COMMENTARY

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Revisiting induction chemotherapy before radiotherapy for head and neck cancer, part I: carcinoma of non-nasopharyngeal sites

“Future novel approaches will likely feature radiographic, proteomic and genomic biomarkers used to define prognostic groups and guide treatment selection with greater precision. Because of its flexibility and adaptability, induction will likely continue to be a ‘testing site’ for new chemotherapeutic, targeted or immunologic agents.”

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The early background of induction chemotherapy

For decades, systemic chemotherapy has been combined with locoregional radiation for the treatment of head and neck cancers. Combined-modality therapy initially demonstrated advantages such as radiosensitization and improved response rates. Delivering chemotherapy before radiation (the ‘induction’ or ‘neoadjuvant’ approach) became a particularly attractive strategy, as full-dose chemotherapy administration was more tolerable when given as induction, and it might enable selection for subsequent radiation or surgery based on treatment response. Yet despite generations of clinical trials exploring induction chemotherapy, many fundamental questions remain incompletely answered: Which patients benefit the most? With which agents? For which treatment goals?

In this set of paired reviews, we revisit the history of induction chemotherapy, the present status of these questions and future areas of inquiry. The reviews are divided by the categories of non-nasopharyngeal

and nasopharyngeal carcinomas, due to the unique history and biology of these cancer types. This first review will consider squamous cell carcinomas of the oral cavity, oropharynx, larynx and hypopharynx. Nasopharyngeal carcinoma will be addressed separately [1].

Early trials combining chemotherapy with radiation found encouraging response rates with cisplatin, especially when it was combined with 5-fluorouracil (5FU). By the 1990s, induction chemotherapy with cisplatin/5FU was the most common method of treating advanced head and neck cancer, although most of the evidence came from small, underpowered studies. This problem was addressed by meta-analyses, including the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), which eventually combined 93 trials including over 17,000 patients utilizing individual patient data [2,3]. The MACH-NC study group found significantly improved overall survival from the use of concurrent chemotherapy as compared with radiation alone, but no

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advantage was seen from induction chemotherapy. Intriguingly, however, while concurrent chemotherapy reduced distant failure (hazard ratio: 0.88), induction chemotherapy reduced distant failure further (hazard ratio: 0.73), although the difference was not significantly different from the rates seen with concurrent chemotherapy ($p = 0.12$). This meta-analysis also found that platinum-containing chemotherapy regimens produced the greatest advantage in overall survival. This evidence, along with a few notable, adequately powered multi-institutional trials [4,5], established radiation with concurrent platinum-based chemotherapy by the mid-2000s as the standard of care for locally advanced head and neck cancer. Nonetheless, questions remained about the possibility of better distant control with induction chemotherapy.

Induction as a strategy for organ preservation

Induction was also investigated as a strategy for organ preservation in sites that would otherwise be managed surgically. This approach was most readily applicable to advanced laryngeal cancers, which can be successfully treated with laryngectomy, but at the cost of a reduced quality of life from losing one's natural voice. Published in 1991, the landmark Veterans Administration Larynx Trial compared upfront surgery followed by postoperative radiation versus induction cisplatin/5FU followed by definitive-intent radiation for responders and surgery for nonresponders [6]. This strategy was able to achieve laryngeal sparing in nearly two-thirds of patients without compromising overall survival. Similar outcomes were seen in the European Organization for Research and Treatment of Cancer (EORTC) 24891 trial using induction cisplatin for hypopharyngeal cancers [7,8].

Still, the ideal timing of chemotherapy was unclear. The Radiation Therapy Oncology Group (RTOG) 91-11 study attempted to address this by randomizing patients with advanced larynx cancer to induction cisplatin/5FU followed by radiation, concurrent chemoradiotherapy with cisplatin, or radiation alone [9]. The long-term outcomes demonstrated improved rates of laryngeal preservation with concurrent chemotherapy (82%) versus induction (68%) or radiation alone (64%) [10]. However, the primary composite end point of 'laryngectomy-free survival' showed no significant difference between the induction and concurrent arms (29 vs 24%, respectively). This

discrepancy was driven by an unexplained trend toward a higher 10-year death rate with concurrent chemotherapy (72 vs 61%; $p = 0.08$). There was no evidence of greater treatment-related late toxicity with concurrent chemotherapy, and only deaths 'unrelated to cancer or treatment' were significantly higher in the concurrent arm by post hoc analysis ($p = 0.03$). Although possibly a chance occurrence, and while acknowledging the limited power of unplanned analyses conducted at long-term follow-up, this finding raises the question of whether unrecognized sequelae of concurrent chemoradiation increased late toxicities and deaths. While RTOG 91-11 generally showed concurrent chemotherapy to be superior in terms of the goal of laryngeal preservation, induction chemotherapy in larynx cancer has remained a defensible option due to this uncertainty.

