Is There a New Role for Induction Chemotherapy in the Treatment of Head and Neck Cancer?

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The majority of deaths from locally advanced head and neck cancer are due to complications of uncontrolled locoregional disease, and this pattern of failure must be altered to improve patient survival. Over the past 25 years, thousands of patients with head and neck cancer have been enrolled in clinical trials to test whether the addition of platinum-based chemotherapy to local treatment modalities of surgery and radiotherapy improves overall survival. These studies have taken two approaches. In the first approach, several cycles of neoadjuvant or induction chemotherapy (most commonly cisplatin and infusional 5-fluorouracil) precede definitive locoregional therapy (i.e., surgery). The second approach is chemoradiotherapy, the concurrent administration of radiotherapy and chemotherapy.

Of the two approaches, only chemoradiotherapy has succeeded in changing outcomes. Numerous phase III trials that have compared radiotherapy alone to chemoradiotherapy...
have shown that the latter statistically significantly improved locoregional control and that the magnitude of improvement is sufficient to have an impact on overall survival (1–5). As a consequence of these findings, over the last decade, chemoradiotherapy has become the standard of care for the management of unresectable head and neck cancers and nasopharyngeal cancers (i.e., stage T3, stage T4, or lymph node–positive cancers) and for the nonoperative management of locally advanced oropharyngeal cancers. By contrast, only two (6,7) of more than 30 randomized trials have demonstrated that induction chemotherapy confers a survival advantage. In addition, induction chemotherapy has little impact on reducing locoregional failure, despite its rapid reduction of tumor size and the fact that approximately 70%–85% of patients treated with induction chemotherapy have a major response.

The inability of induction chemotherapy to improve locoregional control is illustrated by the results of two randomized trials in patients with resectable stage III or IV larynx cancer. One trial (8) compared induction chemotherapy followed by radiotherapy with radiotherapy alone, and the other trial compared induction chemotherapy followed by radiotherapy with laryngectomy plus adjuvant radiotherapy (9). In the former study (8), induction chemotherapy followed by radiotherapy achieved a similar local control rate, as did radiotherapy alone, but was associated with substantially worse toxicity. In the latter study (9), induction chemotherapy followed by radiotherapy achieved worse local control than laryngectomy plus adjuvant radiotherapy. In addition, a comparison of chemoradiotherapy versus induction chemotherapy followed by radiotherapy and chemoradiotherapy versus radiotherapy alone as strategies to preserve the larynx showed statistically significantly higher rates of locoregional control and larynx preservation (78% and 88%, respectively) with the concurrent chemoradiotherapy approach (8).

Chemoradiotherapy is now the standard of care for organ preservation in patients with this disease (8). However, despite this improvement in locoregional control, it should be pointed out that chemoradiotherapy does not provide a survival advantage over induction chemotherapy or radiotherapy alone for larynx cancer. This is principally because local recurrence of larynx cancer, unlike that of other head and neck cancers, can be effectively managed with salvage surgery.

Underscoring these observations are the results of four meta-analyses that examined the effect of chemotherapy added to locoregional therapy on survival (10–13). All four meta-analyses showed that patients treated concurrently with chemotherapy and radiotherapy had a small but statistically significant survival benefit compared with patients treated with radiotherapy alone. In the largest of these meta-analyses, which included 87 trials and more than 16 000 patients (13,14), chemoradiotherapy conferred an absolute survival benefit of 8% at 5 years (hazard ratio [HR] = 0.81, 95% confidence interval [CI] = 0.76 to 0.88; P < .001), whereas the effect of induction chemotherapy on survival was not statistically significant (HR = 0.95, 95% CI = 0.88 to 1.01; P = .38).

Given the limited data in support of the use of induction chemotherapy, why has its role remained controversial? There are at least five reasons: 1) Induction chemotherapy consistently demonstrates a systemic effect to suppress the development of metastases. 2) Response to induction chemotherapy is predictive of response to subsequent radiotherapy. 3) A subset analysis of trials of cisplatin and 5-fluorouracil induction chemotherapy compared with locoregional treatment alone from one meta-analysis (13) showed a survival gain of 5%. 4) Some trial results suggest that the pattern of treatment failure and the main cause of death may be shifting from locoregional control to metastatic disease. 5) Preliminary reports suggest that there are combination chemotherapy regimens more efficacious than cisplatin and 5-fluorouracil (15,16).

