin, although further study is needed to confirm this finding.
Bolke et al., 2008	Study of 5 patients with head and neck cancer	Among 5 patients, 2 cases of unusually severe radiation dermatitis developed, with confluent, moist desquamation in the radiation field (grade 3). Radiotherapy was discontinued, with topical corticosteroids and systemic antibiotics given with subsequent resumption of radiotherapy.	Cetuximab may have the potential to enhance the severity of radiation dermatitis in head and neck cancer patients; a systematic monitoring of cutaneous side effects in this patient population is needed.
Azad, 2009	Case report	Single case report of patient who developed a severe painful skin reaction within the radiotherapy field, requiring hospitalization 1 week after finishing radiotherapy; moist desquamation occurred with erythematous rash on the lower half of the face and upper neck	Clinicians must be made aware of the risk of severe radiation dermatitis in head and neck cancer patients treated with cetuximab and radiotherapy and implement appropriate strategies for prevention and treatment in these patients.
Berger & Belka, 2008	Case report	Single case report of a patient who developed a severe skin reaction secondary to cetuximab in combination with radiotherapy; within hours of cetuximab infusion, vesicular and pustular eruptions developed followed by hemorrhagic lesions. Therapy was continued without worsening of reaction; healing occurred by 3 months	Clinicians should be alert to the possibility of severe skin toxicity when adding an EGFR inhibitor to radiotherapy.
Vano-Galvan, de las Heras, Harto, & Jaen, 2008	Case report	Case report of single patient who developed grade 3 radiation dermatitis and EGFRI cutaneous toxicity requiring treatment interruption and topical treatment with chlorhexidine-based cream and topical steroid	Dermatologists need to be aware of potential side effects with combined therapy and optimal treatment strategies to enhance patient compliance and effectively manage toxicity while avoiding modification of prescribed radiation therapy or cetuximab regimen.
Budach, Bolke, & Horney, 2007	Case report	Case reports of 2 patients who developed severe radiation dermatitis with necrosis after a total of 58 Gy and 5 infusions of cetuximab (grade 4) in radiation field, compared with grade 1 acneiform rash outside of the radiation portals	Severe inflammatory or cytotoxic cutaneous side effects may occur in patients treated with radiation therapy and cetuximab.

Note: EGFRI = epidermal growth factor receptor inhibitor; EORTC = European Organisation for Research and Treatment of Cancer. Based on information from Giro et al. (2009), Tejwani et al. (2009); Bolke et al. (2008); Budach, Bolke, & Horney (2007); Pryor et al. (2009); Koutcher et al. (2009); Berger & Belka (2008); Vano-Galvan et al. (2008); and Azad, (2009).

ited information exists on the optimal management of coexisting EGFRI-associated rash and radiation therapy. However, consensus guidelines were published in 2008 by Bernier and colleagues. Developed by an advisory board of 11 radiation oncologists, medical oncologists, and dermatologists, these guidelines note general and grade-specific clinical approaches for the management of dermatitis in this specific patient population. The board notes that cetuximab-associated rash usually appears in the irradiated field within 3 to 5 weeks after the initiation of therapy. The group determined that when EGFRI-associated rash and radiation dermatitis coexist within irradiated fields, the clinical management should be based on the grade of dermatitis, with grade 1 patients receiving treatment recommendations for EGFRI-associated rash outside of irradiated fields. For grades 2 and above, recommendations for the specific grade of dermatitis should be followed (Bernier et al., 2008).

General management approaches for radiation dermatitis patients on combined-modality therapy with EGFRI agents and radiation call for maintenance of hygiene and gentle cleansing of the skin prior to radiation therapy. Clinicians should avoid topical moisturizers, gels, emulsions, and dressings before radiation therapy treatments, as they can cause a bolus effect, increasing the radiation dose to the epidermis (Bernier et al., 2008). When necessary, anti-infective measures could be utilized, such as chlorhexidine cream. For grade 2 or 3 reactions, topical approaches such as drying gels and antiseptics, anti-inflammatory emulsions, zinc oxide paste, or silver sulfadiazine creams may be used. These treatments must be administered after radiation therapy. The advisory board did not recommend the use of doxycycline at this stage and advised observation of blood counts and an appropriate infectious workup when needed. For grade 4 reactions, where skin necrosis or ulceration may occur, the board recommended verification of the radiation dose and distribution and recruitment of specialized wound care specialists to manage skin toxicity (Bernier et al., 2008).

