

### Commentary: Induction Chemotherapy for Head and Neck Cancer: Hypothesis-Based Rather Than Evidence-Based Medicine

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#### LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the history of clinical trials using surgery, radiation, and chemotherapy in head and neck cancer.
2. Explain the benefit of chemoradiotherapy in locally advanced head and neck cancer.
3. Describe the role of adjuvant chemotherapy with cisplatin and 5-FU followed by chemoradiation with or without taxanes.
4. Evaluate the toxicity of adding taxanes and the need for further clinical trials adding taxanes.

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#### INTRODUCTION

In recent years, we have faced the argument that sequential therapy with the combination of a taxane, a platinum, and 5-fluorouracil (5-FU) (TPF), followed by concurrent chemoradiation, represents a new acceptable standard of care for locally advanced head and neck (HN) cancer. This argument is based on two premises: (a) previous data showing the superiority of induction chemotherapy containing cisplatin and 5-FU (PF) followed by radiotherapy over radiotherapy alone, and (b) recent data demonstrating the superiority of induction with TPF over induction with PF. However, both the theoretical basis and the clinical evidence supporting induction chemotherapy are weak. Until current randomized studies that compare induction TPF followed by chemoradiotherapy (CRT) with CRT alone are concluded, there is yet no evidence for the superiority of induction chemotherapy. The announcement about a “new standard of care” is, therefore, premature.

#### HISTORICAL OVERVIEW

The theoretical basis for induction chemotherapy was developed in the early 1980s. As high response rates were observed and data were presented suggesting that those who respond are more likely to achieve tumor control, induction chemotherapy spread rapidly in the community. In 1997, a survey of community oncologists found that the single most common treatment approach for patients with locoregional advanced HN cancer was that of induction PF followed by radiotherapy, even though randomized studies and meta-analyses published at the time had not shown any locoregional or survival advantage over radiotherapy alone [1]. Notably, 96% of responders indicated that induction PF was not delivered as part of a clinical study. Ten years later, we are facing a similar scenario: induction TPF chemotherapy followed by concurrent CRT is advertised to the community as a new standard of care, while several randomized studies that have specifically been devised to test its supe-

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riority over concurrent CRT are ongoing and their results are not yet known.

### BIOLOGICAL AND CLINICAL CONSIDERATIONS

There are several biological and clinical reasons, detailed below, that suggest that induction TPF followed by CRT may fail to improve outcome over CRT alone.

Chemotherapy alone is not curative, even in the best circumstances. We have appreciated this in a recent study in which six cycles of PF chemotherapy were delivered, without radiotherapy, for patients with laryngeal cancer who achieved biopsy-proven complete response after one cycle of induction PF [2]. The hypothesis was that these patients, representing only 10%–15% of the patients with locally advanced laryngeal cancer, had been selected as the best responders to chemotherapy and they may achieve cure with chemotherapy alone, avoiding the toxicity of radiotherapy. All these patients failed locoregionally, prompting discontinuation of the study [2]. The failure of chemotherapy delivered without concomitant radiotherapy to impact eventual outcome was previously predicted by Ian Tannock [3]. If a 10-g tumor containing  $10^{10}$  cells is treated with three cycles of induction chemotherapy, each of which kills 50%–90% of the tumor cells, after three cycles, the number of viable cells is close to  $10^8$  (<0.1 g) and the patient is assumed to achieve clinical and radiological complete remission. However, cell reduction has been trivial: we are still facing close to  $10^8$  cells. Moreover, additional chemotherapy may not be helpful if drug-resistant cells have been selected after three courses of chemotherapy.

The shrinkage of the tumor after induction chemotherapy, even if it has been substantial, is not likely to help the radiation oncologist in defining a smaller target volume and sparing more noninvolved tissue. Tissue volumes from which the tumor has shrunk radiographically may still contain a large number of tumor cells that are at the threshold of our ability to detect radiologically. Sparing these tissues may be detrimental. The clinical experience of local failures in all patients receiving chemotherapy alone, even if radiological and histological complete response has been achieved, as well as prudence, dictate that preinduction tumor volumes should be targeted by radiotherapy. No benefit is expected to be gained in this regard.

