Empowering induction therapy for locally advanced head and neck cancer

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Received 24 November 2009; revised 14 April 2010; revised 28 April 2010 & revised 29 April 2010; accepted 30 June 2010

Induction therapy followed by definitive chemoradiotherapy (CRT) has emerged as an option for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck. In this setting, the most studied induction regimen is docetaxel, cisplatin, and 5-fluorouracil (TPF). However, the role of induction therapy remains to be fully validated by studies comparing TPF followed by CRT versus CRT alone. Novel combination regimens that incorporate molecularly targeted agents are increasingly being evaluated in the induction therapy setting. Promising results were shown in phase II trials in which the anti-epidermal growth factor receptor monoclonal antibody cetuximab was added to induction therapy with TPF, docetaxel/cisplatin, or paclitaxel/carboplatin, and in some of these studies, to subsequent CRT. Several issues remain to be addressed, including identifying which patients are most likely to benefit from induction therapy, determining how to optimally incorporate targeted agents into induction therapy and subsequent CRT, and evaluating biomarkers that could be used to select patients for induction therapy containing molecularly targeted agents.

Key words: cetuximab, docetaxel, induction therapy, locally advanced head and neck cancer

introduction

Worldwide, >500 000 individuals are affected annually by head and neck cancer, including malignancies of the oral cavity, pharynx, and larynx, of which the vast majority are squamous cell carcinomas [1]. For the approximately two-thirds of patients who present with locally advanced squamous cell carcinoma of the head and neck (SCCHN), with either significant local extension of primary tumor or regional lymph node involvement, multimodal treatment often involving concurrent chemoradiotherapy (CRT) is required. CRT has been shown to significantly improve overall survival (OS), progression-free survival (PFS), and/or local disease control compared with radiotherapy (RT) alone [2, 3], though the optimal regimen is not yet defined. High-dose cisplatin is widely used as part of CRT, but conclusive phase III studies comparing single-agent cisplatin and combination chemotherapy in this setting are lacking.

Induction (or neoadjuvant) chemotherapy for locally advanced SCCHN has shown high overall responses rates (RRs), including complete responses (CRs) [4]. Most studies comparing induction chemotherapy followed by surgery or RT with definitive local treatment alone did not detect a survival benefit, with the notable exception of two phase III trials that utilized cisplatin plus 5-fluorouracil (5-FU) (PF) [5, 6]. In addition, a European Organisation for Research on Treatment of Cancer (EORTC) study evaluating organ preservation in patients with cancer of the hypopharynx found an OS benefit (the trial was designed to prove equivalence) with induction PF before RT compared with immediate surgery followed by RT [7]. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) study showed that adding induction chemotherapy to locoregional treatment did not produce a significant benefit in OS: the hazard ratio (HR) was 0.96 [95% confidence interval (CI) 0.90–1.02, P = 0.18], with an absolute improvement of 2.4% at 5 years [3]. The HR shifted more in favor of induction when only trials using PF were considered (HR = 0.90, 95% CI 0.82–0.99), a finding consistent with the individual trials mentioned above; however, there was no statistically significant variation among PF, other polychemotherapy regimens, and nonplatinum-containing monotherapy regimens (P = 0.23). In the MACH-NC meta-analysis, concomitant CRT improved both locoregional and distant control, whereas induction chemotherapy improved only distant control, but the effect on distant control was more pronounced than that of concomitant CRT.

Induction regimens incorporating new chemotherapy and targeted drugs have been evaluated in an effort to further improve patient outcome. In addition, insights gained on the role of human papillomavirus (HPV) in etiology and prognosis may contribute to refining the management of this disease.
We review the current data regarding novel induction regimens and their potential impact on the management of SCCCHN.

**taxane-containing induction therapy**

After a series of phase I/II studies [8–10], two pivotal phase III studies evaluated the addition of docetaxel to induction PF (TPF) before definitive RT or CRT (Table 1): (i) the EORTC 24971/TAX323 study, in which induction TPF was administered for four cycles followed by RT alone in patients with unresectable SCCHN, with PFS as primary end point and (ii) the TAX324 trial that evaluated induction TPF for three cycles followed by CRT with weekly carboplatin in patients with either resectable and unresectable SCCHN, with OS as primary end point [11, 12].

In the EORTC study, 358 patients were stratified by primary tumor site and randomized to receive either TPF or PF every 3 weeks for four cycles. The patients without disease progression then received RT starting 4–7 weeks after completing chemotherapy [12]. After a median follow-up of 32.5 months, median PFS was 11.0 months with TPF compared with 8.2 months with PF (HR = 0.72, 95% CI 0.57–0.91; P = 0.007) and median OS was 18.8 versus 14.5 months (HR = 0.73, 95% CI 0.56–0.94; P = 0.02). In the TAX324 trial, 501 patients were stratified by primary tumor site and nodal status and randomized to receive TPF or PF every 3 weeks for three cycles [11]. The TPF regimen in this study included higher cisplatin and 5-FU doses than the EORTC study (see Table 1). After a median follow-up of 42 months, induction TPF more than doubled median OS compared with PF (71 versus 30 months, HR = 0.70, 95% CI 0.54–0.90, P = 0.006), extended median PFS (36 versus 13 months, HR = 0.71, 95% CI 0.56–0.90, P = 0.004), and tended to produce a higher RR (72% versus 64%, P = 0.07) but not higher CR (17% versus 15%, P = 0.66). Adding docetaxel reduced the locoregional failure rate (30% versus 38%, P = 0.04) but did not affect the occurrence of distant metastases (P = 0.14).

