Induction Chemotherapy for Head and Neck Cancer: Will History Repeat Itself?

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Abstract
Locally advanced squamous cell head and neck cancer remains a therapeutic challenge for multidisciplinary teams. Despite high objective response rates, induction chemotherapy has not resulted in tangible benefit in multiple randomized trials. In recent years, as most evidence solidified the role of concurrent chemotherapy and radiation as either primary or postoperative therapy for locally advanced head and neck cancer, induction chemotherapy fell out of scope and practice. The failure of older randomized trials to show a survival benefit from induction chemotherapy can be attributed to several factors. It is possible that the predominance of locoregional failure did not allow any added benefit from better systemic control to translate into a survival advantage. Alternatively, seemingly active chemotherapy regimens may have been suboptimal. Nevertheless, recent developments have altered our perception of head and neck cancer and its treatment. Locoregional control has dramatically improved with concurrent chemoradiotherapy. Of note is that none of the previously conducted randomized trials of induction chemotherapy used concurrent chemoradiotherapy in the control arm. Moreover, we witnessed the development of better combination regimens that improved efficacy in the induction setting. The previously standard cisplatin/5-fluorouracil (5-FU) combination is being replaced by the triple combination of taxane/cisplatin/5-FU. Randomized trials showed that increased activity with the triplet regimen resulted in improved long-term disease control and survival. Finally, cetuximab, an active epidermal growth factor receptor inhibitor, is entering clinical practice and is expected to change the standard of therapy. With the emergence of more efficacious systemic therapies, the role of induction therapy warrants reevaluation. A number of randomized trials are planned or currently ongoing to investigate concurrent chemoradiotherapy with or without induction. These trials are anticipated to redefine the role of induction chemotherapy for head and neck cancer. (JNCI 2005;3:393–403)

Head and neck cancer is diagnosed in about 39,000 persons annually in the United States.1 Locally advanced disease at presentation is common. Traditional treatment involves surgery and/or radiation therapy, which cures a relatively small fraction of patients (40% or less).2 As the responsiveness of squamous cell carcinomas to chemotherapy became apparent, multiple studies of using induction chemotherapy before definitive locoregional therapy were launched. A strong rationale exists for administering chemotherapy up front, including potentially increased drug delivery at the untreated tumor site with an intact vasculature, early eradication of micrometastatic disease, and better tolerability by the patient than in the postoperative or postradiation setting. It seems plausible that chemotherapy will enhance both local and distant control and improve survival or, at a minimum, increase organ preservation rates in resectable tumors. Initial clinical observations led to numerous phase III randomized trials that, when taken together, failed to show a conclusive survival advantage from induction chemotherapy.3,4 Fortunately, significant progress was made in the treatment of head and neck cancer in the past decade. In the 1990s, concurrent chemoradiotherapy emerged as a standard non-surgical therapy of locoregionally advanced head and neck cancer.5 In addition, newer drugs, such as the taxanes, were introduced that increased the activity of chemotherapy combinations. In this new era, the focus has once more shifted to the investigation of induction chemotherapy.

Chemotherapy Regimens
A variety of chemotherapy combinations have been tested as induction therapy for head and neck cancer.

Key Words
Squamous cell cancer, induction chemotherapy, head and neck cancers, systemic cancer therapies, chemoradiotherapy

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Table 1 shows the activity of contemporary platinum-based regimens as derived from a comprehensive review of the literature. The objective response rates achieved after induction chemotherapy are good surrogates of survival outcomes. In recent randomized trials comparing different chemotherapy regimens, better objective response rates after induction translated into improved survival. Cisplatin and 5-fluorouracil (5-FU), a regimen originally developed at Wayne State University, has been the most widely used chemotherapy regimen. Standard doses are considered cisplatin 100 mg/m² on day 1 and 5-FU 1,000 mg/m²/day, as a continuous infusion for 5 days, repeated every 3 weeks. A total of 3 cycles of induction have been used in most studies. Response rates achieved with the cisplatin/5-FU combination range between 54% and 94%, with a mean of 80%. Carboplatin plus paclitaxel is another commonly used induction regimen that achieves overall response rates of 66% to 89% (mean 82%). In addition to the every-3-week schedules of administration, weekly carboplatin and paclitaxel regimens have also been studied, with very promising antitumor activity.

