Treatment of Recurrent Squamous Cell Carcinoma of the Skin With Cetuximab

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Background: Squamous cell carcinoma of the skin (SCCS) is rarely encountered by medical oncologists owing to success of local therapies. When advanced SCCS requires systemic palliation, treatment with conventional chemotherapy, such as cisplatin, is often precluded by a patient’s age or medical comorbidities. Cetuximab is a human and mouse chimeric antibody against epidermal growth factor receptor, a tyrosine kinase receptor richly expressed by SCCS cells, including lymph node metastases. This drug, approved for treatment of squamous cell carcinoma of the upper aerodigestive tract as well as colorectal cancer, is well tolerated. Toxic effects include acneiform rash and diarrhea. Preclinical data suggest that epidermal growth factor receptor is important in SCCS carcinogenesis.

Observations: Herein, we report 2 cases of elderly patients with extensive, in-transit recurrence of SCCS who have been treated with palliative cetuximab. The drug was well tolerated, with the exception of acneiform rash requiring dose reduction in 1 patient. Both patients had excellent responses to cetuximab: the first patient had complete response by week 16 of treatment and the second a near-complete response by week 12. In both cases, initial response to cetuximab was evident by week 4 of therapy.

Conclusions: To our knowledge, these are the first reported cases of cetuximab use in patients with SCCS. The encouraging responses justify the prospective study of cetuximab in SCCS.

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Nonmelanoma skin cancer is the most common malignant neoplasm diagnosed in white individuals in the United States. The American Cancer Society estimates that over 1 million new cases occur annually. Most patients receive successful local therapy. Death from the disease is very rare, with a case-fatality rate of 0.25% (approximately 2000 cases per year). Squamous cell carcinoma (SCC) of the skin (SCCS) represents approximately 15% of all nonmelanoma skin cancers.

Patients with advanced SCCS include those with extensive local recurrence of SCCS after surgical resection and radiotherapy or with metastatic disease. Such patients have few therapeutic options. Progressive disease leads to substantial morbidity and, ultimately, mortality. Clinical trials are difficult to conduct because of the small number of patients. Consequently, systemic treatment for advanced SCCS is based on small, single-arm trials or case series. Cisplatin-based, combination chemotherapy is the most commonly used treatment. Response rates can be high; however, the toxic effects of cisplatin are often prohibitive and include nausea, vomiting, nephrotoxic effects, and hearing loss. Given that SCCS is a disease of elderly individuals, the administration of cisplatin is frequently precluded by a patient’s age or medical comorbidities. Furthermore, most patients treated with chemotherapy for locally recurrent SCCS have received radiotherapy. Among analogous patients with SCC of the upper aerodigestive tract, prior treatment with radiotherapy predicts poor local response to conventional chemotherapy, such as cisplatin.

Cetuximab is a recombinant human and mouse chimeric antibody that competitively inhibits epidermal growth factor receptor (EGFR). This drug is active in the treatment of SCC of the upper aerodigestive tract, which richly expresses EGFR, even in cisplatin- or radiation-refractory disease. Cetuximab is well tolerated, particularly compared with conventional chemotherapy, and its common toxic effects include hypersensitivity reactions, acneiform rash, and diarrhea. We describe 2 elderly patients with extensive, in-transit recurrence of SCCS following surgery and radiation who have been treated with first-line cetuximab.