A third study of TPF versus PF in patients with laryngeal or hypopharyngeal SCCHN was conducted by the French Head and Neck Oncology Radiotherapy Group with laryngeal preservation as its primary end point [13]. A total of 213 patients were randomized without prior stratification to induction TPF or PF for three cycles and then were evaluated for response 3–5 weeks after completing chemotherapy. Patients who responded to induction therapy were treated with RT or CRT, per study site standard practice; those who did not respond underwent total laryngectomy followed by radiation with or without additional chemotherapy. The 3-year laryngeal preservation rate was increased from 57.5% with PF to 70.3% with TPF (P = 0.03) after a median follow-up of 36 months. There was no difference between TPF and PF in 3-year OS (60% in each arm) and 3-year PFS (58% versus 44%, P = 0.11), although the RR after induction was significantly higher in the TPF arm (80% versus 59%, P = 0.002).

Finally, a fourth phase III randomized trial conducted by the Spanish Head and Neck Cooperative Group investigated the addition of paclitaxel to PF before definitive treatment [14]. In this multicenter phase III trial, 382 treatment-naive patients with locally advanced SCCHN were randomized to receive three cycles of PF alone or in combination with paclitaxel. In both arms, patients proceeded to receive cisplatin-based CRT if they had a major response (>80% in the primary site). At a median follow-up time of 23.2 months, the addition of paclitaxel resulted in greater time to treatment failure (TTF, 20 versus 12 months, P = 0.006) as well as higher RR after induction (80% versus 68%, P = 0.001). The patients receiving induction paclitaxel plus PF tended to have longer median survival (43 versus 37 months, P = 0.06), particularly those with unresectable disease (36 versus 26 months, P = 0.04).

Across all these studies, severe toxic effects have been generally comparable with or without the taxane, although TPF seems to produce higher rates of grade 3/4 neutropenia and febrile neutropenia than PF [11–13]. Nevertheless, in TAX324, the lower rate of prolonged neutropenia with TPF reduced the rate of treatment delays (29% versus 65%, P < 0.001) [11]. Also, there was a trend toward fewer toxic deaths with TPF versus PF in the EORTC study (2.3% versus 5.5%, P = 0.17) [12]. Moreover, induction with a docetaxel or paclitaxel triplet was generally associated with lower rates of severe thrombocytopenia and mucositis compared with PF [11–14]. The toxicity profile for taxane-containing induction seems therefore manageable, with the addition of a third agent enhancing efficacy and allowing the other two drugs to be given at lower better tolerated doses.

Taken together, the results of these four phase III randomized trials have proven the superiority of a triplet, with docetaxel or paclitaxel added to PF, as induction regimen. These observations show the potential impact of induction chemotherapy in improving both locoregional and distant control and the overall outcome of patients with locally advanced SCCHN.

