Efficacy and Skin Toxicity Management with Cetuximab in Metastatic Colorectal Cancer: Outcomes from an Oncologic/Dermatologic Cooperation

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Abstract

Purpose: The aim of this study was to investigate the efficacy of the combination of irinotecan/cetuximab and to plan related skin toxicity management with an oncologic/dermatologic team. **Patients and Methods:** Thirty-four patients with epidermal growth factor receptor (EGFR)–expressing metastatic colorectal cancer received cetuximab 400 mg/m^2 as an initial dose and 250 mg/m^2 weekly thereafter. In addition, patients received irinotecan 180 mg/m^2 every 2 weeks. **Results:** Thirty-two patients were evaluated for response rate (RR) and skin toxicity to establish the best management. In our study, the responses observed with cetuximab treatment were complete response in 1 patient (3%), partial response in 11 patients (34%), disease stabilization in 6 patients (19%), and progressive disease in 14 patients (44%). Of 34 patients evaluable for cutaneous toxicity, 10 patients (29%) presented with grade 1 eruption, 13 (38%) with grade 2 eruption, and 4 (12%) with grade 3 eruption. Allergic reactions such as flushing and urticaria (grade 2) were seen in 2 patients (6%). **Conclusion:** Cutaneous reactions consisted of follicular rash, xerosis, painful fissures in palms and soles, alterations in hair growth, and mucositis. In the majority of patients (80%-90%), the worst recorded skin effects were mild (grade 1) to moderate (grade 2). The incidence of severe cases (grade 3) was approximately 15%. All dermatologic effects were reversible and generally without sequelae within 4 weeks after treatment discontinuation. We observed significant correlations between degree of cutaneous toxicity and increased RR. Correct identification and treatment by oncologic/dermatologic cooperation of EGFR cutaneous side effects help to improve quality of life.

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Introduction

Colorectal carcinoma (CRC) is a major cause of morbidity and mortality in most industrialized nations and remains among the top 3 most common malignancies in men and women worldwide.[1,2] Colorectal cancer is the fourth most common cancer in the United States, with an estimated 112,340 new cases and an estimated 52,180 deaths in 2007.[2] In Italy, the CRC diagnosis was 24,289 new cases and 9322 deaths in 2005.[3]

The pathologic stage is the most reliable prognostic factor for patients with CRC. If CRC is detected at an early stage (localized to the bowel mucosa), it is generally treatable and is

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often curable, with a 93% 5-year survival rate.[1] However, the involvement of adjacent organs or lymph nodes reduces the 5-year survival rate to 67%. In metastatic disease, the 5-year survival rate decreases to only 8%.[1,3] Metastatic disease is present in approximately 20% of patients at the time of first CRC diagnosis.[4] However, 50% of patients with localized disease develop metastasis.[5,6]

For > 40 years, the standard treatment for patients with mCRC was systemic chemotherapy with 5-fluorouracil (5-FU; bolus, continuous infusion, with or without leucovorin [LV]). Median survival with 5-FU/LV–based chemotherapy was 10-12 months.[7] Newer chemotherapeutic agents such as irinotecan and oxaliplatin have had a significant impact on treatment strategies for patients with metastatic CRC (mCRC) when used in combination with 5-FU–based therapy. Based on data from trials of Saltz et al[8] and Douillard et al,[9] the FDA approved irinotecan in combination with bolus and infusional 5-FU/LV as first-line therapy for mCRC. In 2002, the FDA approved oxaliplatin as second-line therapy for mCRC and, in 2004, as first-line therapy.