The emergence of taxane-based induction

Enthusiasm for induction chemotherapy resurged with the availability of a novel class of drugs, the taxanes. These complex molecules inhibit microtubule depolymerization, interfering with mitosis. The first-in-class taxane, paclitaxel, was isolated from the Pacific yew tree in the 1960s. Due to early difficulties with production, clinical trials in head and neck cancer could not take place until the 1990s [11]. In 2005, Hitt *et al.* published a trial treating patients with three cycles of cisplatin/5FU before cisplatin chemoradiotherapy, and randomizing for the addition of paclitaxel [12]. This trial showed a significant improvement of overall survival with paclitaxel/cisplatin/5FU (TPF), which also resulted in less acute toxicity due to reduced 5FU dose in that arm. In 2007, the same issue of the *New England Journal of Medicine* featured the EORTC 24971/TAX 323 and TAX 324 trials [13,14]. Both trials randomly assigned for the addition of the taxane docetaxel to induction cisplatin/5FU, before either radiation alone (TAX 323) or before chemoradiotherapy using carboplatin (TAX 324). Both trials showed significant improvements in progression-free and overall survival rates with the addition of docetaxel.

The GORTEC 2000-01 study used a similar design for advanced larynx and hypopharynx cancers [15,16]. Patients were randomized to cisplatin/5FU induction with or without docetaxel, before definitive radiation with optional concurrent chemotherapy. Larynx preservation at 10 years was significantly improved from 47% to 70%, but there were no differences in

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disease-free or overall survival rates. These four Phase III trials convincingly showed that adding a taxane could improve response and potentially improve survival compared to induction with cisplatin/5FU. However, none of these trials directly compared induction chemotherapy to the by-then-accepted standard of concurrent cisplatin-based chemoradiation alone. While two of the trials featured concurrent chemoradiation after induction (Hitt *et al.* and TAX 324) [12,14], 12% and 21% of patients, respectively, did not proceed from induction to radiation due to disease progression or toxicity from induction. Thus, while these studies established the TPF regimen as a new standard for induction, it remained unclear as to whether the benefits would outweigh the potential harm caused by reduced compliance to radiotherapy.

Induction as a strategy to reduce distant metastases

Supporting continued investigation were observations of a ‘failure shift’, with regimens that included induction chemotherapy resulting in higher rates of locoregional failure, versus the higher distant metastasis rates seen with concurrent-only chemoradiotherapy. This was especially seen in patients with advanced nodal disease [17]. Arguments were made that correct exploitation of induction chemotherapy might reduce distant failures (as in the MACH-NC meta-analysis) and thus increase survival. Two Phase III trials published in 2014 tested this hypothesis. The Spanish Head and Neck Cancer Group randomized patients to induction with TPF, induction with cisplatin/5FU (PF; before taxane induction results were known), or no induction before cisplatin chemoradiation [18]. Powered for progression-free survival, this trial found no significant advantage to induction versus chemoradiation by intention-to-treat analysis. Disturbingly, and in keeping with prior studies, about 30% of the induction patients did not proceed to chemoradiation, primarily due to hematologic toxicity. In the per-protocol analysis, induction chemotherapy improved the median progression-free survival by 5.2 months, but this only represented 81% of the randomized patients.

In the DeCIDE trial, patients were randomized to induction TPF before chemoradiation with docetaxel, 5FU and hydroxyurea [19]. To maximize the potential effects on distant failure, this trial was limited to patients with nodal stage N2a or greater. However, similar to the Spanish

trial, DeCIDE found no differences in overall survival, although the study was underpowered for this primary end point due to slow accrual and lower-than-expected event rates. However, in this high-risk group, induction chemotherapy did significantly lower the rate of distant metastasis as first failure. There was also a trend toward improved overall survival with induction, in the higher risk subset of nodal stage N2c or greater. However, rates of hematologic toxicity in the induction arm again limited compliance with concurrent treatment, and thus the study was negative for survival differences.