REPORT OF CASES

CASE 1

Patient 1, a white man, presented at age 73 years with a rapidly growing, erythema-
atous, left scalp nodule. In October 2004, findings from a shave biopsy documented SCCS. The patient underwent complete excision by Mohs microsurgery in December 2004. In September 2005, he had recurrence of SCCS adjacent to the original resection scar. Mohs microsurgery was repeated, with histologic findings demonstrating SCCS within the dermis, without connection to the overlying epidermis. Although local recurrence was favored, in-transit metastasis could not be excluded. The patient was treated with adjuvant, intensity-modulated radiation therapy, completing 60 Gy to the temporal scalp in December 2005. In February 2006, he developed in-field recurrence. He underwent a third Mohs procedure in March 2006, and the histologic findings described poorly differentiated SCCS with satellitosis and perineural invasion. Two additional nodules within a 2-cm radius were biopsied, and the findings from both showed SCCS with positive margins. Computed tomography of the neck showed only postoperative changes, with no cervical adenopathy. A fourth Mohs procedure was performed 3 weeks later to encompass the 2 biopsied lesions, and clear margins were obtained. Within 2 weeks, the patient developed multiple subcutaneous nodules in a circumferential area around the wound, both within and outside the radiation field. Findings from 2 preauricular biopsy samples were positive for SCCS. At a multidisciplinary review, salvage surgery was not recommended owing to multiple, rapidly progressive in-transit metastases. The patient was referred to the medical oncology department for palliative therapy.

At medical oncology intake, the patient was noted to have multiple nodules across the left parietal scalp and preauricular area. His recent Mohs excisions were healing by secondary intent. He also had matted left submandibular lymphadenopathy measuring 2.5 × 1.5 cm (Figure 1A). Treatment with cetuximab was initiated on May 19, 2006. Within 1 week, the patient developed a characteristic acneiform rash on his face, posterior neck, upper back, and anterior chest. Despite treatment with topical emollients, a 3-day pulse of prednisone at 60 mg daily, and minocycline hydrochloride, a grade 3 rash evolved after 3 doses of cetuximab (Figure 2). A 2-week treatment break was required (Figure 2). Nonetheless, at week 4 the patient had marked flattening of skin nodules and decrease in size of palpable adenopathy (Figure 1B). Over the next 3 months, the patient had complete resolution of skin nodules and adenopathy (Figure 1C). Owing to flares of the grade 3 rash, 2 dose reductions have been required to date, and he has experienced no other toxic effects attributable to cetuximab. The patient’s response is currently maintained with weekly treatments of cetuximab, 150 mg/m².

CASE 2

Patient 2, a white woman, was diagnosed at age 71 years with moderately to poorly differentiated SCCS of the nasal tip and columnella. Owing to multiple medical comorbidities that precluded a major cosmetic reconstruction, the patient was treated with primary radiation. Treatment with 59.6 Gy of electron radiation was completed in November 2005. Two months later, the patient had a recurrence on her columnella, which was treated with Mohs microsurgery in February 2006. Six weeks later, the patient developed a nodule on her right upper lip that proved to be an in-transit metastasis. A concurrent papule on the left nasal sill was also in-transit SCCS. A second Mohs microsurgery was performed, and the lesion healed by secondary intent. A computed tomographic scan of the neck was negative for pathologic adenopathy. In May 2006, a new nodule appeared at the Mohs surgical site. Findings from a biopsy confirmed recurrent SCCS. At a multidisciplinary review, salvage surgery was not recommended owing to the patient’s medical comorbidities, which included severe chronic obstructive pulmonary disease, coronary artery disease, and congestive heart failure. She was referred to the medical oncology department for palliative therapy.
At medical oncology intake, the patient was noted to be wheelchair dependent, with an Eastern Cooperative Oncology Group performance status of 2. She had a complex nasal defect. Inferior to the nasal flap were 4 confluent subcutaneous nodules, with a punch biopsy site at the center. A 4-mm nodule was present within her right upper lip incision (Figure 3A). Treatment with cetuximab was begun on May 30, 2006. After 2 weeks, the patient developed grade 1 acneiform rash on her chin, which thereafter improved. During the first 12 weeks of therapy, the patient experienced near-complete resolution of her lesions. The nasal sill nodules resolved, exposing a portion of her prior Mohs surgical bed, and the nodule within her lip incision shrank from 4 to 2 mm (Figure 3B). Aside from a mild rash, the patient has experienced no notable toxic effects from cetuximab. The patient’s response is currently maintained with weekly treatment with cetuximab, 250 mg/m², 5 months after initiation.

