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Induction Chemotherapy in Head and Neck Cancer

A Critical Review of 25 Years of Clinical Trials

Danny Rischin, MD

1. INTRODUCTION

It has been known for more than 20 yr that cisplatin-based combination chemotherapy can achieve overall response rates of 70 to 90%, with complete response rates of 20 to 50% in patients with previously untreated locally advanced head and neck cancer (1,2). The use of chemotherapy prior to radiation or surgery is commonly referred to as induction or neoadjuvant chemotherapy. Investigators hypothesized that the addition of an active induction regimen prior to definitive radiotherapy or surgery would have a significant beneficial impact on the outcome of treatment for patients with locally advanced squamous cell carcinoma of the head and neck. As well as the potential to decrease distant metastases, it was hoped that significant tumor shrinkage could contribute to improved local-regional control, and facilitate organ preservation (3). Early single-arm trials confirmed the activity of platinum-based induction regimens and established that sequential induction chemotherapy and radiation was feasible, without any apparent increase in radiation toxicity (4).

2. RESULTS OF PHASE III TRIALS AND META-ANALYSES

Based on promising phase II results, numerous phase III trials of induction chemotherapy have been conducted. In general, these trials have failed to demonstrate any improvement in local control or survival, although the incidence of distant metastases was frequently reduced (3). Several metaanalyses, including a detailed analysis based on individual patient data, have failed to show any significant benefit with induction chemotherapy (5–7). There was a risk reduction of 5% that corresponded to an absolute benefit of 2% with induction chemotherapy that was not statistically significant. None of the 31 induction trials included in the meta-analysis was significant for overall survival. However, a subgroup analysis did show that induction chemotherapy with cisplatin and 5-fluorouracil (5-FU) was different from other regimens, with a hazard ratio of 0.88 (95% CI: 0.79–0.97).

Proponents of induction chemotherapy frequently highlight two studies that they contend support the case for induction chemotherapy as a worthwhile strategy in head and neck cancer. One is the study by Domenge et al. (8) who reported on the Group d’Etude des Tumeurs de
la Tete et du Cou (GETTEC) trial that tested the addition of cisplatin and 5-FU prior to radiotherapy or surgery and radiotherapy. The GETTEC trials were included as two studies in the meta-analysis, neither of which was significant, but the two groups were pooled for publication. In the published analysis there was a significant difference in overall survival, but not in event-free survival, local-regional control, or distant metastases. These results are intriguing as it is generally much harder to show a difference in overall survival than in event-free survival in head and neck cancer trials owing to the competing causes of death in this population.

The other trial that is frequently discussed is the trial of Paccagnella et al. (9), which tested the addition of induction chemotherapy prior to surgery for operable patients and prior to radiation for inoperable patients. There were no significant differences between the group that received induction chemotherapy and the group that did not. However, a subgroup analysis of the 171 inoperable patients showed an improvement in overall survival (3-yr survival 10 vs 24%, *p* = 0.04) and disease-free survival (DFS) (3 yr DFS 26 vs 34%, *p* = 0.06). There was an imbalance in the number of patients with T4 disease between the arms, and on multivariate analysis the effect of chemotherapy on overall survival became of borderline significance (*p* = 0.06). Even though 37% of patients had stage 3 disease, only 27% were deemed to be operable. Radiotherapy could be stopped for 2 wk after 40 Gy or if Grade 3 or 4 mucositis occurred, a strategy that is likely to have an adverse effect on outcome, particularly in patients being treated with radiation alone. No details about the actual duration of radiotherapy and dose delivered are included in the manuscript. The overall results in the control arm are very poor, which raises the question about whether the induction chemotherapy partly compensated for suboptimal radiation therapy.

3. DISCORDANCE BETWEEN AVAILABLE EVIDENCE AND USE OF INDUCTION CHEMOTHERAPY

Despite the largely negative results from randomized trials, induction chemotherapy has been widely used outside of clinical trials, particularly in the United States. Harari and colleagues (10,11) have reported on the results of community cancer specialists in the United States, who surveyed the management of patients with locoregionally advanced, nonmetastatic head and neck cancer. The specialists were equally divided among otolaryngologists, radiation oncologists, and medical oncologists. By 1996, most of the randomized trials of induction chemotherapy as well as the metaanalyses had been published. In addition, many editorials and reviews had concluded that there was no role for induction chemotherapy, apart from possibly selecting patients for larynx preservation, and that it should not be used outside of a clinical trial (5,12,13). Even so, the 1996 survey revealed that 61% of respondents identified induction chemotherapy as their most common approach for the management of patients with locoregionally advanced head and neck cancer. Between 1996 and 2000, there were few new data on sequential chemoradiation, but increasing evidence of benefit for concurrent chemoradiation was found in randomized trials (14–16). Metaanalyses of individual patient data published in early 2000 confirmed a benefit for concurrent but not sequential chemoradiation (7). Concurrent chemoradiation was preferred by 39%; surprisingly, 31% still favored induction chemotherapy. Induction chemotherapy continues to be widely used even though its use as part of standard care has not been supported by the available evidence at any time over the last 20 yr, with the possible exception of larynx preservation.