The PARADIGM trial published in 2013 had a slightly different design [20]. Control arm patients received concurrent chemoradiation with cisplatin. The experimental arm started with three cycles of TPF induction, then radiation with weekly carboplatin (thought to be typically better tolerated than cisplatin) if the patient responded to induction, or weekly docetaxel with accelerated radiation if there was no response. Ideally, this design was aimed at shifting treatment intensity (and toxicity) to the higher risk patients, while improving compliance rates among lower risk patients and thus maintaining the benefits of completing concurrent chemoradiation. Notably, there were no substantial differences in completion of concurrent therapy in this trial, although induction TPF was still associated with high rates of toxicity. Similar to DeCIDE, the PARADIGM trial was underpowered due to slow enrollment and lower than expected event rates. There were no significant differences between the arms for survival outcomes. While the distant metastasis rate was lower in the induction arm (7 vs 11%), this was offset by a higher rate of locoregional failures (13% vs 8%), ultimately resulting in no difference in total failure rate between the arms.

Together, these three major Phase III trials (Hitt *et al.*, DeCIDE, and PARADIGM) were not able to establish a survival advantage for TPF induction over standard cisplatin-based concurrent chemoradiation. This was largely explained by treatment-limiting toxicity, or possibly by the use of carboplatin rather than cisplatin in the concurrent component of therapy, such that improvements in distant control were negated by higher rates of locoregional failure. Since radiation therapy is the definitive treatment that drives locoregional control, administration of agents that interfere with radiation compliance and completion are difficult to justify in

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routine practice in the absence of a clear survival benefit. However, important shortcomings in these studies were noted. First, both DeCIDE and PARADIGM were underpowered for their primary end point. This was partially explained by lower-than-expected event rates, perhaps due to the rising incidence of human papillomavirus (HPV)-associated oropharyngeal cancers (OPC) and their predominance in the study populations. HPV-associated OPC is genetically distinct from cancers traditionally associated with tobacco and alcohol and carries a much better prognosis [21]. The importance of HPV as a prognostic factor was not well appreciated when these trials were designed, and patients were not stratified by this biomarker. Second, only DeCIDE limited enrollment to patients at high risk for distant metastasis. A trend for survival benefit was indeed seen in a high-risk subset of this study, but was limited by lack of power.

Induction to select for reduced-intensity radiation-based treatment

While these trials appeared to mark the end of induction, the arrival of EGFR inhibitors revived interest in the induction strategy. EGFR is highly expressed on head and neck squamous cell carcinomas and is quantitatively associated with worse outcomes [22]. In 2006, the US FDA approved the monoclonal EGFR antibody cetuximab for head and neck cancers, based on a randomized trial showing a 20-month median survival advantage in favor of concurrent cetuximab versus radiation alone [23]. Furthermore, 94% of patients in that trial completed all cycles of cetuximab, a much higher completion rate than typically seen with concurrent cisplatin. Although the subsequent multi-institutional trial RTOG 0522 found no advantage in adding cetuximab to chemoradiation with cisplatin [24], the demonstrated effect and tolerability of the drug seemed to hold promise for the management of head and neck cancer.

One potential use was illustrated in the French TREMPIN trial for laryngeal cancer [25]. Patients received TPF induction chemotherapy, and then were randomized to radiation with concurrent cisplatin or cetuximab. The implication was that cetuximab might improve the overall tolerability and completion rate of the chemoradiation phase of treatment and perhaps an advantage in survival might emerge. However, this trial found no differences in larynx preservation, laryngoesophageal dysfunction-free survival, or

overall survival between the two arms, albeit with limited power to exclude any differences. The Spanish Head and Neck Cancer Group recently presented preliminary results from their trial 2007-01, which expanded this same concept to other sites [26]. Patients with unresectable disease (43% of whom had OPC) received TPF induction and were then randomized to cisplatin or cetuximab concurrent to radiation. Designed as a noninferiority trial, this study also found no difference in response rates or locoregional control between arms, although survival results are pending. While neither TREMPIN nor this study included a standard of care comparator, they do offer the useful knowledge that if patients begin treatment with TPF induction (e.g., due to excessive delays beginning radiotherapy), they may receive concurrent cetuximab-radiation if they are unable to tolerate additional cisplatin, without fear of significantly compromising outcomes.

The French GORTEC group also recently presented early results of their trial 2007-02 [27]. Like the DeCIDE study, this trial limited enrollment to patients at high risk for distant metastasis, who in this case had nodal stage N2b or higher (with over 65% of participants having at least stage N2c). The control arm received radiotherapy with concurrent carboplatin/5FU, a standard European regimen. The experimental arm received induction TPF followed by concurrent cetuximab and radiation. After 32 months of median follow-up, there were no differences in progression-free survival, overall survival, or locoregional control. Provocatively, and reminiscent of the DeCIDE results, distant metastasis-free survival was improved and distant metastasis as a first event was significantly reduced in the induction arm. However, acute toxicity with induction was also higher, most strikingly with 17% of patients developing febrile neutropenia and 7% dying during induction chemotherapy. Detailed toxicity results are yet to be published, but these treatment-related mortality rates were substantially higher than the 0–3% seen in other trials using induction TPF [19,20]. This trial reiterated that induction TPF followed by concurrent cetuximab-radiation did not produce any survival benefit, and there were persistent concerns regarding toxicity.