The National Comprehensive Cancer Network (NCCN) recently published a task force report on the management of dermatologic and other toxicities associated with EGFRI agents in patients with cancer (Burtness et al., 2009). In this comprehensive report, the authors noted that it is imperative for clinicians to determine the presence of in-field radiation toxicity compared with systemic skin toxicity when administering an EGFRI agent and concomitant radiation, as radiation itself can produce significant skin toxicity. As previously mentioned, irradiated tissue (where radiotherapy was completed 6 months to 1 year prior to administration of EGFRI agents) can produce a sparing effect of rash in the radiated site. However, concomitant therapy with an EGFRI agent and radiation therapy can produce a more confluent papular-pustular eruption in the irradiated skin with increased in-field toxicity (Burtness et al., 2009). The report acknowledges that the emerging literature points to increased skin toxicity in selected patients receiving cetuximab and radiation therapy for HNC.

Recommendations for treatment include the use of topical mometasone for in-field dermatitis, based on several randomized clinical trials. For patients with superinfection and radiation dermatitis, the report suggests that topical antibiotics and steroids can be used, cautioning that the topical antibiotics can be applied to the eroded area, with topical steroids on the non-eroded, inflamed tissue (Burtness et al., 2009). The authors of the report note that systemic doxycycline has not been recommended by some clinicians for grade 2 or 3 radiation dermatitis, but they acknowledge that no data are yet available to recommend for or against the use of systemic doxycycline in this setting (Bernier et al., 2008).

The NCCN report describes grade 4 toxicity in patients receiving cetuximab and radiation therapy as an indication for discontinuing the EGFRI agent or possibly interrupting the radiation course. Hospitalization and pain and symptom management may be needed for selected patients. A potent topical steroid may be of use in this setting with specific patients. However, the board calls for caution when implementing this treatment. See Figure 3 for a proposed algorithm incorporating recommendations from both NCCN and the consensus panel with recently available data.

Additionally, clinical trials have shown that the use of prophylactic oral antibiotics of the tetracycline family (minocycline, 100 mg daily, or doxycycline, 100 mg twice daily) decreases the incidence of moderate/severe skin toxicities by up to 50% in patients with colorectal cancer receiving EGFRI therapy (Scope et al., 2007; Lacouture et al., 2010).

