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Chemoradiation Therapy: The Evolving Role in Head and Neck Cancer and Its Application to Oral Cavity Tumors

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Overview of combined modality therapy

Induction chemotherapy

Early clinical trials demonstrated that treatment-naïve patients with locally advanced head and neck cancer had a high response rate to systemic chemotherapy. In 1982, investigators at Wayne State University were the first to report on the results of a two-drug combination using cisplatin and 5-fluorouracil (FU) [2]. Of 26 evaluable patients, 19% had a complete response and a 70% partial response rate (overall response rate of 89%) after three cycles of induction therapy. Although similar results have been demonstrated by other investigators using other combination regimens, cisplatin and 5-FU became the most commonly used induction regimen for the next two decades.

Because of the high response rates, there was initial enthusiasm about the potential benefit of induction chemotherapy before surgical resection. Unfortunately, the high response rates failed to result in a statistically significant survival. Similarly, adjuvant chemotherapy after surgical resection has failed to demonstrate a survival advantage. Although many adjuvant studies are methodologically flawed, a recent, well-conducted Radiation Therapy Oncology Group (RTOG) trial confirmed the lack of a survival advantage for adjuvant therapy. In this study, patients underwent surgical resection followed by standard radiation or three cycles of cisplatin and 5-FU followed by standard radiation [3]. Results demonstrated no improvement in outcome with the addition of systemic chemotherapy. It must be noted that in a subset of patients with "bulky" disease, patients who received systemic chemotherapy had improved outcome, which must be seen as a hypothesis-generating observation that warrants further investigation.

Induction chemotherapy also has been investigated as a part of combined modality therapy before radiation therapy. These investigations may be divided into three distinct settings: resectable patients who desire organ preservation, patients who have unresectable squamous carcinomas, and patiemts who have locally advanced nasopharynx cancers. In the resectable patient population, a radiation-based organ preservation approach was used most commonly in patients with laryngeal, hypopharyngeal, and base of tongue tumors. In this cohort of patients, surgical resection could lead to significant function loss. Early phase II studies indicated that induction chemotherapy followed by radiation has acceptable toxicity, comparable survival outcome to historical surgical controls, and reasonable rates of organ preservation.

Two sentinel phase III studies have compared induction chemotherapy with radiation to primary surgery with postoperative radiation. The

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Veterans Affairs Laryngeal Cancer Study Group randomized 332 patients with stage III-IV laryngeal cancer to total laryngectomy with postoperative radiation or induction chemotherapy with three cycles of cisplatin and 5-FU followed by definitive irradiation (66–76 Gy). Local recurrences were increased in the induction chemotherapy/radiation arm ($P = 0.0005$), although distant metastases were fewer ($P = 0.016$). The 2-year survival rate was 68% for both treatment arms. The larynx preservation rate was 64% with induction chemotherapy and radiation [4]. An analogous result was shown by the European Organization for Research and Treatment of Cancer in patients with locally advanced hypopharyngeal cancer [5]. Unlike the Veterans Administration trial, however, a complete response was required after two cycles to go on to the third cycle of chemotherapy and definitive radiation. The median survival obtained with induction chemotherapy and radiation was 44 months versus 25 months for immediate surgery (P = ns). At 3 years, 42% of patients who received induction chemotherapy and radiation retained a functional larynx. Treatment failures at local, regional, and second primary sites occurred at the same frequency (12%, 19%, and 16%, respectively, for surgery and 17%, 23%, and 13%, respectively, for induction chemotherapy radiation). These trials have been criticized because they lack a third treatment arm with radiotherapy alone.

Fewer data are available for the role of induction therapy in the unresectable patient population. Paccagnella conducted a randomized trial in which patients were separated into two cohorts: resectable and unresectable [6]. Within each cohort, patients were randomized to no induction or four cycles of cisplatin and 5-FU. Induction therapy did not improve survival in the surgical cohort; however, survival was significantly increased in patients who received induction chemotherapy followed by radiation as opposed to induction therapy alone. These results have been updated and remain statistically significant after 10 years of follow-up. The 5- and 10-year overall survival rates were 21% and 16%, respectively, for chemoradiation and 8% and 6%, respectively, for radiation alone ($P = 0.04$) [7].

As new drugs are being developed they are being incorporated into induction regimens in an attempt to improve the efficacy with hopes of improving survival. Two randomized trials have investigated the use of aggressive three-drug regimens as induction therapy before definitive radiation. Hitt reported the results of a phase III trial of cisplatin and 5-FU compared with cisplatin, 5-FU, and paclitaxel [7]. Patients who received the three-drug regimen had an increase in progression-free (21.7 versus 17.7 months; $P = 0.024$) and overall survival (median survival not reached versus 37.7 months; $P = 0.038$) [7]. Similarly, Vermorken and van Herpen [8] reported the results of a randomized phase III trial of cisplatin and 5-FU versus cisplatin, 5-FU, and docetaxel followed by radiation therapy. The three-drug regimen demonstrated an improved response (67.8% versus 53.6%; $P = 0.007$), progression-free survival (HR 0.72, 95% confidence interval 0.56–0.91; $P = 0.006$), and overall survival (HR 0.73, 95% confidence interval 0.57–0.94; $P = 0.016$). Both studies provide strong support for the further investigation of novel induction regimens in the treatment of locally advanced disease.

Concurrent chemoradiation

An alternative method for combining chemotherapy and radiation therapy is to give them concurrently. There are several postulated mechanisms for radiosensitization: (1) alteration in repair of sublethal cell damage, (2) alteration of cell cycle kinetics, favoring G_2/M arrest, and (3) elimination of clonogens responsible for accelerated repopulation. Preclinical data indicate that several commonly used chemotherapy agents can enhance radiation efficacy, including cisplatin, 5-FU, mitomycin, hydroxyurea (Hydrea), bleomycin, actinomycin D, and doxorubicin (Adriamycin). Numerous phase I/II data demonstrate that these agents can be administered concomitantly with radiation therapy; however, it is at the expense of increased toxicity. Based on promising phase II data, investigators evaluated chemoradiation in comparison to radiation alone in patients with locally advanced squamous carcinoma of the head and neck. The French Head and Neck Oncology and Radiotherapy Group conducted a randomized phase III trial using radiation alone compared with chemoradiation with carboplatin and 5-FU in 226 patients with advanced oropharyngeal cancers [9]. Results showed an improvement in 5-year survival (22% versus 16%; log rank $P = 0.05$), disease-specific survival (27% versus 15%; $P = 0.01$), and local-regional control (48% versus 25%; $P = 0.002$) favoring the combined therapy arm. The results of the intergroup trial comparing radiation alone versus