CASE STUDY

A 65-YEAR-OLD AFRICAN AMERICAN MAN WITH ODYNOPHAGIA AND SWELLING ON THE LEFT SIDE OF THE NECK

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BACKGROUND

JW, a 65-year-old African American man, visited his physician to complain about odynophagia and swelling on the left side of the neck, both of 4-months’ duration. The swelling had increased in size and intensity during the previous week, and the patient reported that he was beginning to feel as if he was having trouble swallowing food. JW denied weight loss, fever, respiratory difficulty, nausea, and vomiting. He had a 37-pack-per-year history of smoking and admitted to using moderate amounts of alcohol (ie, consuming 4–5 glasses of wine/week). His medical history included mild hypertension but no personal or family history of cancer. Physical examination revealed 2 firm, nontender, moderately fixed masses in the lymph nodes measuring 2 cm × 2 cm and 4 cm × 4 cm. Both masses were between the hyoid bone (the U-shaped bone at the base of the tongue that supports the muscles of the tongue) and the cricoid cartilage (the cartilage found at the base of the lower larynx). In addition, the vocal cords were fixed, which indicated deep involvement of the tumor.

Computed tomographic (CT) scanning showed a flat tumor that was 3 cm in diameter. The tumor originated in the posterior hypopharyngeal wall (directly behind the larynx in the middle of the hypopharynx), involved the vocal cords, and encased the carotid artery. Direct laryngoscopy confirmed the examination and CT findings. A tumor biopsy was done, and analysis of the biopsy specimen showed a moderately differentiated squamous cell carcinoma. This finding was to be expected because squamous cell carcinoma accounts for 95% of all head and neck cancers (HNCA). Esophagoscopy results were negative. The tumor was diagnosed and staged as T2N2M0 or stage IVA cancer of the hypopharynx according to American Joint Committee of Cancer (AJCC) staging criteria. JW received an Eastern Cooperative Oncology Group performance status rating of 1. Based on National Comprehensive Cancer Network (NCCN) guidelines, it was recommended that the patient receive combined cisplatin chemotherapy and radiation therapy.1

DISCUSSION

Head and neck cancer is a devastating disease associated with severe morbidity as a result of the disfiguring facial effects of the tumor. Our patient had several risk factors that are associated with the development of HNCA. These included age greater than 50 years, African American ethnicity, male sex, and history of smoking and alcohol use. The patient’s use of tobacco and alcohol put him at a substantially higher risk for developing a second primary cancer of the lung, esophagus, or other areas in the head and neck. Signs and symptoms that would have aided a healthcare professional in developing a differential diagnosis of HNCA based on this patient’s presentation included difficulty and pain associated with swallowing, vocal cord fixation, and a swollen mass on the left side of the neck. The vocal cord fixation and the swollen mass indicate advanced disease.

The NCCN guidelines recommend CT studies, laryngoscopy, esophagoscopy, and a biopsy for a definitive diagnosis of HNCA, which our patient received.1 He was diagnosed with advanced (ie, stage IVA) squamous cell carcinoma of the hypopharynx. The hypopharynx extends from the superior border of the hyoid bone to the lower border of the cricoid cartilage. This muscular tube also extends from the oropharynx to the cervical esophagus. Because staging is thought to be the most definitive predictor of prognosis in HNCA, prompt staging is essential.

Sixty percent of patients with hypopharyngeal cancer have regional spread to the lymph nodes at diagnosis. A tumor staged as T2 is more than 2 cm but less than 4 cm in diameter and invades more than 1 site in the hypopharynx. (In contrast to other tumor types that utilize the AJCC staging criteria, for cancers of the larynx and hypopharynx, the T ranking also refers to the distance of spread outside the originating organ.) Stage N2 indicates the presence of more than 1 positive ipsilateral node less than 6 cm in diameter. Stage M0 disease indicates the absence of distant metastases. The presence of distant metastases upon diagnosis of HNCA is relatively uncommon. Instead, like our patient, most patients are diagnosed with lymph node involvement. Based on the presence of disease in the vocal cords and around the carotid artery, it was decid-
ed that this patient’s primary tumor was unresectable. For this reason, chemoradiation was recommended.

