Cutaneous Eruption Related to Human Epidermal Growth Factor Receptor Inhibitors in Stage IV Colon Cancer

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Mrs. L, a 59-year-old Caucasian woman, presented to the oncology clinic for a follow-up visit after hospitalization for anemia and uncontrolled diarrhea. She initially presented to the emergency department with a complaint of shortness of breath and uncontrolled diarrhea. She had experienced cramp-like abdominal pain for the previous six months. Two days before her emergency room visit, Mrs. L developed a foul-smelling vaginal discharge. Upon examination, she was found to have a rectovaginal fistula and was admitted to the hospital for additional testing. Mrs. L was diagnosed with adenocarcinoma of the colon, based on findings from a colonoscopy and computed tomography scan of the abdomen and pelvis with infusion. She was scheduled for hysterectomy and tumor resection in two days.

Medical History and Surgical Report

Mrs. L is 5’8” tall and weighs 201 pounds; her body mass index is 30.6. She appears healthy. Vital signs and her physical examination are healthy except for the following. Her abdomen is distended, with hypoactive bowel sounds in all four abdominal quadrants. Her liver enzymes are elevated (alanine aminotransferase (ALT) = 60 units/L, aspartate aminotransferase (AST) = 80 units/L, alkaline phosphatase (AP) = 180 units/L (normal ranges: ALT = 6–40 units/L, AST = 10–35 units/L, AP = 33–130 units/L). In addition, her liver is enlarged and can be palpated three fingertips below the ribs.

Mrs. L is married with two children and works in an office setting. She does not routinely seek health care except for illness treatment. She has not had a prior colonoscopy and has not had a Pap smear in 20 years. She quit smoking 30 years ago and drinks socially. Her father died from lymphoma and her mother died of complications from Parkinson disease. She has private insurance and is satisfied with her insurance plan.

In July 2007, Mrs. L underwent a total abdominal hysterectomy with a bilateral salpingo-oophorectomy and sigmoid resection of the colon with a colostomy. The pathology report confirmed T4N2G3 adenocarcinoma of the colon (stage IV). She recovered after five weeks without complications. In August 2007, Mrs. L’s carcinoembryonic antigen (CEA) reading was 56 mcg/L. Five weeks after surgery, Mrs. L began a chemotherapy regimen of FOLFOX (folinic acid, fluorouracil, and oxaliplatin), bevacizumab, and cetuximab.

Chemotherapy Overview

Since the late 1990s, FOLFOX has been a standard of care for metastatic colon cancer (Goldberg et al., 2004; Saltz et al., 2007). Bevacizumab is a monoclonal antibody against epidermal growth factor receptor (VEGF), and cetuximab is a monoclonal antibody against epidermal growth factor receptor (EGFR). Cetuximab is approved as a single agent for the treatment of metastatic colon cancer that expresses wild-type K-ras (Hurwitz et al., 2005). A chemotherapy regimen of FOLFOX and bevacizumab every two weeks has been used; FOLFOX and bevacizumab have been combined with cetuximab in multiple clinical trials (see Table 1).

In August, 2007, Mrs. L was enrolled in a clinical trial of FOLFOX, bevacizumab, and cetuximab (for National Comprehensive Cancer Network guidelines, visit www.nccn.org/professionals/physicians_gls/pdf/colon.pdf; for clinical trial enrollment information, visit www.nccn.org/clinical_trials/patients.asp). On day 1, the first chemotherapy treatment was administered (390 mg/m² IV push and 4,680 mg continuous 5-fluorouracil, 388 mg/m² folinic acid, 83 mg/m² oxaliplatin, 447 mg bevacizumab, and 242 mg/m² cetuximab). On day 14, cetuximab was held for a grade 3 rash. Numerous small pustules and erythematous papules in the hair follicles developed during the first two weeks of treatment. The skin lesions were acneform and were located on the
Table 1. Clinical Trials Using Cetuximab in Combination With Folinic Acid, Fluorouracil, Oxaliplatin, and Bevacizumab

<table>
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<tr>
<th>STUDY</th>
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<tbody>
<tr>
<td>CA225-004 ST</td>
<td>“Phase I study of Erbitux® (cetuximab) in patients with advanced cancer: A detailed characterization of serum pharmacokinetics, safety, and immunogenicity following single doses and repeated weekly administration.”</td>
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<tr>
<td>CA225-005 ST</td>
<td>“Phase I study of Erbitux® (cetuximab) in patients with advanced cancer: Single dose effects on epidermal growth factor receptor (EGFR) in normal skin and tumor tissue followed by repeated weekly dosing and safety assessments.”</td>
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<td>CA225-045 ST</td>
<td>“An exploratory pharmacogenomic study of cetuximab monotherapy in patients with metastatic EGFR-positive colorectal carcinoma.”</td>
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<tr>
<td>CA225-259 ST</td>
<td>“A multicenter, open label, nonrandomized, phase II study to assess the activity and safety of cetuximab plus irinotecan in subjects with EGFR-detectable metastatic colorectal carcinoma.”</td>
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Note. Based on information from National Cancer Institute, 2009.