**randomized studies to validate the induction therapy approach**

Conclusive results with induction therapy improving clinical outcomes over contemporary CRT are still needed to establish induction therapy as standard treatment for locally advanced SCCCHN. Four phase III randomized trials, all with induction TPF, are either completed or ongoing. The phase III study conducted by the Spanish Head and Neck Cancer Cooperative Group, not statistically powered to show a difference in OS between treatment arms, has already reported results [15]. A total of 439 patients with unresectable locally advanced SCCHN were randomized to induction TPF or PF for three cycles, followed by CRT, or CRT alone. Compared with CRT alone, the two induction regimens combined significantly improved median TTF, defined as time from randomization to progression, recurrence, surgery, death, withdrawal due to adverse events or no locoregional control (12.5 versus 5.0 months, HR = 0.57, 95% CI 0.45–0.74, P < 0.001) [15]. No formal statistical comparison was made between the TPF and PF arms. OS differences were not statistically significant, though median values were numerically higher in the TPF arm (37.2 months) than in the PF (33.6 months) or CRT arms (27.1 months). Toxicity was a concern and resulted in substantial patient dropout in the induction therapy arms; prophylactic granulocyte colony-stimulating factor (G-CSF) was...
Table 1. Phase III trials of induction TPF versus PF in locally advanced squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Primary end point</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermorken et al. [12]</td>
<td>N = 358; unresectable (100%), oropharynx (46%), T4 (70%), N2–N3 (72%)</td>
<td>TPF(^a) × 4 cycles → RT(^b)</td>
<td>PFS</td>
<td>TPF extended median PFS (11.0 versus 8.2 m, (P = 0.007)) and median OS (18.8 versus 14.5 m, (P = 0.02)) compared with PF. TPF increased RR (68% versus 54%, (P = 0.006)) but not CR rate (8.5% versus 6.6%) after induction. TPF produced more grade 3/4 neutropenia, but fewer toxic deaths and less grade 3/4 thrombocytopenia, stomatitis, and nausea.</td>
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<td></td>
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<td>PF(^c) × 4 cycles → RT(^b)</td>
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<tr>
<td>Posner et al. [11]</td>
<td>N = 501; unresectable (35%), low surgical curability (31%), organ preservation (34%), oropharynx (53%), T4 (43%), N2–N3 (64%)</td>
<td>TPF(^d) × 3 cycles → CRT(^*)</td>
<td>OS</td>
<td>TPF extended median OS (71 versus 30 m, (P = 0.006)) and median PFS (36 versus 13 m, (P = 0.004)) compared with PF. TPF tended to increase RR (72% versus 64%, (P = 0.07)) but not CR rate (17% versus 15%, (P = 0.66)) after induction. TPF produced more grade 3/4 and febrile neutropenia, but fewer treatment delays and less grade 3/4 thrombocytopenia and lethargy.</td>
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<td>PF(^e) × 3 cycles → CRT(^*)</td>
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<tr>
<td>Hitt et al. [14]</td>
<td>N = 439; unresectable (100%), oropharynx (43%), T4 (77%), T4N2–N3 (45%)</td>
<td>TPF(^f) × 3 cycles → CRT(^g)</td>
<td>TTF</td>
<td>Induction TPF and PF increased median TTF compared with CRT alone (13.4 and 12.3 versus 5.0 m; (P &lt; 0.001) for comparison of induction therapy versus CRT). Median OS was numerically higher with TPF (37.2 m) than PF (33.6 m) or CRT alone (27.1 m) ((P = \text{NS})). Higher rates of grade 3/4 neutropenia and mucositis with induction therapy, but only febrile neutropenia higher with TPF than PF.</td>
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<td>PF(^h) × 3 cycles → CRT(^g)</td>
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<tr>
<td>Pointreau et al. [13]</td>
<td>N = 213; larynx or hypopharynx; T4 (15%), N2–N3 (37%)</td>
<td>TPF(^i) × 3 cycles → RT or CRT(^h)</td>
<td>3-year LPR</td>
<td>TPF significantly increased 3-year LPR (70.3% versus 57.5%, (P = 0.03)) but not 3-year OS or PF. TPF increased RR (80% versus 59%) and CR rate (38% versus 29%) after induction ((P = 0.002)). TPF produced more grade 4 neutropenia and febrile thrombocytopenia, and less grade 3/4 thrombocytopenia and stomatitis.</td>
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<tr>
<td></td>
<td></td>
<td>PF(^i) × 3 cycles → RT or CRT(^h)</td>
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</table>

\(^a\)TPF = docetaxel 75 mg/m\(^2\) on day 1, cisplatin 75 mg/m\(^2\) on day 1, and continuous infusion of 5-FU 750 mg/m\(^2\)/day on days 1–5 of a 3-week cycle \([11]\).  
\(^b\)RT was delivered over 7 weeks in a conventional fractionated regimen (66–70 Gy), accelerated regimen (70 Gy), or hyperfractionated regimen (74 Gy) \([11]\).  
\(^c\)PF = cisplatin 100 mg/m\(^2\) on day 1, and continuous infusion of 5-FU 1000 mg/m\(^2\)/day on days 1–5 of a 3-week cycle \([10, 11]\).  
\(^d\)TPF = docetaxel 75 mg/m\(^2\) on day 1, cisplatin 100 mg/m\(^2\) on day 1, and continuous infusion of 5-FU 1000 mg/m\(^2\)/day on days 1–4 of a 3-week cycle \([10]\).  
\(^e\)CRT consisted of weekly carboplatin AUC 1.5 for 7 weeks plus RT to a total dose 70–74 Gy \([10]\).  
\(^f\)CRT consisted of cisplatin 100 mg/m\(^2\) on days 1, 22, and 43 plus RT to a total dose of 66–70 Gy \([14]\).  
\(^h\)Patients who responded to induction therapy received either RT to a total dose of 70 Gy or CRT depending on the practice of the study center \([12]\).  
\(^i\)5-FU, 5-fluorouracil; CR, complete response; CRT, chemoradiotherapy; LPR, laryngeal preservation rate; NS, nonsignificant; OS, overall survival; PFS, progression-free survival; RR, response rate; RT, radiation therapy; TTF, time to treatment failure.
incorporated to treatment to attenuate febrile neutropenia [15]. Investigators carried out their efficacy analysis on a ‘treated patient’ basis instead of the typical ‘intent-to-treat’ basis, imposing a caveat on the interpretation of their results.

DeCIDE (clinicaltrials.gov, NCT00117572) is a phase III trial originally planned to accrue 400 patients. The accrual closed with 285 patients enrolled (the revised target was 280). DeCIDE is evaluating whether induction TPF followed by RT concurrently with docetaxel, 5-FU, and hydroxyurea prolongs OS compared with the same CRT regimen alone in patients with N2 or N3 locally advanced SCCHN. The relevance of this study may be limited because the CRT regimen is not platinum based.

