Systemic Therapy for Squamous Cell Carcinoma of the Head and Neck

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KEYWORDS

• Squamous cell head and neck cancer • Platinum chemotherapy
• Epidermal growth factor receptor • Chemoradiation

KEY POINTS

- The use of systemic therapy for squamous cell cancer of the head and neck (SCCHN) has evolved, and cytotoxic therapy is now an integral component of the combined-modality treatment of locally advanced disease.
- An increasing understanding of the molecular basis of SCCHN has led to the development of agents targeting epidermal growth factor receptor, such as cetuximab and afatinib.
- Further advances are required for the treatment human papillomavirus–negative disease, which often is associated with a poor prognosis.

SYSTEMIC THERAPY FOR LOCALIZED DISEASE

Definitive Chemotherapy with Radiation

Meta-analyses evaluating the efficacy of multimodality approaches to the treatment of squamous cell cancer of the head and neck (SCCHN) have consistently supported concurrent chemoradiation (CCRT), reporting an improved overall survival (OS) of 8% to 11% in both surgically resectable and unresectable patients.[1] However, higher locoregional dose density delivered with CCRT results, predictably, in a higher degree of regional toxicity, including severe mucositis with associated pain and diminished nutritional intake.[2,3] Despite the demonstrated regional control and survival benefits, analysis of failure patterns has not demonstrated consistent decline in distant metastasis with CCRT in comparison with radiotherapy alone.[4] Similarly, studies of induction chemotherapy, followed by chemoradiation, have failed to improve survival or decrease the risk of distant metastases.[5,6]

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Surg Oncol Clin N Am 24 (2015) 437–454
http://dx.doi.org/10.1016/j.soc.2015.03.004 **surgonc.theclinics.com**

Thus, for locally advanced cancers of the head and neck, definitive CCRT is the current treatment standard.

Long-term results of a trial evaluating the contribution of platinum-based chemotherapy added to radiotherapy demonstrated a significant improvement in locoregional control (LRC) and larynx preservation compared with either induction chemotherapy or radiation therapy alone.[7,8] Locoregional failure has traditionally been the predominant manner of recurrence; nearly 90% of patients who present with distant metastasis also harbor concurrent locoregional cancer.[9] CCRT has become an essential component of the treatment paradigm in patients with potentially curable disease. Disease-free survival (DFS) was demonstrated in the Radiation Therapy Oncology Group (RTOG) 91-11 study[8] to be significantly prolonged in patients who received CCRT compared with radiotherapy alone (5-year OS and DFS were 22% and 27% vs 16% and 15%, respectively). There were disconcerting late deaths after CCRT that were not readily explained by tumor or treatment toxicity.

Single-Agent Platinum-Based Therapy

For patients in whom the primary site of malignancy is truly unresectable, OS after standard single-modality local radiotherapy was measured at less than 25%.[10,11] A phase III randomized trial conducted by the Head and Neck Intergroup from 1982 to 1987 compared radiotherapy alone to CCRT with weekly cisplatin at 20 mg/m^2.[12] The median survival of 13 months did not differ significantly between the two treatment arms, and the CCRT regimen was not adopted. This study was followed in 1987 by an RTOG phase II trial evaluating the efficacy of concurrent radiation and high-dose cisplatin, using a dose of 100 mg/m^2 given every 21 days. This schedule yielded a complete response (CR) in 71% of patients, with a 4-year survival of 34%.[13] The results suggested dose dependency of the observed improvement in response and survival, and the study was followed in 1992 by a second-generation trial by the Head and Neck Intergroup.[14]

This phase III Intergroup trial compared radiotherapy alone with 2 different schedules of chemoradiotherapy in patients with locally unresectable disease. The first regimen used concurrent high-dose cisplatin and radiation (the RTOG regimen, 100 mg/m^2 on days 1, 22, and 43), and the second involved a split course of single-daily fractionated radiation and 3 cycles of concurrent infusional 5-fluorouracil (5-FU) plus bolus cisplatin (cisplatin at 75 mg/m^2 given every 4 weeks). With a median follow-up of 41 months, the 3-year projected OS for patients receiving high-dose cisplatin-based chemoradiation was 37% compared with 23% for those in the arm receiving radiotherapy alone (P = .014). The addition of concurrent single-agent cisplatin at 100 mg/m^2 significantly improved survival over radiotherapy alone. Toxicities of grade 3 or greater occurred in 89% of patients receiving high-dose cisplatin, predominantly mucositis with dysphagia (43 of 95 patients), leukopenia (40 of 95 patients), and to a lesser extent nausea with vomiting.

Patients receiving high-dose cisplatin are at risk of auditory toxicity, for which they may be monitored with serial comprehensive hearing tests during the course of therapy. This approach is warranted for such symptoms as diminished auditory acuity or tinnitus. Patients receiving CCRT with cisplatin also require regular assessment and repletion of volume status, particularly during high-dose therapy, to minimize renal complications from potential insults, including direct cisplatin-induced nephrotoxicity and prerenal insufficiency secondary to diminished oral fluid and nutritional intake. Patients typically receive liberal amounts of intravenous fluid immediately surrounding each cisplatin administration (approximately 2.5 L), and frequently require additional intravenous hydration during the course of each 21-day cycle. Many continue to