Case Study

Ms. B is a 42-year-old woman with metastatic colorectal cancer in her liver and lungs. Although she has received multiple cycles of chemotherapy, including combinations such as 5-fluorouracil, capecitabine, oxaliplatin, and irinotecan, a recent computed axial tomography scan showed that her disease was progressing. After testing for the presence of an epidermal growth factor receptor (EGFR) in her original tumor pathology, Ms. B began treatment with cetuximab and irinotecan chemotherapy weekly for four out of six weeks. A loading dose of cetuximab was given with irinotecan, which was well tolerated. When the patient came in for the second week’s treatment at the maintenance dose, she exhibited several scattered acne-like lesions that were a mild papulopustular type, similar to previous acne-like skin eruptions the patient had experienced on and off during her lifetime. The healthcare team ultimately decided to proceed with the second maintenance dose.

Five days after the second dose, the patient called the clinic complaining of a severe acne rash. When she arrived at the clinic, she wore a handkerchief over her face to cover her skin lesions. Once in the examination room, she removed the handkerchief to reveal a severe, acneiform rash with follicular papulopustular lesions covering her cheeks, nose, forehead, and scalp, which were very distressing for Ms. B (see Figure 1). Although the rash was not pruritic, the patient described it as uncomfortable, particularly because of the extensive scalp involvement. The rash had spread in a “V” pattern to her chest and back. Therapy was held, and the patient was sent for a dermatology consult for suggestions in management of the rash.

Discussion

Epidermal growth factor receptor therapy: Cellular processes depend on cell membrane receptors to control the intercellular signal transduction pathways. These pathways are responsible for cell proliferation, apoptosis, angiogenesis, adhesion, and motility (Baselga, 2002). The EGFR is one of the cell membrane receptors that control these activities, specifically growth and survival of tumor cells, and is expressed in many different types of solid tumors, including head and neck, colorectal, pancreatic, lung, prostate, and breast cancers (Baselga; Wood, 2002). Targeting the EGFR pathways has led to the development of new anticancer agents. Compared to conventional chemotherapy, targeted therapies with increased specificity are potentially more efficacious because they may lessen the toxicities that patients may experience (Baselga; Wood).

Cetuximab (Erbitux™, ImClone Systems Incorporated & Bristol-Myers Squibb Company, Princeton, New Jersey) is indicated for the treatment of EGFR-expressing metastatic colorectal carcinoma in patients refractory to or intolerant of irinotecan-based chemotherapy (ImClone Systems Incorporated & Bristol-Myers Squibb Company, 2004). Skin reactions are common in patients receiving cetuximab therapy: in fact, approximately 90% of patients receiving the monoclonal antibody will experience skin reactions of varying severity (ImClone Systems Incorporated & Bristol-Myers Squibb Company). Other side effects of therapy include the potential for severe infusion reactions and pulmonary toxicity. Once dermatologic toxicities

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occur, future doses of cetuximab may need to be modified and the rash may be treated according to recommendations.

**Physiology of epidermal growth factor receptor skin reactions:** Cetuximab specifically binds to the EGFR on tumor and healthy cells, thus inhibiting the binding of epidermal growth factor and other ligands (ImClone Systems Incorporated & Bristol-Myers Squibb Company, 2004). Because EGFR is expressed constitutively in many healthy epithelial tissues, particularly skin and hair follicles, dermatologic toxicity in varying degrees is quite common with administration of the drug.

**Dermatologic effects of cetuximab:** Most patients treated with cetuximab experience an associated acneiform follicular rash frequently to the face, scalp, chest, and upper back (Busam et al., 2001; Cohen, 2003; Monti, Mancini, Ferrari, Rahal, & Santoro, 2003). This rash may manifest one to three weeks after the start of therapy and stabilizes or resolves with repeated therapy. For the majority of patients, an acneiform rash is not dose limiting; therefore, patients can continue with scheduled treatments without delays (Busam et al.; Needle, 2002). The acneiform rash is the result of an inflammatory process rather than infectious process and has been described as a sterile pustular form of folliculitis (Busam et al.; Needle; Salz et al., 2004). A prior history of acne is not associated with severity of the rash, and once the drug is discontinued, the rash clears without scarring (Needle).