FOLFOX (5-FU/LV/oxaliplatin) and FOLFIRI (5-FU/LV/irinotecan) appear to be the most effective schedules in terms of efficacy and tolerability. Phase III trials evaluating combination therapy have reported median overall survival times in the range of 14.8-21.5 months. Although an increasing number of options are available for the treatment of patients with advanced CRC, the long-term prognosis remains poor. This has driven the development of new therapies that target the specific aberrations that are potentially involved in tumor cell proliferation and growth.[10]

The FDA (February 2004) and European Agency for the Evaluation of Medicinal Products (June 2004) have approved cetuximab, a human epidermal growth factor receptor (HER1/epidermal growth factor [EGF] receptor [EGFR])–targeted monoclonal antibody (MoAb), in association with irinotecan after patients experience progression after receiving irinotecan as a single antitumor agent.[7]

Cetuximab

Growth factors and their receptors are vital to normal cellular dynamics because they regulate cell growth, proliferation, differentiation, migration, angiogenesis, and cell death. Epidermal growth factor receptor is a monomeric 170-kD transmembrane glycoprotein that possesses intrinsic tyrosine kinase (TK) activity. Epidermal growth factor receptor belongs to the family ErbB, of which 4 receptors have been characterized: HER1 (EGFR or *c-erbB1*), HER2 (*neu* or *c-erbB2*), HER3 (*c-erbB3*), and HER4 (*c-erbB4*). Epidermal growth factor receptor is encoded by the *c-erbB1* protooncogene and is expressed on normal and malignant cells, primarily of epithelial origin. Epidermal growth factor receptor is a transmembrane entity that consists of 3 important regions to help serve its function as a cell-signaling receptor.

Epidermal growth factor and transforming growth factor–α are the 2 major extracellular endogenous ligands that activate EGFR. However, other endogenous ligands that can function to activate EGFR include amphiregulin, heparin-binding EGF, and betacellulin.[11] When a ligand binds to the extracellular domain of EGFR, receptor dimerization occurs. After internalization, receptor-ligand binding induces phosphorylation and subsequent activation of TK.[12] As a consequence, signaling pathways such as Ras/Raf/mitogen–activated protein kinase, phosphatidylinositol 3-kinase, Akt/JAK, STAT kinases, and protein kinase C are activated, and gene transcription is regulated.

Dysregulation of the EGFR pathway also is associated with malignancy.[13] In addition to increased expression of the receptor and its ligands individually, autocrine or paracrine loops and aberrant downstream signaling are among the possible mechanisms that mediate cell cycle progression, resistance to apoptosis, angiogenesis, invasion, and migration.[14] Epidermal growth factor receptor expression predicts poor outcome in patients with CRC. Furthermore, coexpression of EGF and EGFR predicts a more aggressive disease.[15]

Cetuximab is a chimeric immunoglobulin G1 MoAb that targets the extracellular domain of the EGFR, competitively inhibiting ligand binding and, therefore, EGFR activation.[16] Cetuximab exerts its antitumor effects through ligand-independent processes, stimulating receptor internalization. Cetuximab mechanisms of action include inhibition of cell-cycle progression,[17] induction of apoptosis,[18,19] inhibition of angiogenesis,[20,21] and decreased invasion and metastatic spread.

Because of the expectation that many biologic agents lack efficacy alone, cetuximab was first tested in combination therapy. An initial observation suggested that cetuximab had the ability to make patients whose disease was irinotecan resistant responsive to irinotecan and led to a strategy of adding cetuximab to irinotecan in such patients.

The BOND (Bowel Oncology with Cetuximab Antibody) trial, an open-label, multicenter study, randomized 329 patients with stage IV, EGFR-expressing colorectal adenocarcinomas to receive the combination of irinotecan plus cetuximab or cetuximab alone (400 mg/m^2 as an initial dose and 250 mg/m^2 weekly thereafter).[7] Irinotecan was administered at the same dose and schedule that the patients had previously followed.