As the NCCN guidelines recommend, healthcare professionals should not lose sight of supportive care options that can positively affect outcomes in patients such as ours. Management should include nutritional support, smoking-cessation counseling, treatment of pain and other symptoms, future dental care to address radiation effects, and pharmacologic or nonpharmacologic therapy for xerostomia and mucositis.

Patients with stage IVA HNCA, such as JW, have a poor survival rate and a high recurrence rate. As a result, the healthcare team needs to think ahead to other treatment options that may be available for treating this patient’s relapses. Recently, the US Food and Drug Administration (FDA) has approved the epidermal growth factor receptor (EGFR) inhibitor, cetuximab, for use in patients with metastatic HNCA who have failed traditional chemotherapy. Additional published literature has suggested that gefitinib, another EGFR inhibitor, combined with cetuximab, and the cyclooxygenase-2 (COX-2) inhibitor, celecoxib, may have a role in treatment of relapsed, advanced HNCA. In addition, phase III trials are evaluating the use of the growth factor, palifermin, to reduce the incidence of mucositis in patients with HNCA.

**GEFITINIB PLUS CELECOXIB**

A study combining the EGFR inhibitor, gefitinib, with the COX-2 inhibitor, celecoxib, was recently completed at the Dana Farber Cancer Institute in patients with recurrent or metastatic HNCA. The rationale for this combination included findings that single-agent trials of EGFR inhibitors in HNCA had limited success and evidence that EGFR and COX-2 are overexpressed in patients with HNCA. The investigators hypothesized that dual, nonoverlapping mechanisms of action by targeted agents may be effective in HNCA. Moreover, gefitinib and celecoxib are administered orally, which is convenient for the patient and the healthcare staff.

This phase I clinical trial was completed in 19 patients with HNCA with inoperable disease or disease progression after at least 1 previous regimen of concurrent cisplatin or carboplatin-based chemotherapy plus radiation therapy or of induction 5-fluorouracil or taxane chemotherapy followed by radiotherapy. Patients received 1 of 3 different dose levels: gefitinib 250 mg once daily plus celecoxib 200 mg twice daily, gefitinib 250 mg once daily plus celecoxib 400 mg twice daily, or gefitinib 500 mg once daily plus celecoxib 400 mg twice daily. Cycles consisted of 28 days of continuous therapy, and patients were evaluated every 2 cycles for objective response (ie, every 8 weeks). Therapy continued until the disease progressed or other circumstances developed that warranted removal of a patient from the study. Considered as a group, patients received a median of 3 cycles of treatment.

Complete information was collected from 18 patients. Four of the 18 patients had a partial response (22%; 95% confidence interval, 2%–42%), and 6 of the 18 patients had stable disease (33%; 95% confidence interval, 11%–55%). Of the 4 patients with a partial response, 1 had received the lowest dose of gefitinib and celecoxib, 2 had received the intermediate dose, and 1 had received the highest dose. The median duration of response was 19 weeks (range: 16–66 weeks), and the median overall survival was 24 weeks (range: 11–70 weeks). All of the dosage levels given during the study were well tolerated by patients, and no dose-limiting toxicities were reached. The most common adverse effects were rash (in 63%), diarrhea (in 58%), heartburn (in 21%), and anemia (in 32%).

As a result of these findings, Wirth et al concluded that the partial responses obtained by using this combination therapy in 4 patients with incurable HNCA warranted additional study to determine whether gefitinib and celecoxib may have a role in treating HNCA. Therefore, a phase II study of gefitinib 500 mg daily plus celecoxib 400 mg twice daily was recommended.