Docetaxel has shown substantial activity as a single agent and in combination regimens in head and neck cancer. The combination of cisplatin and docetaxel has been studied in a number of European clinical trials. The European Organization for Research and Treatment of Cancer (EORTC) studied docetaxel 100 mg/m² followed by cisplatin 75 mg/m², both administered on day 1, repeated every 3 weeks, without prophylactic colony-stimulating factor support in patients with locally advanced, recurrent, or metastatic head and neck cancer. Results were not reported separately for the locally advanced group; in a subgroup of 18 patients with chemotherapy-naïve locally advanced or recurrent head and neck cancer without distant metastasis, the regimen produced an impressive overall response rate of 89%. Mel et al. reported results of a phase II trial of cisplatin/docetaxel in patients with locally advanced unresectable squamous cell head and neck cancer. They noted a response rate of 55% (with 30% complete responses [CRs]) in 37 evaluable patients. Finally, Cruz et al. conducted a phase II randomized trial of docetaxel 85 mg/m² on day 1 plus cisplatin 40 mg/m² on days 1 or 2 or standard cisplatin plus 5-FU (PF), both repeated every 3 weeks to a maximum of 4 cycles, in patients with stage III or IV squamous cell carcinoma of the head and neck. In a preliminary analysis of the first 30 patients enrolled, the activity of the two regimens was comparable. However, their toxicities differed. Docetaxel/cisplatin was associated with a higher rate of grade 3/4 neutropenia, while PF resulted in more frequent severe mucositis and nausea/vomiting.

## Triple Combinations, Platinum-Based

The addition of a taxane to PF has been the subject of intense investigation. Hitt et al. studied a triple combination consisting of paclitaxel 175 mg/m² as a 3-hour infusion on day 1, cisplatin 100 mg/m² on day 2, and 5-FU 500–750 mg/m²/day as a 24-hour continuous infusion on days 2 to 6, repeated every 3 weeks,
for a total of 3 cycles, followed by locoregional therapy. Because of considerable toxicities, the 5-FU dose was reduced from 750 to 500 mg/m²/day during the course of the study. The ORR in 69 evaluable patients was 87%, including 58% CRs. The 5-year time to progression and the 5-year overall survival rates of 56% and 44%, respectively, were encouraging. A phase III trial (also discussed in this article) was subsequently conducted by the same group.

Many groups have studied the addition of docetaxel to PF (TPF), in some cases with leucovorin (TPFL).²¹–²⁶ Locoregional therapy was not consistent among studies. TPF or TPFL was highly active, with overall response rates that ranged between 71 and 100%. The predominant toxicities encountered with TPF were hematologic: grade 3/4 neutropenia was universal (83% to 95% of patients), with febrile neutropenia seen in 16% to 19% of patients; grade 3/4 stomatitis was observed in 17% to 30% of patients.²²,²³ In subsequent phase III trials discussed in this article, dosages in the TPF regimen varied considerably; cisplatin doses ranged between 75 and 100 mg/m² and 5-FU between 3,750 and 4,000 mg/m². Currently, triple combinations with docetaxel (or paclitaxel), cisplatin, and 5-FU are viewed as the emerging chemotherapy standards for induction chemotherapy in head and neck cancer.