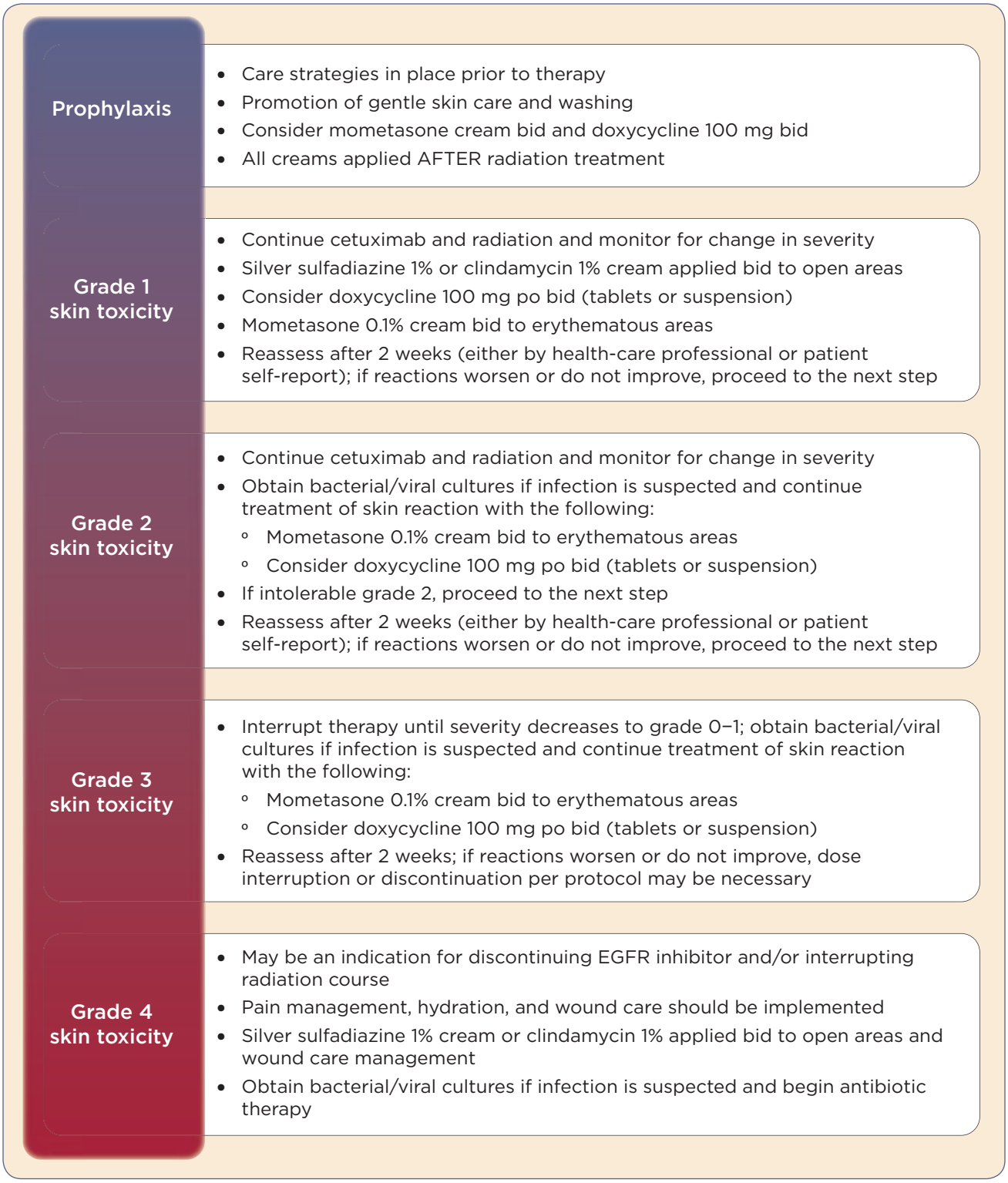

Figure 3. Proposed algorithm for rash management in patients receiving cetuximab and concurrent radiation therapy. EGFR = epidermal growth factor receptor. Based on information from Burtness et al., 2009; Bernier et al., 2008.

These findings suggest that for patients undergoing treatment with radiotherapy and cetuximab, it is advisable to begin oral antibiotic therapy prior to the development of toxicity. Further study is needed to confirm the optimal approach for patients receiving radiation therapy and EGFRI agents.

Case Study

Mr. S. is a 47-year-old man who began noticing a sore throat and difficulty swallowing in midsummer. Initially, the pain was intermittent and was treated with antibiotics without improvement. In the fall, when his symptoms persisted and became progressively worse, he noticed bilateral neck swelling. He went to his primary care physician who immediately sent him to an ear, nose, and throat (ENT) specialist. The ENT physician appreciated bilateral neck adenopathy as well as a lesion on the epiglottis extending into the vallecula involving the lingual surface of the epiglottis.

Biopsy of one neck node revealed poorly differentiated, invasive squamous cell carcinoma (SCC). A rigid esophagoscopy was performed, and biopsies from the base of the tongue confirmed SCC and human papillomavirus (HPV)-positive status. A positron-emission tomography/computed tomography (PET/CT) scan showed a hypermetabolic laryngopharyngeal mass with extension into the base of the tongue and epiglottis, as well as bilateral level II neck nodes (right node measured 2.3 × 2.2 cm with a standardized uptake value [SUV] of 6.7, and left node, 2.0 × 2.5 cm with an SUV of 9.2). Evaluation revealed no evidence of distant metastases. Laboratory studies (complete blood cell count [CBC] and complete metabolic panel [CMP]) were normal.

The patient's medical history was unremarkable, and he had undergone no prior surgeries. His social history included the following findings: operated his own electrical company, married, nonsmoker, and recently quit drinking a 12-pack of beer daily. Family history revealed distant relatives with ovarian and pancreatic cancers but no lung or oral cavity cancers. Mr. S. was clinically diagnosed with T2 N2c SCC of the base of the tongue. He had lost 6 lb in the past 2 months and occasionally had seen blood in his sputum without any dyspnea.

