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Review

Induction chemotherapy for oral cavity cancer patients: Current status and future perspectives

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SUMMARY

There is a lack of data from phase III randomized studies to support an ideal approach for locally advanced oral cavity cancer patients. In general, surgery, radiotherapy and chemotherapy are valid treatment options, and combined approach is usually indicated given poor clinical outcomes with single modality therapy. The aim of this study is to review the current status and future perspectives of induction chemotherapy for locally advanced oral cavity cancer patients.

Introduction

Global yearly estimates for new oral cavity cancer cases are 263,000, with 127,000 expected deaths related to disease [1]. Most patients have locally advanced disease at the time of diagnoses and tumor presentation is often characterized by local invasion and lymph node involvement [2].

Performance status, patient age and preferences, and tumor features (stage, primary site, operable status) are usually taken into account when designing treatment plans. Extensive data from phase III randomized studies to support an ideal approach for locally advanced oral cavity cancers patients are lacking. Treatment strategies are established based on head and neck clinical trials that mostly included a small proportion of patients with oral cavity cancer. In general, surgery, radiotherapy and chemotherapy [3–5] are valid treatment options. Combined approach is usually indicated given poor clinical outcomes with single modality therapy [6].

Systemic therapy is often integrated into the treatment of head and neck cancer patients. The MACH-NC Collaborative Group meta-analysis recognized concurrent chemoradiation as a standard of care for management of locally advanced head and neck cancer. Concurrent chemoradiation therapy was associated with a statistically significant improvement in overall survival compared to radiation therapy alone (hazard ratio of death: 0.81 [0.78–0.86]). In contrast, induction chemotherapy was associated with a marginal, not statistically significant improvement in survival (hazard ratio of death: 0.96 [0.90–1.02]). Differences in patterns of failure were observed in patients exposed to concomitant chemotherapy and induction chemotherapy strategies: concurrent treatment primarily improved locoregional recurrence and survival; induction treatment improved the rate of distant metastases, with no impact on locoregional control. Nonetheless, the improvements in distant metastases rates were not enough to translate into better overall survival. While these data are not sufficient to support induction chemotherapy as a standard treatment approach, they indicates that some patients may derive benefit from induction approach, especially as locoregional control is optimized and distant metastases become an important cause of death [7].

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In addition to decreasing the risk of distant metastases, the rationale for induction chemotherapy includes: primary tumor reduction (which could be associated with less toxicities related to subsequent surgery and/or radiotherapy) and the opportunity to evaluate for tumor response and possible adjustments of subsequent therapy as appropriate (a strategy better evaluated so far in laryngeal HNSCC) [8].

As we continue to identify differences in etiology (including contributions of viral infections and tobacco), molecular pathology, prognosis and treatment options within and between the multiple HNSCC subsites, it is important to ascertain the role of each therapeutic modality according to the primary site of the disease. Therefore, the aim of this study is to review the current status and future perspectives of induction chemotherapy specifically for locally advanced oral cavity cancer patients.

Induction chemotherapy in non-surgical treatment protocols

Primary surgery followed by adjuvant treatment is considered the standard of care for locally advanced oral cavity cancer patients. However, non-surgical treatment might be an alternative option in some patients [9].

Induction chemotherapy (two versus three drugs) followed by (chemo) radiotherapy studies

Several studies have assessed the role of induction chemotherapy (two versus three drugs) followed by radiotherapy with or without concurrent chemotherapy for non-surgical management of the patients with locally advanced head and neck cancers.

Hitt et al randomized 382 untreated stage III or IVA-B patients to receive three cycles of induction chemotherapy with cisplatin and fluorouracil (PF) or paclitaxel, cisplatin, and fluorouracil (PCF). After induction, patients with a partial (more than 80% reduction of the primary disease) or complete response received chemoradiotherapy (cisplatin – days 1, 22, and 43 – concomitantly with conventional radiotherapy). Complete response rates after induction chemotherapy were significantly higher in the PCF arm (33% PCF versus 14% PF; $p < 0.001$). No difference in overall survival was observed (43 months PCF versus 37 months PF; $p = 0.06$) but the median time to treatment relapse was 20 months in the PCF group compared to 12 months in the PF group ($p = 0.006$). The subset analysis of unresectable patients showed superior outcomes in favor of the PCF arm (overall survival was 36 months in the PCF arm versus 26 months in the PF arm; $p = 0.04$). In regards to acute toxicity during induction chemotherapy, the PF arm had significantly more mucositis grade 2–4 than the PCF arm (53% PCF versus 16% PF; $p < 0.01$), whilst alopecia was more frequent in PCF group (10% PCF versus 2% PF; $p < 0.01$).No other differences in toxicities were seen between the groups [10].