The overall response rate (RR; ORR) for 218 patients who received irinotecan/cetuximab was 22.9% (P = .007), whereas 111 patients who received cetuximab alone demonstrated a 10.8% RR (P = .007). The median time to progression was 4.1 months for the combination group and 1.5 months for the cetuximab-alone group.[7]

A more recent phase II trial also assessed the safety and efficacy of single-agent cetuximab in patients with chemotherapy-refractory mCRC who expressed EGFR.[22] The findings were similar to those of previous trials. Unfortunately, responses did not correlate with the degree of EGFR expression as predicted by preclinical studies.[23] This might be a result of the imprecision of quantifying HER1/EGFR expression or possibly because EGFR might not be the most appropriate marker for predicting response to therapy.

Another mechanism might be advocated to explain the apparent lack of correlation between EGFR status and efficacy of EGFR-targeted therapy with MoAbs. It is also possible that the detection of EGFR expression, which is usually performed in the primary tumor, does not always correlate with the EGFR status in metastatic sites, thus making cancer cells in these sites resistant to therapy.

Techniques such as gene expression profiling can help to identify predictive markers of response, allowing the selection of patients more likely to respond to therapy. Although different trials, particularly those with different regimens, should be compared with caution, the RR from this trial was equivalent to the level of activity observed with second-line FOLFOX (9.9%).[24] Based on these data, cetuximab was recently approved for patients with mCRC in the United States and Europe in association with irinotecan after irinotecan alone and for progression. The side effects observed in this trial were manageable and similar to those previously reported. Therapeutic antibodies can induce hypersensitivity and other infusion-related reactions.

The side effects of cetuximab are fairly mild. The most common is a papulopustular reaction along with drying and fissuring skin frequently associated with pruritus and paronychia. Hypersensitivity infusion reactions are less frequent (occurring in 3% of patients), with mortal hypersensivity reactions occurring in < 1 in 1000. Although some degree of rash occur in most patients, severe eruptions resulting in significant pain, pruritus, or infectious sequelae are rare.

In the BOND trial, papulopustular reactions occurred in approximately 80% of the patients in each group, but grade 3/4 toxic effects on the skin were observed in only 9.4% and 5.2% of the combination therapy and monotherapy groups, respectively.[7] There were papulopustular reactions in 225 of 253 patients (88.9%).

Of note, the development and severity of the rash have been correlated with an increased likelihood of an objective response, but the mechanism underlying this correlation is only partially clear.[25] Cetuximab has received marketing authorization in the European Union, the United States, and Asian and Latin American countries for treatment of EGFR-expressing mCRC after failure of irinotecan.[26]

Patients and Methods

Inclusion criteria for patients included the following: age ≥ 18 years; histologically confirmed mCRC; irinotecan-refractory disease; Karnofsky performance status (PS) > 80%; adequate hematologic parameters (neutrophil count > 1500 cells/μL, platelet count > 100,000 cells/μL, hemoglobin > 9 g/dL, and white blood cell count > 3000 cells/μL); and renal and liver function (creatinine and bilirubin < 1.5 × upper limit of normal [ULN]; alanine aminotransferase and aspartate aminotransferase < 5 × ULN). Patients were pretreated with up to 3 chemotherapy lines. At study entry, the patients had to have ≥ 1 bidimensionally measurable index lesion and immunohistochemical evidence of EGFR expression in the primary tumor or in a metastasis.

Epidermal growth factor receptor was analyzed using the DAKO test at our pathology institute. All patients had to provide written informed consent.

Study Design and Treatment

This was an open-label, uncontrolled phase II trial conducted at 2 centers in Italy. All patients were treated with cetuximab/irinotecan. In week 1, cetuximab was given as a 2-hour infusion at an initial dose of 400 mg/m^2 starting with a test dose of 20 mg for 10 minutes to monitor for any systemic adverse reactions before continuation of the first dose. Further weekly doses of 250 mg/m^2 were given as 1-hour infusions without a further test dose. A histamine receptor antagonist was administered 30 minutes before every cetuximab infusion. There was a 1-hour rest period after cetuximab administration, after which irinotecan treatment was started as a 1-hour infusion at a dose of 180 mg/m^2 every 2 weeks. Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria. Treatment was continued until the patient progressed, experienced unacceptable toxicity, or withdrew consent.