A third phase III randomized trial (‘Paradigm’ study; clinicaltrials.gov, NCT00705068) is evaluating whether TPF plus CRT increases 3-year OS compared with CRT alone in PS 0–1 patients with locally advanced SCCHN. Depending on their response to induction, patients in the experimental arm will receive weekly carboplatin or docetaxel concurrently with radiation for 7 weeks. The patients in the control arm will receive a different CRT regimen, with cisplatin on days 1 and 22 with radiation once or twice daily for 6 weeks. The study was prematurely closed due to slow accrual (total enrollment, 145 patients). The use of different CRT regimens across arms will likely hamper the interpretation of whether induction TPF itself actually extends survival in this study.

Finally, the Gruppo di Studio sui Tumori della Testa e del Collo (GSTTC) conducted a randomized phase II trial of induction TPF followed by CRT (with PF as chemotherapy regimen) or CRT alone. This study randomized 101 patients with unresectable stage III–IV SCCHN to receive either (i) RT with concurrent cisplatin 20 mg/m² days 1–4, plus 5-FU 800 mg/m²/day as a 96-h continuous infusion during weeks 1 and 6 of RT or (ii) three cycles of TPF (docetaxel 75 mg/m² and cisplatin 80 mg/m² on day 1 and 5-FU 800 mg/m²/day as a 96-h infusion, every 3 weeks) followed by the same CRT regimen. CR rates (primary end point) were higher with TPF (50% versus 21.2%, \( P = 0.004 \)) and median PFS and OS were 30.4 and 36.6 months versus 19.7 and 33.3 months in the TPF induction arm and CRT alone arm, respectively [16]. Toxic effects during CRT were not different between the two arms. Based on these promising findings, the GSTTCC is conducting the third of the phase III trials addressing essentially the same question, with patients with stage III/IV SCCHN randomized to receive RT, in this case with concurrent PF or cetuximab preceded, or not, by three cycles of induction TPF.

**Incorporating targeted agents into induction therapy**

The epidermal growth factor receptor (EGFR) is frequently overexpressed in SCCHN and is associated with poor survival [17, 18]. Cetuximab is a recombinant immunoglobulin G1 monoclonal antibody that blocks the extracellular domain of EGFR, thereby preventing ligand binding and activation of receptor-mediated signaling pathways that lead to tumor growth [19]. Cetuximab has shown efficacy in SCCHN, improving OS in combination with platinum-based chemotherapy in patients with untreated recurrent or metastatic SCCHN [20], and combined with RT in patients with locally advanced disease [21]. The concurrent addition of cetuximab to RT plus cisplatin is also under study in a recently completed RTOG phase III trial (RTOG 0522); results are not yet available. We will review clinical results with another promising strategy, the incorporation of cetuximab into induction therapy regimens for locally advanced SCCHN (Table 2).

**Adding cetuximab to TPF**

The feasibility of adding cetuximab to induction TPF in patients with locally advanced SCCHN was shown in a phase I trial conducted at the Dana-Farber Cancer Institute [22]. The primary objective was to determine the maximum tolerated dose of 5-FU combined with docetaxel and cisplatin every 3 weeks plus the standard dose of cetuximab. Of the three 5-FU dose levels explored (750, 850, and 1000 mg/m²), 850 mg/m² daily as a continuous infusion for the first 4 days of each cycle was identified as the maximum tolerated dose. At this dose level, 3/13 patients had a dose-limiting toxicity (mucositis, diarrhea, and febrile neutropenia). An average seven cetuximab doses were delivered of the nine intended. Of the 20 patients with oropharyngeal cancer (71% of the 28 total assessable patients), 65% had HPV-positive tumors; all patients had PS of 0% and 92% stage IV SCCHN. All assessable patients achieved a partial radiographic response after induction and 16/20 patients (80%) who underwent a biopsy of the primary site before starting CRT had a pathological CR. All 28 patients proceeded to receive concurrent CRT per treating institution practice. Survival results were not mature.

Induction TPF plus cetuximab was also evaluated in a phase II trial in patients with unresectable locally advanced-stage IV SCCHN and PS 0–1, with RR as the primary end point [23]. G-CSF was administered prophylactically. After induction, patients received weekly cetuximab plus accelerated RT with a concomitant boost to a total dose of 69.9 Gy. When assessed on an intent-to-treat basis, the RR after four cycles of induction was 78%, and the CR rate improved with the additional cycles (CR rates of 14% and 24%, after two and four cycles, respectively). The most common grade 3/4 events were neutropenia (26%) and febrile neutropenia (24%), with two toxic deaths during induction. Survival results have not yet been reported.