Another biological consideration is the accelerated repopulation of surviving tumor clonogens that occurs during an extended total treatment time [4]. Most clinical and preclinical data suggest that accelerated repopulation occurs toward the end of a fractionated radiotherapy course; however, this phenomenon is not exclusive to radiotherapy. The delivery of three cycles of induction chemotherapy extends the total treatment time by approximately 9 weeks. The de-

finite therapy (CRT) is delivered after a lengthy course of therapy that reduces tumor volume but does not eliminate it, causing accelerated repopulation of surviving clonogens even before CRT is started, rather than at the end of the CRT course. This poses a theoretical impediment to the patient's chance of cure.

The most important clinical consideration, apart from the toxicity of the induction therapy (induction TPF had a toxic death rate of 3.7% even before CRT was started [5]), is the fact that a certain number of patients receiving induction chemotherapy do not proceed to receive definitive therapy. The causes for omitting definitive therapy include the toxicity of induction or patient refusal to proceed with CRT after the bulk of their disease has been reduced by induction chemotherapy. Early randomized studies of induction chemotherapy followed by standard local treatment versus radiotherapy alone reported that, while toxicity to chemotherapy was not a factor in survival, the number of patients who withdrew from the studies and those who did not comply with treatment were greater in the chemotherapy groups, which was the likely cause of an inferior outcome of patients receiving induction chemotherapy [6]. Rosenthal et al. [4] noted that this phenomenon is similar to that faced by a surgeon following an excisional biopsy of tumor: the patient may query why more treatment is required, because all visible tumor has been removed.

Patient attrition during or after induction chemotherapy is not confined to earlier studies. Hitt et al. [7] recently reported the results of a randomized study for advanced HN cancer comparing induction using carboplatin and 5-FU (CF) with induction using paclitaxel plus CF (PCF), followed in both arms by CRT. The results showed that PCF was better tolerated and resulted in a higher complete response rate than with CF. A detailed flowsheet of patient numbers in each phase of the study was provided (Figure 2 in the paper). In the PCF arm, 9 of 189 (5%) patients dropped out during PCF chemotherapy. In addition, of 129 patients achieving a partial or complete response who were eligible to proceed with CRT, an additional 15 patients (12%) dropped out and did not receive definitive therapy. Thus, 13% of the patients assigned for the better-tolerated PCF induction regimen dropped out and did not receive the definitive treatment. This rate was even higher in the less well-tolerated CF arm. These high rates of dropout may explain the differences in outcome between the two arms. Furthermore, at least some of these patients would likely have completed their definitive therapy had induction chemotherapy not been delivered. Taking into account the fact that this was a prospective, randomized study, where diligent data acquisition and patient follow-up were likely performed by study coordinators, can these dropout rates be

even higher outside study, and in the community, where >96% of HN cancer patients are treated? The answer is most probably, yes. These dropout rates, in addition to toxic deaths, are likely to negate any potential benefit offered by induction chemotherapy.

## CONCLUSIONS

These biological and clinical shortcomings of induction chemotherapy are reflected by the large majority of the randomized studies in HN cancer. These studies demonstrated no or marginal benefit of cisplatin-containing induction chemotherapy over radiotherapy alone regarding locoregional control, disease-free survival, or survival, and are cited in recent meta-analyses [8, 9]. Conveniently, proponents of induction chemotherapy often cite the only two randomized studies showing a benefit of induction chemotherapy, ignoring the many studies that have demonstrated no benefit [5].

It is possible that the advantages of taxane-containing chemotherapy over CF are large enough to overcome the lack of benefit of induction chemotherapy reported to date. Several randomized studies of taxane-containing induction chemotherapy followed by CRT, versus CRT alone, are currently ongoing. The results of these studies will be known in the near future. Until these results are known, the superiority of induction TPF chemotherapy followed by CRT over CRT is still a hypothesis. The claim that this is a new standard of care is baseless, for the time being. Proposing it to the community at this time, without presenting the potential downside of induction chemotherapy and the lack of current evidence for its superiority over CRT alone, is problematic.

## DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The author indicates no potential conflicts of interest.

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