The evaluation of efficacy was performed locally according to the Response Evaluation Criteria in Solid Tumors system, using computed tomography scans and after each 12-week cycle.

Results

From May 2004 to October 2006, 54 patients were screened for EGFR-expressing tumors. In 25 samples, EGFR was undetectable. Characteristics of the other 34 patients at study entry are expressed in Table 1.

The median number of cycles administered was 12 (range, 1-70 cycles). Two patients were unevaluable: 1 because of discontinued treatment as a result of worse Karnofsky PS and 1 because of withdrawn consent.

In our study, the responses to cetuximab treatment included complete response (CR) in 1 patient (3%), partial response (PR) in 11 patients (34%), stable disease (SD) in 6 patients (19%), and progressive disease (PD) in 14 patients (44%). The median response was 8 months (range, 3-17 months). The relationship between objective response and skin toxicity is shown in Table 2.

In another study, Roé et al observed PR in 23% of patients, SD in 47%, and PD in 29%.[27] Ninety percent of patients with grade 2/3 skin toxicities had a partial remission or SD, whereas 66% of patients with grade 0/1 skin toxicities had PD.

Patients were evaluated for skin toxicity weekly during the first month and every 2 weeks thereafter. Twenty of the 32 patients (62%) developed a rash characterized by a pustular papular erythematous eruption usually distributed in the seborrhoeic areas (Figure 1). The rash was predominantly situated on the face: nose, cheeks, nasolabial folds, chin, and forehead (Figure 2). Other locations included shoulders, trunks, and the V-shaped area of the upper chest and/or back (Figures 3 and 4).

Table 1 Patient Characteristics (N = 34)

Characteristic	Number of Patients (%)
Median Age, Years (Range)	62.5 (34-75)
Sex	
Male	21 (61.7)
Female	13 (38.3)
Median Karnofsky Performance Status, % (Range)	90 (70-100)
Disease Stage at Diagnosis	
Dukes B	5 (15)
Dukes C	13 (38)
Dukes D	16 (47)
Previous Radical Surgery at Diagnosis	20 (60)
Previous Adjuvant Therapy	19 (56)
Metastatic Sites	
Lung	19 (56)
Liver	22 (64)
Lymph node	7 (21)
Local recurrence	3 (9)
Bone	3 (9)
Peritoneum	2 (6)
Number of Metastatic Sites	
1	24 (70.5)
≥ 2	10 (29.5)
Number of Previous Cancer Treatments (%)	
2	5 (15)
3	22 (64)
4	7 (21)

Table 2 Response in Relation to Incidence and Severity of Skin Toxicity

Response	Severity of Skin Toxicity				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
CR	0	0	0	1	0
PR	1	2	6	2	0
SD	1	1	4	0	0
PD	4	6	3	1	0

Five patients (16%) developed a rash on the scalp, arms and/or legs, abdomen, and buttocks but did not develop the rash on the palms, soles, or mucosa. In some cases, we observed diffuse erythema with follicular papules and pustules and diffuse telangectasia in the facial area co-localized to the follicular rash and resembling rosacea. There were no reports of scarring, but we noticed a degree of hyperpigmentation in some patients. The erythematous follicular papules often evolved into pustules forming yellow crusts. The eruption was not associated with comedones or cysts and was not related to abnormal microbial infection.

Figure 1 Pustular Papular Erythematous Eruption on the Upper Body



Figure 2 Rash Predominantly Situated on the Face*



*Specifically the nose, cheeks, nasolabial folds, chin, and forehead.

Bacterial cultures were performed when there was possible infection. No secondary infection appeared concomitantly in our patients. In previous studies, *Staphylococcus aureus* colonization and herpes simplex type I had occasionally

Figure 3 Trunk Rash



Figure 4 Upper Chest Rash



Figure 5 Fissures in Hand



Figure 6 Paronychia



been cultured from some persistent lesions. The onset of the eruption was usually within 1-3 weeks of starting therapy. In exceptional cases, it can occur at a much later point.