In this issue of the Journal, Zorat et al. (17) report the 5- and 10-year results of a multicenter trial that was initiated in 1986 to evaluate the contribution of induction chemotherapy to the survival of a population of patients with stages III and IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or paranasal sinuses. A total of 237 eligible patients with operable or inoperable disease were randomly assigned to receive definitive local therapy alone (surgery and adjuvant radiotherapy for operable patients or radiotherapy alone for inoperable patients) or four courses of induction chemotherapy with cisplatin and 5-fluorouracil, followed by definitive local therapy, as determined by operability status at study entry.

In the primary outcome analysis of induction chemotherapy versus locoregional therapy alone, Zorat et al. (17) reported that overall survival was not improved by the addition of induction chemotherapy (5-year survival with versus without induction chemotherapy: 23% versus 16%; 10-year survival with versus without induction chemotherapy: 19% versus 9%; P = .13). In a subset analysis, no statistically significant difference in survival was detected among operable patients who received induction chemotherapy versus local therapy alone (5-year survival: 31% versus 43%, 10-year survival: 23% versus 14%; P = .73). However, among inoperable patients, patients in the induction chemotherapy group had statistically significantly better survival than patients who did not receive induction chemotherapy (5-year survival: 21% versus 8%; 10-year survival: 16% versus 6%; P = .04). Zorat et al. also observed differences between the treatment groups in the pattern of failure. In both the primary analysis and the subset analyses, patients who received induction chemotherapy had a statistically significant reduction in distant metastatic rate compared with patients who did not receive induction chemotherapy. However, induction chemotherapy was associated with a statistically significant reduction in the locoregional failure rate only in the subset of patients with inoperable disease.

Do these results point to a new role for induction chemotherapy in head and neck cancer? Zorat et al. initiated their trial 18 years ago. Since then, treatment advances have led to changes in the standard of care, from radiotherapy alone to concurrent chemoradiotherapy when surgery is not planned. On the basis of the observed complementary effects of concurrent chemoradiotherapy and induction chemotherapy to decrease locoregional failure and to suppress distant metastases, respectively, this approach is being tested in several phase II single-institution studies (18–20). These studies have demonstrated the feasibility of this approach and have reported encouraging survival rates using a variety of drug and radiotherapy regimens.

The contribution of induction chemotherapy to concurrent chemoradiotherapy must be formally tested in prospective randomized trials of patients with well-defined specific primary sites and stages of disease. Results of the subset analysis in the trial by Zorat et al. (17) support testing the addition of induction chemotherapy to chemoradiotherapy among patients with unresectable disease. The definition of “resectability” may be argued. However, this approach makes sense for treatment of advanced
regional nodal disease (i.e., N2N3) and large primary tumors because these disease stages are associated with an increased risk of distant dissemination. For most intermediate-stage cancers (i.e., T1–2N1), this approach is probably excessive, and the survival benefit over that for the current standard of care would be small, if any, and potentially offset by toxicity.

To definitively test these hypotheses, two prospective randomized phase III trials of chemoradiotherapy with and without induction chemotherapy targeting different patient populations will soon be activated through the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG). The ECOG trial will enroll patients with unresectable cancers, using standard definitions of resectability that have been used previously (3), while the SWOG trial will evaluate non-operative management of advanced-stage oropharynx cancer. The latter trial will use tumor response to induction chemotherapy as a surrogate biomarker for sensitivity to chemotherapy and radiotherapy and as the determinant of subsequent treatment (chemoradiotherapy for organ preservation or surgery). Both trials will incorporate assessments of function and quality of life. These trials are designed to address the role of induction chemotherapy in advanced disease and therefore have the potential to redefine the current standard of care. Although the “best” combined-modality approach remains controversial, chemotherapy clearly has a major role in the management of most patients with advanced head and neck cancer.

REFERENCES