**Adding cetuximab to TP**

The addition of cetuximab to a ‘backbone’ of cisplatin and docetaxel (TP) has been investigated as well. Cetuximab was combined with TP induction (TPE) and subsequent cisplatin-based CRT in a phase II study conducted at the University of Pittsburgh Cancer Institute [24]. Thirty-nine patients with PS 0–1 and previously untreated locally advanced SCCHN or undifferentiated head and neck cancer received three cycles of induction therapy with TPE, with antibiotic prophylaxis, and then standard RT to a dose of 70 Gy concurrently with weekly cisplatin and cetuximab (XPE regimen). Maintenance therapy with weekly cetuximab was continued for up to 6 months. Overall, 36 patients (92%) received three cycles of induction therapy, including 34 patients who received all nine weekly
Table 2. Phase II trials of cetuximab in induction therapy of locally advanced squamous cell carcinoma of the head and neck

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Treatment</th>
<th>Primary end point</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argiris et al. [24]</td>
<td>N = 39; oropharynx (59%), N2–3 (92%), stage IVA–B (92%)</td>
<td>TPE* (3 cycles) → XPEb (7–8 weeks) → cetuximab maintenance (6 months)</td>
<td>RR after induction</td>
<td>RR of 86% after induction and 100% after CRT, including CR rates of 5% and 24%, respectively 2-year PFS and OS: 80% and 88%, respectively Grade 3/4 neutropenia (77%) and febrile neutropenia (10%) during induction; mucositis (51%) and dysphagia (48%) during CRT</td>
</tr>
<tr>
<td>Mesia et al. [23]</td>
<td>N = 50; oropharynx (48%), stage IVA–B (100%), T3–4 (94%), N2–3 (82%)</td>
<td>TPF + cetuximab induction (4 cycles) → accelerated RT + cetuximab (6 weeks)</td>
<td>RR after 2 versus 4 induction cycles</td>
<td>RR of 76% after 2 cycles and 78% after 4 cycles of induction, including CR rates of 14% and 24%, respectively Grade 3/4 neutropenia (26%) and febrile neutropenia (24%) during induction</td>
</tr>
<tr>
<td>Kies et al. [26]</td>
<td>N = 47; oropharynx (89%), T3–4 (30%), N2–3 (98%)</td>
<td>Weekly paclitaxel, carboplatin, and cetuximab induction (6 weeks) → platinum-based CRT or RT based on tumor stage/site</td>
<td>CR rate after induction</td>
<td>RR of 96%, including CR rate of 19% after induction 3-year OS rate: 91%; 3-year PFS rate: 87% Grade 3/4 rash (45%) and neutropenia (21%) during induction</td>
</tr>
<tr>
<td>Wanebo et al. [27]</td>
<td>N = 74; tonsil (33%), T3–4 (61%), N2–3 (66%)</td>
<td>Weekly paclitaxel, carboplatin, and cetuximab induction (6 weeks) → weekly paclitaxel, carboplatin, and cetuximab CRTf (8 weeks) → cetuximab maintenance (6 months)</td>
<td>1-year EFS</td>
<td>Pathological CR in 67% after induction and 98% after CRT Outcome data are immature Grade 3/4 mucositis/stomatitis (32%) and neutropenia (31%)</td>
</tr>
</tbody>
</table>

*TPE = docetaxel 75 mg/m²; cisplatin 75 mg/m² day 1; cetuximab 250 mg/m² day 1, 8, 15 every 3 weeks.
*bXPE = radiotherapy 70 Gy 2 Gy/fraction; cisplatin 30 mg/m²; cetuximab 250 mg/m² weekly.
*TPF = docetaxel 75 mg/m² day 1; cisplatin 75 mg/m² day 1; continuous infusion of 5-fluorouracil 750 mg/m²/day days 1–5 every 3 weeks; cetuximab 250 mg/m² weekly.
*Paclitaxel 135 mg/m²/week; carboplatin AUC 2/week; cetuximab 400 mg/m² first week, then 250 mg/m² weekly.
*Paclitaxel 90 mg/m²/week; carboplatin AUC 2/week; cetuximab 400 mg/m² first week, then 250 mg/m² weekly.
*Paclitaxel 30 mg/m²/week; carboplatin AUC 1/week; cetuximab 250 mg/m² weekly; radiation 50 Gy, 2 Gy/fraction.
*CR, complete response; CRT, chemoradiotherapy; EFS, event-free survival; RR, response rate; RT, radiotherapy.

**doses of cetuximab, 33 patients (85%) then completed XPE per protocol, and 31 patients (79%) received maintenance cetuximab for a median of 5 months. The RR to induction was 86% (using RECIST), including two CRs (5%), whereas all patients who completed CRT had objective responses, including 24% with CR. High CR rates as assessed by [18F]fluorodeoxyglucose–positron emission tomography (PET) were observed in the primary site (59% after TPE and 77% after XPE). The 2-year PFS and OS were 80% and 88%, respectively, after a median follow-up of 16 months. Six patients had disease progression, which was locoregional in five cases. Toxic effects were predictable and manageable: neutropenia (77%) was the most common grade 3/4 toxicity during induction, whereas mucositis (51%), dysphagia (48%), and hypomagnesemia (36%) were the most common during CRT. Severe mucositis was only seen in one patient (3%) and neutropenic fever in 10% of patients during TPE induction therapy [24]. An analysis by HPV status is pending.**