**GEFITINIB PLUS CETUXIMAB**

Although the standard of care for metastatic cancer of the hypopharynx is generally cisplatin chemotherapy plus radiation, several phase II studies have supported further investigation of the EGFR-inhibitor cetuximab combined with platinum-based regimens in the treatment of metastatic HNCA. Moreover, although cetuximab and gefitinib inhibit EGFR, each does so through a different mechanism of action. Specifically, gefitinib is a tyrosine kinase inhibitor, and cetuximab is a monoclonal antibody directed against EGFR.

To explore the results of more complete EGFR blockade than that obtainable with a single EGFR inhibitor, a recent phase I trial examined the safety, pharmacokinetic, and pharmacodynamic effects of EGFR blockade obtained by combining gefitinib and cetuximab in 29 patients with advanced cancers that expressed EGFR. Sixteen patients in the study had colorectal carcinoma, 12 had HNCA, and 1 had non-small cell lung cancer (NSCLC). Patients were treated with weekly cetuximab and daily gefitinib in 1 of 5 dose-ranging schemes (eg, dosage level 1 consisted of cetuximab 320 mg/m² as a loading dose followed by cetuximab 200 mg/m² weekly in combination with gefitinib 100 mg daily). The median age of patients was 60 years (range: 38–80 years), and 66% of the patients were men. A complete response was obtained in 1 patient with HNCA, a partial response was obtained in 4 patients with colorectal cancer, and disease was stabilized in 3 patients (2 with HNCA and 1 with
NSCLC). Grade 3 toxicities occurred in 4 patients and included venous thrombosis, reversible deafness, and abdominal pain in 3 patients who received cetuximab and gefitinib and interstitial lung disease/dyspnea in 1 patient who had received only gefitinib. The combination of gefitinib and cetuximab was found to result in a level of inhibition of phosphorylated EGFR superior to that obtained by using single-agent therapy. No pharmacokinetic interactions between the 2 agents studied were found. As with gefitinib plus celecoxib, a phase II study of gefitinib plus cetuximab was recommended.

**Palifermin for Mucositis**

Because stage IVA HNCA is incurable, improving or maintaining quality of life while extending overall survival is a key goal of therapy for patients with advanced HNCA. Oral mucositis is the most significant and debilitating acute complication associated with radiotherapy and chemotherapy. In fact, severe mucositis may develop in as many as 77% of patients with HNCA.8

Palifermin, a laboratory-manufactured, modified version of a naturally occurring human protein called keratinocyte growth factor, is approved by the US FDA for treating severe inflammatory disease of the mucous membranes in patients with hematologic malignancies who are receiving myelotoxic therapy that requires hematopoietic stem cell support. In these patients, palifermin 60 µg/kg/day is typically given for 3 days before and 3 days after myelotoxic chemotherapy for a total of 6 doses. After administration, the drug undergoes targeted binding to the cell-surface receptors of the epithelial cells lining the mouth and gastrointestinal tract. There, it stimulates epithelial cell proliferation and differentiation and upregulates cytoprotective mechanisms. Palifermin is currently not approved for use in patients with non-hematologic malignancies. This is because palifermin’s potential to stimulate solid tumor growth has not been determined in large-scale clinical trials, which raises a theoretical safety concern. In addition, large-scale efficacy has not been established in patients with solid tumors.

Initial results of phase I and II studies in 145 patients have shown that palifermin appears to be safe in patients with HNCA.9-10 Therefore, the safety and efficacy of palifermin therapy in reducing the incidence of severe oral mucositis in patients with advanced HNCA who are receiving radiotherapy and chemotherapy is currently being evaluated in 2 phase III clinical trials. These results are expected by late 2006.11,12 Both trials have a randomized, double-blind, placebo-controlled, parallel-assignment study design and a primary outcome of incidence of severe oral mucositis. Secondary outcomes include safety, patient-reported outcomes, and HNCA mortality. One of the trials will also explore an alternate weekly palifermin administration schedule.

**REFERENCES**