Before consulting with the radiation and medical oncologists, Mr. S. was seen by his dentist and had his right mandibular and maxillary wisdom teeth extracted. The rest of his teeth were in excellent condition. Anxious to begin therapy, Mr. S. began on cetuximab therapy until he healed from his extractions. Shortly after beginning cetuximab, he developed a typical EGFR rash and was placed on minocycline. Meanwhile, Mr. S. had a feeding tube placed before beginning radiation treatments. He was then treated definitively with radiation therapy along with concurrent chemotherapy, weekly cisplatin, and cetuximab. He received 7,000 cGy, using seven-field intensity-modulated radiation therapy (IMRT) treatment planning, with 6 megavolt photons.

Mr. S. developed a significant skin reaction early on during his chemoradiation treatment. He presented with the EGFR rash and erythema, grade 1 (National Cancer Institute's [NCI's] Common Terminology Criteria for Adverse Events, version 4.02) within 2½ weeks of radiation (2,600 cGy/13 fractions). By the fourth week, after receiving 3,400 cGy/17 fractions, Mr. S.'s skin reaction quickly increased to grade 3 with an impetiginized radiation dermatitis (secondary bacterial infection; see Figure 4). In part, it was thought that the intensity of his skin reaction was due to the addition of cetuximab. Because there were no standardized evidence-based skin care guidelines for combined therapy, Mr. S. was offered multiple skin care products from the medical and radiation oncologists to help with the EGFR rash, patchy crusty papulopustules, moist desquamation, and associated pain and pruritus caused by the skin reaction. Mr. S. developed depression from the disfigurement and associated treatment-related symptoms.

Discussion

Caring for patients receiving combined-modality therapy can be challenging. Toxicities may stem from each type of individualized therapy (radiation or chemotherapy) but increase when

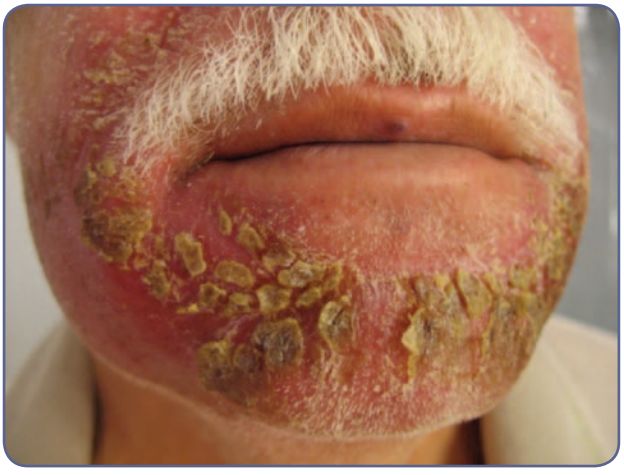

Figure 4. Grade 3 skin reaction with impetiginized radiation dermatitis.

therapies are combined. Oncology nurses and advanced practice nurses need to know whether prophylactic treatment should be the standard approach to care and what the role of prophylactic tetracycline analog agents should be in this setting.

In the absence of evidence-based skin care guidelines to treat patients receiving combined-modality therapy, consensus statements should offer oncology nurses general recommendations in the care of this patient population. Understanding the timeline for when skin reactions commonly occur during therapy is important in educating the patient. Typically, radiation-induced skin reactions become visible after the second week of radiation (2,000 cGy/10 fractions; Korinko & Yurick, 1997). EGFRI skin reactions are seen after a few days of initiating therapy and peak 2 to 3 weeks after beginning therapy. Studies show that when EGFRI agents are combined with radiation, skin reactions may be delayed, appearing 3 to 5 weeks after starting treatment (Bonner et al., 2007).

Gentle daily washing and drying of the skin is encouraged (Roy, Fortin, & Larochelle, 2001). At present, the use of trolamine emulsion or prophylactic pentoxifylline does not appear to lessen the severity of skin reactions (Elliott, et al., 2006; Aygenc, Celikkanat, Kaymakci, Aksaray, & Ozdem, 2004). Skin hydration and application of moisturizers are recommended (Haas & Moore-Higgs, 2010; McQuestion, 2006). The NCCN task force recommendations and the consensus guidelines published by Bernier et al. in 2008 currently offer the most comprehensive guidelines for care in this setting.