**COMMENT**

The advent of molecularly targeted therapies has dramatically changed treatment approaches in oncology. This paradigm shift was pioneered by imatinib mesylate, which targets the \( bcr-abl \) oncogene in chronic myelogenous leukemia, and trastuzumab, which targets the erb2/HER2 receptor in breast cancer. Numerous other drugs have been designed to target growth and survival pathways important in carcinogenesis. One such pathway is initiated by EGFR, a tyrosine kinase receptor. Phosphorylation of EGFR results in a cascade of proliferative and antiapoptotic signaling, through mitogen-activated protein kinase, phosphotidylinositol-3 kinase, and signal transducer and activator of transcription.⁶ Epidermal growth factor receptor is overexpressed in a number of malignant neoplasms. Agents targeting this pathway have been approved in the treatment of nonsmall cell lung cancer (erlotinib hydrochloride, gefitinib), SCC of the upper aerodigestive tract (cetuximab), colon cancer (cetuximab, panitumumab), and pancreatic cancer (erlotinib). Anti-EGFR antibodies (cetuximab, panitumumab) block the extracellular domain of the receptor, inhibiting ligand binding. The small molecule inhibitors (erlotinib, gefitinib) block the intracellular tyrosine kinase inhibiting phosphorylation and activation of downstream signaling cascades.

Epidermal growth factor receptor is an attractive potential target in SCCS. When studied by immunohistochemical analysis, EGFR expression is noted in normal keratinocytes; it is expressed at increasingly higher levels in SCCS and in lymph node metastases from SCCS.⁷⁻¹¹ In keratinocyte cultures, epidermal growth factor stimulates proliferation and suppresses markers of terminal differentiation. This is blocked by the EGFR tyrosine kinase inhibitor PD 153035.¹² With EGFR blockade, keratinocytes are more susceptible to induction of apoptosis by UV-B radiation or matrix detachment.¹³ In vitro and mouse models indicate that EGFR activation within malignant epithelial cells induces signal transducer and activator of transcription 3 activation, which drives carcinogenesis, and that EGFR blockade abrogates this response.¹⁴ Other preclinical research suggests that EGFR blockade may inhibit telomerase activity in SCCS and thus suppress tumor growth.¹⁵

Owing to the relative rarity of advanced SCCS, there are no prospective clinical trials of novel targeted therapies in the published literature. Glisson et al.¹⁶ recently reported in abstract form a phase II trial of the oral agent gefitinib in patients with metastatic or recurrent SCCS (http://clinicaltrials.gov/show/NCT00054691). A total of 20 patients were evaluable for response at the time of their report, of a planned enrollment of 40. Glisson et al.¹⁶ observed a 15% partial response rate and a 45% stable disease rate.

Three other prospective trials of anti-EGFR therapy in advanced SCCS are ongoing. Gefitinib is being evaluated in the neoadjuvant treatment of patients whose disease is amenable to local therapy with surgery or radiation (http://clinicaltrials.gov/show/NCT00126555). A second trial examines erlotinib with postoperative radiotherapy in high-risk patients (http://clinicaltrials.gov/show/NCT00369512). The third study examines cetuximab in patients whose tumors express a high level of EGFR (http://clinicaltrials.gov/show/NCT00240682).
In conclusion, we have described 2 elderly patients with advanced SCCS who were treated with first-line cetuximab. The drug was well tolerated, with the exception of acneiform rash requiring dose reduction in 1 patient. Response to cetuximab was evident in both cases by week 4 of therapy. By week 16, 1 patient had a complete response, and the other a near-complete response. Although follow-up is limited, both responses were sustained after 5 months of maintenance therapy. To our knowledge, these are the first published cases of cetuximab use in SCCS, as well as the first documented responses. Clearly, these encouraging results justify further study of cetuximab in SCCS.

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REFERENCES