The severity of skin reactions was graded as follows: grade 1: asymptomatic, macular, or papular erythematous eruption in an acneiform distribution; grade 2: like grade 1, with symptoms such as pruritus; grade 3: extention of the eruption and development of confluent lesions, painful lesions, and minor ulceration; and grade 4: exfoliative or ulcerating dermatitis. Of the 34 patients evaluable for cutaneous toxicity, 10 patients (29%) had a grade 1 eruption, 13 (38%) a grade 2 eruption, 4 (12%) a grade 3 eruption, and 7 (21%) did not have an eruption. Patients with grade 3 skin toxicity (12%) delayed therapy for 7 days, and then chemotherapy was restarted when skin toxicity returned to grade 2.

Allergic reactions were seen in 2 patients (6%). These included grade 2 flushing and urticaria. In these 2 cases, infusion time was doubled (no systemic corticosteroid was used as premedication).

There is no specific treatment for the rash caused by EGFR agents. In the literature, treatment for anti-EGFR adverse reactions includes the following: drying agents, topical antiseptics, topical antibiotics, systemic antibiotics, topical retinoids, and topical or systemic steroids. Treatment also included the use of mild skin cleansers and topical antibiotics such as erythomycin or clindamycin.

Erythromycin 4% gel was used once daily for inflammatory pustules localized in large body areas including shoulders, upper chest, and back. If the gel was too irritating, erythromycin was exchanged for phosphate clindamycin oil in cream twice a day. These treatments were also used for the face (phosphate clindamycin 1.2 g and oil 100 g in cream).

Topical antibiotic therapy was performed until resolution of skin toxicity. We used greasier vehicles on the limbs because folliculitis was less frequent in these areas, and xerosis was much more common. Seven patients required the oral antibiotic doxycycline 100 mg daily for 2 months. Antihistamines such as cetirizine provided relief for patients with grade 2/3 pruritus.

The second most frequent toxicity symptom was xerosis, which was observed in 16 patients (50%). After 6-8 weeks of treatment, our patients developed xerosis with scaly, dry, itchy skin prevailing on the arms, legs, and areas previously affected by the acneiform eruption.

We used topical antibiotic ointments. Soap substitutes, bath oil, and treatment with moisturizing emollient provided good control of the symptoms. We chose an ointment-based preparation in order to avoid exacerbation of dry skin conditions.

Eczema and secondary complications occurred rarely in areas less resistant to infection. The development of eczema can be treated with topical low-dose corticosteroids in conjunction with antibiotics to avoid superinfections. Painful fissures in hands (Figure 5) and feet, and paronychia (Figure 6) were observed in 14 patients (44%) after 2-4 months of treatment. Paronychia was observed by the swelling of the lateral nailfold, generally on the thumb or big toe.

Our treatment was topical antibiotics. Hydrocolloid dressing was used to promote healing, reduce pain, and prevent infections. No patients developed pyogenic granuloma.

We observed altered hair growth in 9 patients (28%), particularly by overgrowth of eyelashes and slower growth of scalp hair. Five patients (16%) reported mild to moderate mucositis and stomatitis without aphthous ulcers of the oral mucosa or the nasal vestibule. They were treated with oral mystatin. Five patients (16%) were treated with dexamethasone/tobramycin for itchy eyes (Table 3).