Combinations of a platinum (carboplatin or cisplatin) and paclitaxel plus ifosfamide have been evaluated by investigators at The University of Texas M. D. Anderson Cancer Center. Based on encouraging results in recurrent and metastatic head and neck cancer,²⁸,²⁹ Shin et al.³⁰ conducted a phase II trial of carboplatin/paclitaxel/ifosfamide (TIC) as induction therapy in patients with locally advanced head and neck cancer. The induction regimen consisted of paclitaxel 175 mg/m² on day 1, ifosfamide 1000 mg/m² as a 2-hour infusion on days 1 through 3 with mesna, and carboplatin at an area under the curve (AUC) of 6 on day 1, repeated every 3 to 4 weeks. Patients achieving an objective response after the first 2 cycles of induction chemotherapy received 2 additional cycles (i.e., total of 4). Of 52 evaluable patients, 31% had a CR and 50% a partial response (overall response 81%). Five patients (9%) developed neutropenic fever. In another study from the same institution, Khuri et al.³¹ employed paclitaxel/ifosfamide/cisplatin (TIP) as sole therapy for patients with intermediate stage supraglottic or glottic laryngeal cancer. After 3 cycles of chemotherapy, patients achieving less than a complete response proceeded to surgery, whereas patients achieving a pathologic CR received an additional 3 cycles of chemotherapy and local treatment was deferred. Twenty-nine patients were treated on study; CR was achieved in 11 (38%), of whom 9 remain disease-free without locoregional therapy at a median follow-up of 36 months.³² These intriguing results in a highly selected patient population underscore the tremendous therapeutic potential of chemotherapy in head and neck cancer. Although ifosfamide-containing regimens are active, data with platinum/paclitaxel/ifosfamide have been mainly from single-institutional experience. Moreover, the contribution of ifosfamide to the activity of the regimen is difficult to discern.

Randomized Trials Comparing Induction Regimens

PF was considered the reference regimen for induction chemotherapy in head and neck cancer. This notion was confirmed by a meta-analysis by Pignon et al.³³ in which platinum and 5-FU given as induction therapy resulted in superior survival over locoregional therapy alone, albeit marginally, whereas other induction regimens were not as efficacious. Carboplatin/5-FU was compared with PF in a single randomized trial.³⁴ Ninety-six patients with stage IV squamous cell carcinoma of the head and neck were treated with either carboplatin/5-FU or standard PF. PF was superior in terms of objective response rates (92% vs. 76%), which led to survival benefit: the 5-year disease-specific survival (49% vs. 25%, \( P = .03 \)) as well as the 5-year disease-free survival (47% vs. 24%, \( P = .02 \)) favored PF. Therefore, carboplatin/5-FU should be considered an inferior regimen and, thus, the substitution of carboplatin for cisplatin should be generally avoided.

The addition of a taxane, paclitaxel, or docetaxel to PF has been studied in 3 randomized clinical trials, 2 of which have reported results favoring the triple combination³⁵; results of a third trial are pending. A phase III randomized trial conducted by the EORTC randomized 358 patients with unresectable head and neck cancer to receive cisplatin 75 mg/m² on day 1, 5-FU 750 mg/m² continuous infusion for 5 days, and docetaxel 75 mg/m² on day 1, with prophylactic ciprofloxacin; or standard PF (cisplatin 100 mg/m² on day 1, 5-FU 1,000 mg/m² continuous infusion for 5
days). Induction chemotherapy was followed by single-modality radiation therapy (various fractionation schemes allowed) in both arms. TPF was superior to PF in terms of ORR (68% vs. 54%; *P* = .007), progression-free survival (hazard ratio [HR], 0.72; 95% confidence intervals [CI], 0.56–0.91), and overall survival (HR, 0.73; 95% CI, 0.57–0.94). Of particular interest was that the triplet regimen was generally better tolerated. It resulted in lower rates of severe nausea/vomiting and mucositis, which was explained by the use of lower cisplatin and 5-FU doses in this regimen versus standard PF.

A second randomized trial of TPF (TAX 324) used somewhat different doses for cisplatin (100 mg/m²) and 5-FU (1,000 mg/m² as a 4-day infusion). Patients in both arms subsequently received radiation plus weekly carboplatin. Results of this trial are expected in 2006. Finally, a third trial conducted in Spain compared paclitaxel plus PF to PF alone as induction therapy. This randomized trial, which followed favorable phase II results, compared standard PF with PF (using a dose of 5-FU of 500 mg/m²/day) plus paclitaxel 175 mg/m². Preliminary results favored the triple combination in terms of complete response rates and survival; updated results of this study are awaited. In conclusion, results from two phase III trials indicate that the combination of PF plus a taxane is superior to PF and can be considered as the emerging reference regimen for induction chemotherapy for head and neck cancer.