**adding cetuximab to paclitaxel/carboplatin**

Weekly paclitaxel plus carboplatin is an active induction chemotherapy regimen [25]. The feasibility of adding cetuximab to this regimen was shown in a phase II study of 47 patients with locally advanced SCCHN (87% with an oropharyngeal primary) conducted at the MD Anderson Cancer Center [26]. Patients received weekly paclitaxel/carboplatin for 6 weeks in combination with cetuximab and then underwent RT or CRT or surgery based on original tumor stage and site. Patients received cetuximab for a median of six cycles. The most common grade 3/4 toxic effects were rash...
(45%) and neutropenia (21%). The RR was 96% after induction, including a CR rate of 19% overall and a CR rate of 70% in the primary site. At 3 years, OS rate was 91% and PFS rate was 87% [26]. Tumor specimens were available for 26 patients, and 12 of them (50%), all with oropharyngeal primary sites, were HPV positive by in situ hybridization. None of these 12 patients with HPV-positive tumors had disease recurrence.

Cetuximab was also evaluated in combination with induction paclitaxel/carboplatin in E2303, a phase II trial of the Eastern Cooperative Oncology Group [27]. In this study, 74 patients with PS 0–1 and resectable locally advanced SCCHN received weekly paclitaxel/carboplatin plus cetuximab for 6 weeks, and then starting at week 9, radiation (total dose 50 Gy) concurrently with weekly paclitaxel/carboplatin/cetuximab for 5 weeks. The original dose of paclitaxel had to be reduced due to increased toxic effects, mainly neutropenic fever (supportive G-CSF treatment was not allowed). A biopsy of the primary site was done after completion of induction and before starting CRT at week 8, if there was a clinical response, and at week 14 after the first 5 weeks of CRT. The patients with a negative biopsy continued to receive CRT to a total dose of 68–72 Gy, whereas biopsy-positive patients underwent salvage surgery with neck dissection for N1-3 disease. Maintenance cetuximab was then administered to all patients for 6 months. The primary end point is 1-year event-free survival rate, with the pathological RR as a secondary end point. Overall, 66 patients (89%) completed induction therapy. Forty patients underwent biopsy after induction and 31 patients were biopsied after 5 weeks of CRT. All patients with negative biopsies completed the CRT regimen [27]. These findings indicate that induction with cetuximab plus paclitaxel/carboplatin followed by CRT elicits a high rate of pathological CR at the primary site. Mature survival outcomes from these trials as well as an analysis by HPV status are pending.

**ongoing studies of induction therapy involving cetuximab**

Cetuximab is currently being evaluated in additional phase II studies that include an induction arm before definitive treatment (Table 3). Cetuximab is included in the induction arm in two studies, and in definitive treatment following TPF induction in the other three trials. Two studies are randomized phase II comparisons. A study at the Seoul National University Hospital (clinicaltrials.gov, NCT00623558) is exploring whether adding cetuximab to docetaxel/cisplatin induction improves the RR compared with docetaxel/cisplatin alone in patients with unresectable locally advanced SCCHN.

The phase III INTERCEPTOR trial conducted by the Gruppo Oncologico del Nord-Ovest (clinicaltrials.gov, NCT00999700), with an enrollment target of 278 patients, will compare sequential therapy consisting of TPF followed by cetuximab/RT with standard concurrent CRT without prior induction. The primary end point is OS. Finally, an ongoing phase III trial with a planned sample size of 458 patients and OS as primary end point will compare cisplatin-based CRT versus RT plus cetuximab after induction TPF in both arms (clinicaltrials.gov, NCT00716391).

**clinical trials of other targeted therapies in induction**

Information about other targeted therapies in SCCHN is limited due to their less extensive development [28–31]. Among the tyrosine kinase inhibitors, the addition of gefitinib to induction (docetaxel, carboplatin, and 5-FU) and subsequent CRT in a 62-patient, community-based phase II study conducted in the Sarah Cannon Research Consortium did not result in promising efficacy [32], while the combination of lapatinib plus TPF seemed associated to unacceptable renal toxic effects in the EORTC 24051 study [33]. Bevacizumab plus

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**Table 3. Ongoing phase II trials of induction therapy involving cetuximab**