Is there a future for induction chemotherapy?

Current directions of inquiry for induction chemotherapy may be broadly grouped into

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intensification and de-intensification. For intensification, results from the DeCIDE and GORTEC 2007-02 trials suggest that there may still be patients at the very highest risk for metastasis who could benefit from the addition of induction chemotherapy. However, they also indicate that a higher nodal stage, at least according to current staging criteria, may not be sufficient on its own to identify this group. Features such as low neck nodes and matted nodes (a proxy for extranodal extension of disease) are not clearly demarcated by the present American Joint Committee on Cancer staging system but may be more predictive of distant metastatic risk [28]. Protein expression biomarkers of aggressive disease may also identify patients who could benefit from induction taxane chemotherapy [29–31]. Another area open to exploration is oligometastatic disease. Roughly 15% of head and neck cancer patients will present with distant metastases, but a portion of these will have only a few discrete lesions. The increasing sophistication and clinical experience of stereotactic body radiotherapy has made definitive local treatment to these sites a reasonable option [32]. Strategies may emerge combining induction chemotherapy and upfront metastasis-directed treatments prior to locoregional therapy for the primary tumor.

Conversely, induction chemotherapy may play a role in de-intensification of treatment, using induction as a tool to stratify patients by treatment response. This could be especially applicable to good-prognosis HPV-associated OPC. There are two American trials testing induction chemotherapy in this manner which have not yet been completed, OPTIMA HPV (NCT02258659) and the Quarterback Trial (NCT01706939), and one which has just been reported, Eastern Cooperative Oncology Group (ECOG) 1308 (NCT01084083). The ECOG 1308 trial was a single-arm Phase II study in which patients with HPV-associated OPC received induction paclitaxel/cisplatin/cetuximab and cetuximab concurrently with radiation [33]. The radiation was dose-reduced from 69.3 to 54 Gy to the primary site if there was a clinical complete response to induction; involved lymph nodes received 69.3 Gy unless they also were judged to have completely responded. 56 of 80 evaluable patients (70%) achieved a primary-site clinical complete response after induction and 51 patients continued to cetuximab with 54 Gy. At a median follow-up of 35.4 months, the 2-year progression-free survival and overall

survival rates were 80% and 94% among those 51 patients; among patients who received a standard dose of radiation, the rates were 67% and 87%, respectively. The poor outcome for nonresponders may have been confounded by clinical characteristics, which were seemingly as predictive as the response to induction: 2-year progression-free survival was 96% for patients with a history of ten or less pack-years of smoking and less than T4 and N2c stage, versus a rate of 71% for those with T4 or N2c stage or more than ten pack-years of smoking. This is consistent with the multiple recursive-partitioning analysis of RTOG 0129 [21], and it emphasizes that patient selection requires further refinement in order to realize benefits from induction.

Conclusion

As of 2016 induction chemotherapy has no clearly established frontline role in the routine treatment of head and neck carcinomas of the major non-nasopharyngeal sites. Platinum-based concurrent chemoradiation remains the standard option, with the possible exceptions of organ preservation for laryngeal and hypopharyngeal cancers, where induction is at most a reasonable alternative. Evidence from multiple randomized controlled studies indicates that induction before concurrent chemoradiation is not substantially inferior in efficacy, although it is generally more toxic and costly. Thus, outside of a clinical trial the utility of induction chemotherapy is restricted to uniquely pragmatic clinical scenarios where radiation is unavoidably delayed or cannot be tolerated. Some examples are severe pain from advanced disease that renders the radiation setup unstable, or impending airway compromise or neurological dysfunction that necessitates rapid initiation of treatment. EGFR-targeted antibodies are potential substitutes for cisplatin in patients who have completed induction and are proceeding to concurrent chemoradiation. Future areas of study may include intensification of therapy for very high-risk or oligometastatic patients, but selection criteria are not yet optimized. Induction as a strategy for subsequent response-based de-intensification is being explored, especially in HPV-associated disease. However, selection of the ideal candidates for this approach likewise remains undefined. Future novel approaches will likely feature radiographic, proteomic and genomic biomarkers used to define prognostic groups and guide treatment selection with greater precision. Because of its flexibility and

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adaptability, induction will likely continue to be a 'testing site' for new chemotherapeutic, targeted or immunologic agents.

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