Posner et al. (*TAX 324 Study Group*) studied 501 patients with stage III or IVA-B tumors (unresectable disease or patients candidates for organ preservation) who received induction chemotherapy (three cycles given every three weeks) with PF or docetaxel, cisplatin and fluorouracil (TPF) followed by chemoradiotherapy (weekly carboplatin concomitantly with radiotherapy). The estimated three-year overall survival was significantly higher in the TPF group (62% TPF versus 48% PF; $p = 0.006$) as well as the median overall survival (71 months TPF versus 30 months PF; $p = 0.006$). No differences in distant metastases rates were observed between the two groups. Some adverse events during induction chemotherapy were more frequent in the TPF arm [neutropenia grade 3 or 4 ($p < 0.001$); febril neutropenia ($p = 0.04$)] [11]. The update of this study with 5 years of follow up data showed persistent benefits in progression-free survival and overall survival for the TPF group [39].

Likewise, Vermonken et al. (*EORTC 24971/TAX 323 Study Group*) randomized 358 patients stage III or IV with unresectable disease to receive induction chemotherapy with TPF or PF (four cycles every 3 weeks) followed by radiotherapy. Progression-free survival was significantly higher in the TPF group (11.0 months TPF versus 8.2 months PF; $p = 0.007$). A decrease in the risk of death was also lower in the TPF arm (overall survival rates at 3 years: 37% TPF compared to 26% PF; $p = 0.02$). The PF group had more grade 3 or 4 hearing loss, nausea, vomiting, stomatitis, and thrombocytopenia while the TPF group had more grade 3 or 4 neutropenia and leukopenia [12]. After 5 years of follow up, the benefits in progression-free survival and overall survival for TPF group were sustained [13].

A recent meta-analysis of randomized clinical trials in head and neck cancers compared induction chemotherapy with PF or docetaxel/paclitaxel plus PF. The result of this study demonstrated that the use of a three-drug induction chemotherapy regimen resulted in significantly lower locoregional relapses, distant failures, and deaths compared to a two-drug induction regimen [14]. Nonetheless, the majority of relapses occurred at the primary site or in the neck, illustrating the need to develop better strategies for improved locoregional control, particularly for high risk patients.

While *TAX 323* and *TAX 324* showed improved survival for the triple drug arm, and led to the approval of docetaxel by regulatory agencies worldwide for use as part of an induction regimen in locally advanced HNSCC, induction chemotherapy has not been accepted as a standard of care for most patients in routine clinical practice. In both studies, an arm of upfront concurrent chemoradiation was not included. Moreover, the definitive local therapy utilized consisted of either radiation therapy alone (in *TAX 323*), or concurrent carboplatin and radiation therapy (in *TAX 324*). These two modalities could be considered an attenuated approach, which may not confer optimal locoregional control. As such, it is unclear whether the benefits in locoregional control and survival observed in the TPF arms would be sustained in the setting of more intense concurrent chemoradiation therapy with cisplatin-based regimens. Additionally, the survival benefits of *TAX 323* and *TAX 324* may not be applicable to patients who receive surgery as part of their definitive local therapy, given potential differences in locoregional control of surgical versus non-surgical approaches, especially in patients with oral cavity cancers, for which surgical resection is usually recommended as the preferred treatment modality,

Table 1 summarizes the characteristics and results of the aforementioned clinical trials (Pointreau et al. [15] included hypopharynx and larynx cancer patients only). It is important to highlight the small percentage of oral cavity cancer patients that were included in these studies. Considering all trials, oral cavity cancer corresponded to only 12.7% of total cases (Graphic 1), raising the question whether the findings are applicable to this particular patient population and underscoring the need for oral cavity-specific induction clinical trials.

Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy studies

In this section, we summarize the results of clinical trials evaluating induction chemotherapy followed by concurrent chemoradiotherapy versus concurrent chemoradiotherapy upfront for management of patients with locally advanced head and neck cancers.

Haddad et al. (PARADIGM study) assessed 145 head and neck patients who received TPF induction chemotherapy followed by chemoradiotherapy or concurrent chemoradiotherapy (ChemoRT) upfront. Three-year overall survival was 78% in ChemoRT arm versus 73% TPF plus ChemoRT arm ($p = 0.77$). Equally, progression-free