<table>
<thead>
<tr>
<th>Study (main study site)</th>
<th>Patient population</th>
<th>Induction</th>
<th>Definitive treatment</th>
<th>Primary end point</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00623558 (Seoul National University Hospital)</td>
<td>N = 92; PS 0–1; unresectable T4b and/or N2–N3</td>
<td>Docetaxel/cisplatin (3 cycles) ± weekly cetuximab</td>
<td>Not specified</td>
<td>RR</td>
</tr>
<tr>
<td>NCT00736944 (Washington University)</td>
<td>N = 30; PS 0–2; T2–4 and stage III/IVA/IVB</td>
<td>Abraxane, cisplatin, and 5-FU (3 cycles) + weekly cetuximab</td>
<td>Cisplatin-based CRT (or cetuximab + RT for patients who cannot receive CRT)</td>
<td>CR rate at primary tumor site after 2 cycles of induction</td>
</tr>
<tr>
<td>NCT00721513 (Wake Forest)</td>
<td>N = 46; PS 0–1; unresectable stage III/IV or resectable with organ sparing goal</td>
<td>TPF (3 cycles)</td>
<td>Cetuximab (7 weeks) + RT (starting week 2, for 6 weeks)</td>
<td>PFS</td>
</tr>
<tr>
<td>NCT00169247 (Groupe Oncologie Radiotherapie Tete et Cou)</td>
<td>N = 156; PS 0–1; resectable laryngeal or hypopharyngeal SCC</td>
<td>TPF (3 cycles)</td>
<td>Cisplatin-based CRT versus cetuximab + RT in patients responding to induction</td>
<td>Rate of laryngeal preservation</td>
</tr>
<tr>
<td>NCT00599131 (University of Michigan)</td>
<td>N = 106; PS 0–2 resectable SCC of larynx</td>
<td>TPF (1 cycle)</td>
<td>Cetuximab + RT in patients responding to induction</td>
<td>Pathological CR</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; CR, complete response; CRT, chemoradiotherapy; PFS, progression-free survival; PS, performance status; RT, radiotherapy; SCC, squamous cell carcinoma; TPF, docetaxel, cisplatin, and infusional 5-FU.
paclitaxel/carboplatin/5-FU followed by concurrent RT with paclitaxel, bevacizumab, and erlotinib has also been evaluated in a 60-patient phase II study [34]. Preliminary results showed regimen feasibility and promising efficacy, with an RR of 77% after completion of all treatment.

selecting patients for induction therapy

Multidisciplinary evaluation by radiation and medical oncologists should ensure that whichever induction strategy is used will not compromise subsequent definitive therapy, as cumulative toxic effects, such as mucositis or cisplatin-related side-effects, have a major impact on treatment tolerability. As more steps are added to the treatment plan, one of the key concerns is maintaining optimal timing and avoiding delays caused by toxicity or other reasons. Protracted treatment courses with gaps before or during RT administration are known to compromise efficacy [35–37].

Valuable information about the overall feasibility of different approaches to induction therapy has come from a randomized phase II study ('TREMPLIN') conducted by the Groupe d’Oncologie Radiothérapie Tête Et Cou (GORTEC) [38]. This study evaluated RT plus cisplatin versus RT plus cetuximab after three cycles of induction TPF. The study enrolled 153 patients with laryngeal or hypopharyngeal SCCHN, of which 116 were randomized after induction. Fifty-seven percent of patients assigned to CRT could not receive their full planned treatment; that number was 29% for the RT/cetuximab arm. Furthermore, permanent renal failure occurred in nine patients receiving RT plus cisplatin. In terms of efficacy, the 3-month larynx preservation rate (primary end point of the study) was comparable with both approaches, but long-term results have not yet been reported. Optimization of sequential therapy remains an open question, as demonstrated by the different approaches to induction in the design of major phase III trials. The docetaxel trials, TAX 323 and 324, boosted support for induction therapy [11, 12]. However, the definitive local therapy used was either RT alone or carboplatin-based CRT, not cisplatin-based CRT. Furthermore, although the two phase III induction trials conducted in the United States, DeCIDE and Paradigm, have designs that may follow treatment trends present in clinical practice, neither are using standard cisplatin-based CRT. Therefore, even after these studies are completed, the true feasibility and improvement of adding induction to the current cisplatin-based standard of care may remain unclear and still be a lingering caveat.

It is also undetermined which patients may be better candidates for induction. In general, patients who are not likely to tolerate chemotherapy, such as those with PS 2, are not good candidates for induction therapy. The choice to use induction could be made based on extent of anatomical involvement. In an analysis of phase II clinical trials with or without induction preceding CRT, the use of induction appeared to have reduced the risk for distant failure compared with CRT alone [39]. For patients receiving CRT alone, advanced nodal stage (N2c–N3) predicted risk for distant failure and was associated with worse OS, without increasing risk for locoregional failure. These observations would suggest that the effect of induction on distant control may be particularly beneficial for patients with advanced nodal stage disease. With its focus on patients with N2/N3 disease, the phase III DeCIDE trial may shed light on whether sequential therapy particularly benefits those with advanced nodal disease.

molecular biomarkers

Certain molecular biomarkers may help select patients for induction therapy. How these potential markers may be used will depend on whether they are predictive, identifying those likely to benefit from a specific component of therapy, or prognostic, identifying patients with better or worse outcome regardless of treatment received. In the correlative study to the TAX324 trial [40], low expression levels of the marker β-tubulin II were found to be associated with better OS and PFS. This positive effect was more pronounced in patients receiving docetaxel-containing therapy, suggesting that this marker may be both prognostic and predictive.