The acneiform rash may be a powerful indicator of a direct biologic effect of the antibody, and the presence and severity of the rash have been correlated to survival (Busam et al., 2001; Salz et al., 2004). Salz et al. significantly demonstrated that patients with any grade of rash have a superior survival compared to patients without a skin rash; the researchers also determined that patients with grade 3 rash had the longest survival. Additional dermatologic effects of cetuximab include the possible development of paronychia, a painful inflammation of the proximal and lateral nail folds of toes and fingers, with the thumbs and great toes more commonly affected (Busam et al.; Monti et al., 2003; Salz et al.). Unlike the skin rash, this condition does not abate with continued therapy, and for some individuals, the areas do not completely heal for several months after the discontinuation of cetuximab (Salz et al.).

A rare phenomenon related to cetuximab has been the development of trichomegaly, the increased growth of hair, primarily eyelashes and eyebrows. This condition is theorized to result from an EGFR blockade causing the overgrowth of the hair shaft (Dueland, Sauer, Lund-Johansen, Ostensen, & Tveit, 2003).

**Psychosocial consequences of dermatologic side effects:** The visible consequences of a cetuximab-related acneiform rash can be measured objectively, and although the therapy probably is working, the rash can be quite distressing for patients. Dermatologic problems can lead to anxiety and impact self-image and self-esteem, resulting in social isolation and depression (Barankin & DeKoven, 2002; Hanna, Sharma, & Klotz, 2003). Contrary to popular belief, adults are more distressed by the presence of acne than adolescents and report a greater effect on their lives compared to adolescents (Barankin & DeKoven).

**Treatment of Dermatologic Side Effects and Nursing Interventions**

Patients who develop a mild to moderate acneiform rash should continue with cetuximab without dose modification, but for patients who experience a severe acneiform rash, dose modifications are recommended (see Table 1). Although investigators have used topical and oral antibiotics with various success for the acneiform rash, the manufacturers of cetuximab make no specific treatment recommendations for the use of antibiotics other than to advise against the use of topical steroids because of the potential to cause infectious complications (ImClone Systems Incorporated & Bristol-Myers Squibb Company, 2004). The manufacturer does recommend that patients be instructed to limit sun exposure, which can aggravate skin reactions, by using sunscreen and wearing a hat.

Oral antibiotics used to treat acne include tetracycline, erythromycin, minocycline, doxycycline, trimethoprim-sulfamethoxazole, clindamycin, and cephalosporin. Depending on the severity of the acne, topical antibiotic gels and solutions can be used alone or in combination with oral antibiotics. In addition, retinoids and benzoyl peroxide may be treatment options (Berger, 2004).

For the pruritis and dryness experienced by some patients, over-the-counter antipruritic lotions and creams along with emollients can be used. If a patient develops paronychia, soaking and cushioning the affected area have been found to be therapeutic (Busam et al., 2001).

Oncology nurses play a pivotal role in educating patients about possible dermatologic side effects, advising appropriate interventions, and offering emotional support. Oncology nurses need to reassure patients that the rash may diminish with continued therapy and will resolve without scarring after cetuximab is discontinued. Patients should be assessed for signs of depression and self-imposed isolation as a result of an acneiform rash; these patients may benefit from a dermatologist referral.

**Case Study Follow-Up**

Ms. B was referred to a dermatologist and started on oral tetracycline 500 mg twice daily and topical steroids. Although topical steroids are not recommended by the manufacturer of cetuximab, they were used for the severe inflammation of the acneiform rash that Ms. B was experiencing. Unfortunately, she developed gastrointestinal upset and had to discontinue the therapy after taking antibiotics for one week. About three weeks after her rash was diagnosed, she returned to the clinic for assessment (see Figure 2). For the most part, the pustules were gone; however, a

| **Table 1. Erbitux™ Dose Modification Guidelines** |
|-----------------|-----------------|-----------------|
| SEVERE ACNEIFORM RASH | **ERBITUX** | **OUTCOME** | **ERBITUX DOSE MODIFICATIONS** |
| First occurrence | Delay infusion 1–2 weeks. | Improvement | Continue at 250 mg/m². Discontinue Erbitux. |
| Second occurrence | Delay infusion 1–2 weeks. | Improvement | Reduce dose to 200 mg/m². Discontinue Erbitux. |
| Third occurrence | Delay infusion 1–2 weeks. | Improvement | Reduce dose to 150 mg/m². Discontinue Erbitux. |
| Fourth occurrence | Discontinue Erbitux. | – | – |

macular, erythematous pattern remained. Ms. B continued to be distressed about her appearance and was unwilling to continue cetuximab at a reduced dose without assurance that she was responding. Therefore, at the patient’s request and before a response could be reasonably expected, a restaging diagnostic examination was performed. The restaging scans revealed progression of her disease, and Ms. B decided to discontinue therapy.

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**References**


