

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: James L. Abbruzzese, MD

New Treatments in Head and Neck Cancer

Merrill S. Kies, MD
Professor, Thoracic/Head and Neck Medical Oncology
University of Texas M. D. Anderson Cancer Center

H&O What outcomes and toxicities are associated with traditional treatments for head and neck cancer?

MK Squamous cell carcinoma of the head and neck (SCCHN) tends to be a local and regional disease, but our effective and very powerful local treatment approaches may lead to significant anatomic and functional deficits. Treatment at the time of diagnosis of patients with primary tumors of the oral cavity, oropharynx, and larynx has been hampered by significant toxicity, particularly with surgery and radiotherapy. We are able to control tumors and cure many patients, but long-term side effects associated with surgical resection are considerable, including loss of function related to anatomic changes. Side effects associated with radiotherapy include normal tissue fibrosis, scarring, and long-term xerostomia or difficulty swallowing.

For advanced disease, local treatments are curative only for a percentage of patients. A historical issue has been the need not only to reduce the long-term toxic effects of these treatment approaches, but also to increase efficacy so that a higher percentage of patients are cured.

Within the area of head and neck cancer, the prognosis and treatment depend to an extent on the site and stage of the tumor. For example, early-stage lip cancer is very effectively treated with surgical resection, while early stage larynx cancer is very often effectively treated with radiation therapy. In both instances, more than 90% of patients may be cured, with minimal residual treatment-related deficits. On the other hand, a patient who presents with a very large tumor in the larynx, for example, may require a laryngectomy followed by radiation, and could therefore experience the loss of normal voice and a persistent tracheostoma. In recent years, we have relied

more often on radiation therapy for squamous cancers at most head and neck sites, although not for those within the oral cavity. For those patients who present with larger tumors, T3 and T4 disease, chemotherapy given either in sequence or concomitantly with radiation therapy appears to add to the efficacy of treatment and reduce the risk of tumor recurrence, ultimately leading to an improvement in overall survival.

H&O Has chemotherapy been used more frequently in recent years?

MK There has been a sequence of trials over the last 10–15 years showing that the use of concomitant chemotherapy and radiation is superior to radiation therapy used as a single modality in treating patients with unresectable disease. Patients with stage 3 or 4 squamous cell carcinomas of the oropharynx, hypopharynx, and larynx, are often considered candidates for chemoradiation treatment strategies.

H&O What chemotherapeutic agents are currently used in the treatment of SCCHN?

MK Conventional cytotoxic chemotherapy, particularly platinum compounds and taxanes, certainly have activity in treating patients with recurrent SCCHN. Conventional chemotherapeutic programs consist of cisplatin with infusional 5-fluorouracil (5-FU) or, more recently, taxane-and-platinum combinations, which may include paclitaxel and carboplatin, or in some instances docetaxel with cisplatin. These are all active multidrug regimens that will induce tumor regression in about 40% of patients with recurrent SCCHN. Unfortunately, the majority of these tumor remissions are relatively short-lived, with median duration of approximately 3 months. Overall median survival for patients with recurrent SCCHN treated with conventional chemotherapy is in the range of 6–9 months, with very few long-term survivors.

H&O What impact has the development of cetuximab had on the treatment of this disease?

MK The development of cetuximab (Erbix, Bristol-Myers Squibb) certainly is exciting. It is the first targeted agent for which there is compelling data demonstrating

a therapeutic benefit in head and neck cancer. This chimeric human murine monoclonal antibody has demonstrated activity in SCCHN, and phase I and II trials have demonstrated that a percentage of patients with recurrent and refractory disease will obtain a tumor response after treatment with cisplatin and cetuximab.

Trigo and colleagues have shown that approximately 15% of patients with recurrent squamous cell carcinoma resistant to conventional chemotherapy will respond to cetuximab as a single agent. In another recent study, Bonner and colleagues have treated patients with intermediate and locally advanced squamous cancer of the oropharynx, hypopharynx, or larynx in a phase III trial that randomized patients to radiation therapy with or without concomitant cetuximab. This study demonstrated both local control and an overall survival benefit for the patients on the combination arm.

These data were presented at the 2004 annual meeting of the American Society of Clinical Oncology (ASCO), and represent the first phase III demonstration of improved treatment efficacy in head and neck cancer with any targeted compound. More data from this trial are awaited.

H&O Will this study prompt further research on targeted agents in SCCHN?

MK Among Dr. Bonner's notable findings was that radiation-related "in-field" toxicity did not appear to be exacerbated by the addition of cetuximab. This observation is important because not only was there improved overall survival and an observation of improved tumor control in the primary site in the neck, but there also appeared not to be an increase in treatment-related toxicity. This is only one study, but it should prompt further study of the efficacy of targeted compounds.

H&O What other targeted compounds might be useful?

MK A number of other targeted compounds are being investigated in the treatment of head and neck cancer, and of these the oral tyrosine kinase inhibitors, including gefitinib (Iressa, AstraZeneca), have had the most active clinical use. A paper published by Cohen et al described moderate activity for gefitinib in patients with recurrent SCCHN. With 500 mg of gefitinib daily, approximate overall response rates were in the range of 10–15%.

Gefitinib and erlotinib (Tarceva, OSI/Genentech) are also being investigated for use with cytotoxic chemotherapy in the setting of recurrent disease, and with radiation therapy with or without chemotherapy in the setting of previously untreated, locally advanced disease.

H&O What other agents in development seem promising for head and neck cancer?

MK There are a number of new or targeted therapies, including EGFR inhibitors, farnesyltransferase inhibitors, and antiangiogenesis compounds under investigation that are showing promise in the laboratory. On a practical level, closest to the clinic will be some form of combination therapy with EGFR inhibitors and bevacizumab (Avastin, Genentech). There is ongoing work being done with erlotinib and bevacizumab both in head and neck cancer and in lung cancer; with respect to the latter group of patients, Roy Herbst from this institution and others are conducting phase I studies of erlotinib and bevacizumab for patients with advanced non-small-cell lung carcinoma, and they are observing response rates in the range of 20% in patients who have been heavily previously treated with chemotherapy. Cohen et al at the University of Chicago are investigating a similar regimen in patients with recurrent SCCHN, and those data may be available at this year's ASCO meeting.

Until now, most of the targeted agents have been studied in concert with chemotherapy or radiation. Now there is great interest in looking at combinations of targeted agents by themselves. However, there is potential for considerable toxicity; certainly with any of the antiangiogenesis drugs there is concern about the potential for hemorrhagic complications.

H&O In addition to decreasing toxicity, what are the major goals of current research?

MK We have a great need for more effective treatments overall. The majority of patients with head and neck cancer present with stage 3 or 4 disease, and of those patients only a minority are actually cured. Therefore, we need to develop increasingly active systemic strategies with newer targeted compounds, possibly administered in concert with chemotherapy. We hope that it will be possible to reduce the intensity of local treatment so that fewer patients would require surgery without sacrificing treatment efficacy. In order to accurately select patients for therapy, we need to develop some sort of laboratory predictor or signature that will be a signal to us which strategy would be best for a particular patient.

Suggested Reading

Bonner JA, Giralt J, Harari PM, et al. Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: a phase III study of high dose radiation therapy with or without cetuximab [abstract]. *Proc Am Soc Clin Oncol*. 2004;23. Abstract 5507.

Cohen EE, Rosen F, Stadler WM, et al. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol*. 2003;21(10):1980-1987.