Table 3 Management of Skin Toxicity

Side Effects	Grade 1	Topical approach: Antibiotic preparations (Clindamycin, Erythromycin)
	Grade 2	Grade 1 treatment plus systemic: Antihistamines to relieve itching; antibiotics (Doxycycline) to prevent and treat secondary infections
	Grade 3	Grade 2 treatment plus delaying therapy
Dry Skin	Emollient device (soap substitutes, bath oils) Oil-in-water creams/ointments	
Fissures/ Paronychia	Hydrocolloid dressings Topical antibiotics	
Eczema	Topical low-dose corticosteroids Antibiotics to avoid superinfections	
Itchy Eyes	Eyedrops with Dexamethasone and Tobramycin	

Discussion

Since Busam et al[28] first described cutaneous toxicity secondary to EGFR, several reports have been published.[24,29] Cutaneous reactions included follicular rash, xerosis, painful fissures in palms and soles, alterations in hair growth, and mucositis. In the majority of patients (80%-90%), the worst skin effects were mild (grade 1) to moderate (grade 2). In severe cases, grade 3 incidence was approximately 15%. The topical treatments initiated for grade 1 eruptions are also effective for grade 2 eruptions with additional oral antihistamine (hydroxyzine).[30] In grade 3 eruptions, EGFR inhibitors should be temporarily delayed. Patients should continue with topical applications. Systemic antibiotics such as tetracyclines can be considered.[31]

The tips of digits on the hands and feet became dry and scaly. This was accompanied by painful fissures, which can also occur in the nail folds and across the knuckles. Nail changes such as paronychia (10%) were seen in patients who had received EGFR inhibitors for > 2 months. It was seen predominantly on the thumb and big toe and could be associated with granuloma-like lesions. The nails tended to break and crack. Common changes in mucosa included vaginal dryness and oral or nasal ulceration. Changes in hair included slower growth, loss of scalp hair, and hair becoming finer, wavy, and brittle. Eyelashes, however, became elongated, curlier, and rigid in nature. All dermatologic effects were reversible and generally without sequelae within 4 weeks after treatment discontinuation.

In our patients, the most common cutaneous toxicity was follicular eruption. This was present in 62% of patients. We found 80%-86% in other studies.[7,22] Xerosis was observed in 50% of patients, including painful fissures in hands and feet, and paronychia in 44% (similar to the 40% found by Busam et al[28]). Changes in hair growth were observed in 28%. We also observed mucositis in 16% of patients, but this related principally to chemotherapy. As reported in other studies, these adverse effects are dose related and reversible with the discontinuation of treatment.[32] We observed significant correlations between the degree of cutaneous toxicity and increased RR.

The majority of the cases in which we observed response to treatment (1 CR, 8 PRs, 4 SDs) developed grade 2/3 skin toxicity, whereas 60% of patients with grade 1 skin toxicity had PD. The therapeutic management of the cutaneous toxicity has not been well standardized yet.[24,27,32] Perez-Soler et al tried recently to unify criteria about the therapeutic options.[33]

Table 3 reports on the treatment models we used in our study, with satisfying results. Correct identification and treatment of EGFR cutaneous side effects helps to improve QOL.

Conclusion

The cutaneous adverse effects associated with anti-EGFR treatment probably reflect the significance of the EGFR signaling pathway in skin. In normal adult human skin, EGFR is strongly expressed in keratinocytes, in cells of the eccrine and sebaceous glands, in the outer root sheath of hair follicles, and in occasional endothelial cells.[34]

The etiology of skin eruption is unclear. The current theory is that EGFR inhibition results in abnormal epidermal differentiation that leads to follicular obstruction and subsequent inflammation. Although the eruption might appear acneiform clinically, comedones are not present, and the histopatologic features do not resemble acne vulgaris.

No clinical trials assessing the treatment of the papulopustular eruption have been performed, and there are no established guidelines in the dermatologic or oncologic literature for the treatment of these reactions, as far as we know.

As these agents become more prevalent, skin toxicity should be strictly related to clinical outcome, and increased awareness of the incidence, relevance, and treatment options for the dermatologic side effects is needed by dermatologists and oncologists.[35]

We propose a treatment strategy to help aggressively treat dermatologic side effects, thus allowing patients to continue receiving therapy without dose interruption or drug discontinuation.[36]

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