Ongoing analyses may also identify predictive biomarkers for targeted agents. In the case of cetuximab, selection by EGFR protein expression, which was originally considered a potential biomarker, does not appear to have clinical merit. Expression is nearly universal in SCCHN and no clear correlations have been found in clinical trials in SCCHN or other tumor types [41–43]. In a phase II study of TPE induction, low baseline levels of vascular endothelial growth factor (VEGF) and interleukin (IL) 6 correlated with higher likelihood for CR as assessed by PET after three cycles of induction therapy, though the association with PFS may be less strong [44]. Results from the exploratory correlative study to the trial of carboplatin/paclitaxel/cetuximab induction therapy conducted at the MD Anderson Cancer Center point in similar direction. In this analysis of 32 samples, a signature expression defined by high baseline levels of VEGF and IL-4, IL-6, and PDGF, among other hypoxia-related cytokines, correlated with shorter PFS times [45]. Clearly, the predictive value of biomarkers needs to be validated in larger studies appropriately powered.

The most relevant prognostic biomarker emerging in SCCHN, particularly oropharyngeal cancers, is HPV, representing a distinct disease subset associated with better outcomes. Two large retrospective studies have shown that HPV is an independent prognostic factor in patients with locally advanced SCCHN [46, 47]. The effect of HPV on survival was primarily driven by a marked reduction on the risk for locoregional failure in patients with HPV-positive tumors. Interestingly, however, the favorable prognosis of those with HPV-positive status is negated in heavy smokers, for whom outcomes are more similar to the HPV-negative population [46]. The association of HPV with other biomarkers and the modulation of risk according to various patient and tumor characteristics will require further study. The presence of patients with HPV-positive oropharyngeal tumors in prior SCCHN studies may explain the higher RR observed in oropharyngeal tumors compared with oral cavity tumors [48, 49]; in general, the influence of an unquantified HPV-positive patient subset on many of the results described above remains an open issue. While there is little question that, in clinical trials, stratification according to HPV status is imperative, the implications of these findings for patients treated off protocol are still unclear. Treatment intensification may not be necessary.
for many of these patients because of their favorable prognosis. We do not know yet, however, where to set the potentially less aggressive standards for patients with HPV-positive tumors, which could be a question of interest for future trials. Preliminary data from retrospective observations suggest that chemotherapy should still be part of the treatment of patients with HPV-positive disease (despite their better prognosis), as their outcomes appear to be better with CRT versus RT alone [50].

conclusions and future directions

Induction TPF has produced superior outcomes over PF in locally advanced SCCHN and is considered a standard induction regimen. However, the concept of using induction therapy in this setting is still under validation in phase III trials comparing this approach against definitive CRT alone. Preliminary results from the Spanish study [15] provided some interesting observations but did not definitely answer the question. Three other phase III trials are anticipated to define the value of induction therapy as part of the combined modality treatment of locally advanced SCCHN.

Future studies will further optimize the components of induction therapy regimens. Although 5-FU is an integral part of the TPF regimen, it is commonly associated with mucositis, which overlaps with the toxic effects expected with concomitant CRT, and may delay or impair RT delivery during the course of definitive therapy. An alternative strategy will be to build on a platinum/taxane backbone. Phase II studies have shown that it is feasible to add cetuximab to induction with cisplatin/docetaxel and carboplatin/paclitaxel and to subsequent definitive RT or CRT [23, 24, 26]. These and other ongoing studies with cetuximab illustrate the many possible strategies for incorporating targeted therapy into multimodal treatment of locally advanced SCCHN. Efficacy results with such approaches are very promising and warrant further evaluation in randomized clinical trials.

Another possible strategy may be to use the response to induction therapy for patient selection for the choice of subsequent definitive therapy, surgical or nonsurgical, an approach mainly investigated by the group in the University of Michigan. Promising efficacy results were reported in patients with base of tongue, hypopharyngeal, or laryngeal SCCHN (3-year OS rates of 64%–85%) using the response to only one cycle of PF as a guide to assign patients with chemoresponsive tumors to organ-preserving CRT and patient with less responsive or refractory tumors to immediate salvage surgery [51, 52].

The induction therapy setting provides an excellent opportunity to evaluate blood and tissue biomarkers before and after therapy. Prospective collection and analysis of serum and/or tumor tissue for biomarker study is imperative in clinical trials with induction regimens, as is reporting percentage of HPV positivity in phase II trials or stratifying patients on the basis of HPV status. The patients with HPV-negative SCCHN may be more suitable for treatment intensification with multiagent induction regimens, as they are expected to have worse prognosis. Ongoing and planned clinical investigations will define optimal strategies for combining radiation, surgery, traditional chemotherapy, and molecularly targeted agents into the multimodal treatment of locally advanced SCCHN.

funding

This work was partially supported by Bristol-Myers Squibb.

acknowledgement

The authors acknowledge the assistance of the Clinical Insights Inc. editorial team in manuscript preparation.

disclosure

AA has served as a consultant for Bristol-Myers Squibb and Lilly Oncology and received research support from Bristol-Myers Squibb, Lilly Oncology, Imclone Systems, AstraZeneca, and Genentech.

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