Acneform rashes associated with EGFRs can be dose limiting, and dose modification is recommended for a grade 3 or 4 rash (Genoglan & Ceylan, 2007). For Mrs. L, ciprofloxacin for 10 days had no effect on the rash or symptoms. The eruption and the associated symptoms of burning and itching also were unresponsive to RegeniCARE® (Univera). RegeniCARE is a topical ointment used for burns that is undergoing clinical trials for use with EGFR agents that produce an acneform rash. A trial of doxycycline was not effective. Cetuximab was reinstated on day 35 at a reduced dose. Filgrastim (400 mcg per day) was administered for four days starting on day 38. The rash persisted and did not improve after a second 10-day course of doxycycline, which began on day 58.

On day 70, Mrs. L’s CEA was 6 mcg/L. Topical treatment with a compounded emollient product was started per suggestion by the advanced practice nurse after she researched different supportive products for acneform rash treatment. The emollient was applied twice daily; one week later, Mrs. L reported a decrease in symptoms of itching and redness. The rash remained at grade 2 but the symptoms were tolerable, and Mrs. L was able to continue her cetuximab treatment at a reduced dose on schedule. Mrs. L’s CEA was 3.4 mcg/L on day 126, and computed tomography scan showed a partial response. A positron emission tomography scan on day 189 (six months into treatment after six cycles) was normal and showed a complete response. A computed tomography scan on day 203 showed a complete response; 18 days later, Mrs. L’s CEA was 2 mcg/L. Mrs. L received oral magnesium chloride for neuropathy on day 245; her CEA was 1.9 mcg/L on day 301. Oxaliplatin was decreased 25% to 99 mg on day 314 because of neuropathy and was held on day 356 for grade 3 neuropathy, then discontinued. Mrs. L’s CEA scan still was normal on day 332, and her CEA was 1.8 on day 413.

Mrs. L maintained a complete response for 20 months with her chemotherapy regimen and had a good quality of life. After 20 months, she developed a new liver lesion and had a radiofrequency ablation; she currently is being treated with FOLFURI (folinic acid, fluorouracil, and irinotecan).

Discussion

A chemotherapy regimen for advanced colon cancer is FOLFOX, bevacizumab, and cetuximab. The regimen was effective for Mrs. L in treating her stage IV colon cancer, as noted by a complete response with her computed tomography–positron emission tomography scan and CEA level. Cetuximab targets EGFR, a widely expressed cell-surface molecule receptor that is implicated in the development and progression of cancer through effects on the cell cycle, apoptosis, angiogenesis, and metastasis (Genoglan & Ceylan, 2007). EGFR is expressed by human skin basal-epidermal keratinocytes, by outer-root sheath cells, by sebocytes, and in hair follicles. The EGFR ligand system has an essential role in the regulation of the hair cycle as activation of the EGFR stimulates transition from anagen to catagen. To produce new hairs, existing follicles undergo cycles of growth (anagen) and regression (catagen). During each anagen phase, follicles produce an entire hair shaft from tip to root. During catagen, follicles reset and prepare their stem cells so they can receive the signal to start the next growth phase and make the new hair shaft (Alfonso & Fuchs, 2006). The cutaneous adverse effects of cetuximab result from interference with EGFR signaling in the skin, causing the potential side effect of an acneform rash (Genoglan & Ceylan).

When treating acneform rash, use a thick, alcohol-free emollient cream and sunscreen of sun protection factor 15 or higher. For a mild rash, use topical hydrocortisone 1% or 2.5% and clindamycin. For a moderate rash, use hydrocortisone 1% gel or 2.5% cream, clindamycin 1% gel, or pimecrolimus 1% plus doxycycline 100 mg twice daily or minocycline 100 mg daily. For a severe rash, use hydrocortisone 2.5% cream, clindamycin 1% gel, or pimecrolimus 1% cream plus doxycycline 100 mg twice daily or minocycline 100 mg twice daily plus a methylprednisolone dose pack (Eaby, Culkin, & Lacouture, 2008).

Conclusion

Cutaneous side effects occurred with Mrs. L and were treated in several ways. Although evidence-based treatments for the side effects do not yet exist, a grading system for skin toxicities can be used in therapeutic decision making and as a framework for building a stepwise approach to intervention (Eaby et al., 2008). Controlled studies are needed to provide evidence-based treatments for the distressing cutaneous effects. Through the supportive care that enabled her to receive and tolerate her treatment plan, Mrs. L was able to benefit with a complete remission.

The authors take full responsibility for the content of the article. The authors did not receive honoraria for this work. No financial relationships relevant to the content of this article have been disclosed by the authors or editorial staff.
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References


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