Another important issue revolves around who is primarily responsible for managing the patient's skin reactions. Should nurses in the medical oncology offices who see the patient weekly or should radiation oncology nurses who see the patient daily manage skin toxicity? There is no correct answer to this question; rather, both subspecialists should join together to decide their preferences and then provide consistent information to the patient. This approach can improve patient compliance and self-care strategies and avoid treatment breaks.

Nursing Implications

It is critical that oncology nurses and advanced practice oncology clinicians who care for patients receiving EGFRI agents and concomitant radiation therapy for HNC understand the risks for skin toxicity. Although the original trials of this treatment strategy did not show an increase in radiation-induced mucositis or radiation dermatitis, subsequent reports have shown increased toxicity in selected patients. Therefore, as combined therapy is used more frequently, nursing personnel must heighten their awareness of potential toxicity and understand current treatment recommendations and management strategies for this patient population. Accurate grading of rash and radiation dermatitis is essential. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.02 for radiation dermatitis and EGFRI-associated rash are presented in Table 1.

Using existing guidelines and monitoring of new data as they become available are crucial to improving patient outcome. Many of the current recommendations are based on either studies of radiation dermatitis or anecdotal reports. Further study is needed in the form of randomized trials to guide clinicians in evidence-based practice in this setting. Advanced practitioners (APs) and other clinicians must continue to update their knowledge base regarding current treatment strategies for EGFRI-associated rash and radiation therapy in patients with HNC. APs working in education or staff training should integrate optimal management strategies and current evidence-based approaches in the care of this patient population into nursing education forums.

Communication between subspecialties is also key in improving care of the patient with HNC receiving combined-modality therapy with cetuximab and radiation therapy. Providing the patient with consistent information regarding expected skin reactions and optimal treatment strategies prior to starting either form of treatment will promote effective management. Optimally, the information provided by each specialty should be consistent and based on the previously mentioned guidelines. Consensus regarding recommended treatments for rash should include appropriate times for application of suggested creams and lotions. Patients should be reminded about the importance of wearing sun-protective clothing and hats.

A survey of oncology nurses by the Institute for Medical Education and Research (IMER, 2009) at the 2009 Oncology Nursing Society In-

stitutes of Learning conference queried oncology nurses regarding their knowledge of management of skin toxicity associated with the use of EGFRI agents. Although 32% of the nurses surveyed described existing protocols for dermatologic toxicities in their practice settings, 51% of the respondents reported no formalized guideline or protocol to manage skin toxicity. For patients with rash receiving EGFRI therapy and concurrent radiation therapy, the oncology nurse respondents (43%) were uncertain regarding care of rash; 37% reported that skin care products should be given after radiation therapy, whereas 16% did not recommend any emollients, sunscreen, or ointments during treatment. A small number of nurses (4%) reported that skin lotions and emollients should be given prior to radiation therapy, which is contraindicated, as previously discussed. Based on these data reported from the nursing survey, it is clear that additional education regarding management strategies for dermatologic toxicities, including EGFRI-associated rash and concurrent radiation therapy, is needed.

Conclusion

Targeted therapy has produced major advances in the treatment of patients with cancer. Treatment of HNC can be complex, and more than half of patients with SCC of the head and neck present with locally advanced disease that requires combined-modality therapy (Ang, 2008). Some of these patients may receive cetuximab in combination with radiation therapy, with the addition of chemotherapy as well for some patients on clinical trials. Although cutaneous side effects such as radiation dermatitis were not reported as increased in the original clinical trials of cetuximab, subsequent reports in the postmarketing period and additional review of trial data have shown otherwise.

Because of the potential for enhanced skin toxicity, oncology nurses and advanced practice oncology nurses must be aware of the possibility of increased skin effects. Possible treatment strategies should be discussed and implemented early to improve patient response and increase adherence to therapy. Education of oncology nurses by advanced practice nurses and staff educators is important to increase the knowledge base regarding radiation therapy and EGFRI agents in HNC patients. Treatment options have expanded for patients with HNC, but effective side-effect management is essential to reduce toxicity associated with EGFRI therapies used in combination with radiation in this patient population. Further study of optimal rash management strategies for these patients is needed.

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