**Randomized Trials of Locoregional Treatment With or Without Induction Chemotherapy**

Multiple phase III randomized trials that used locoregional therapy as a control standard—surgery or radiation therapy—failed to show that the addition of induction chemotherapy to locoregional treatment produces a survival advantage. This was despite an often observed decreased rate of distant metastasis. Locoregional control was usually poor, regardless of treatment employed, and determined the fate of patients with locally advanced disease. Selected large phase III trials that used platinum/5-FU as the induction regimen are reviewed in Table 2. However, no randomized study has yet evaluated the addition of induction chemotherapy to locoregional therapy that consisted of concurrent chemoradiotherapy. Table 3 shows toxicities with induction chemotherapy in Phase III clinical trials.

The GETTEC group, led by Domenge et al., has published the only positive phase III trial of induction chemotherapy. This was a site-specific trial conducted in France that enrolled 318 patients with locally advanced oropharyngeal cancer. The study was stopped because of slow accrual. With a median follow-up of 5 years, disease-free survival was higher in the induction chemotherapy arm, but the difference did not reach statistical significance (*P* = .11). However, overall survival was superior with induction chemotherapy: the median survival was 5.1 years in the chemotherapy group versus 3.3 years in the control group (*P* = .03).

Another study, conducted in Italy by Paccagnella et al., investigated locoregional treatment with or without induction chemotherapy with 4 cycles of cisplatin/5-FU. Tumor resectability was evaluated before randomization. Locoregional treatment was surgery for patients with resectable tumors and radiation for patients with unresectable tumors. A total of 237 eligible patients with primaries in the hypopharynx, oropharynx, oral cavity, or paranasal sinuses were enrolled, 66 of whom had resectable tumors and 171 unresectable. Although a statistically significant decrease was seen in the incidence of distant metastasis, locoregional control, disease-free survival, and overall survival rates (29% for the induction arm versus 20% in the control arm at 3 years; *P* = .21) were similar in the two treatment arms. However, in the subset of patients with unresectable tumors, a significant improvement in disease-free survival, locoregional and distant control, and overall survival (24% vs. 10% at 3 years; *P* = .04) was found.

Lewin et al. reported results of a randomized phase III trial of induction PF in patients with oral cavity, oropharyngeal, hypopharyngeal, and laryngeal primary tumors. All but the 67 patients with oral cavity tumors had unresectable disease. Locoregional therapy consisted of radiation therapy, which was followed by surgery in selected patients. Survival outcomes were comparable in the two treatment groups. Dalley et al. reported results of a randomized trial of locoregional therapy with or without PF that enrolled 280 patients with head and neck cancer. At a median follow-up of 58 months, nonsignificant improvement in overall survival was achieved with chemotherapy (median overall survival, 33.7 months for the
Depondt et al. reported results of a French randomized trial in which the induction chemotherapy consisted of 3 cycles of carboplatin and 5-FU. Locoregional failure was more frequent in the induction chemotherapy arm (35% vs. 25%; \( P = .04 \)), but distant failure was comparable (14% vs. 19%). No significant differences were seen in event-free and overall survival between the two arms. Finally, a more recent, site-specific study enrolled 195 evaluable patients with locally advanced oral cavity tumors. PF induction resulted in an objective response rate of 82%. Segmental mandibulectomy was less frequently performed in the chemotherapy arm (31% vs. 52%), but survival outcomes were identical.

Pignon et al. conducted a meta-analysis of 63 randomized trials that included more than 10,000 patients and studied locoregional therapy with or without chemotherapy for head and neck cancer. Three categories of trials with regards to the timing of chemotherapy were examined: neoadjuvant (induction), concomitant with radiation, and adjuvant. In the adjuvant setting, chemotherapy showed no significant effect on survival. However, a small but statistically significant improvement in survival was observed with induction platinum and 5-FU (HR, 0.88; 95% CI, 0.77 to 0.96).

### Table 2: Selected Randomized Trials of Platinum-Based Induction Chemotherapy Added to Locoregional Treatment

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>N of patients</th>
<th>Primary sites</th>
<th>Induction regimen (number of cycles)</th>
<th>Locoregional therapy</th>
<th>OS vs. control</th>
<th>DFS vs. control</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Licitra et al.</td>
<td>2003</td>
<td>195</td>
<td>OC</td>
<td>PF × 3</td>
<td>S + RT*</td>
<td>55% vs. 55% at 5 years ( P = .50 )</td>
<td>57% vs. 46% at 5 years ( P = .77 )</td>
<td>Less extensive surgery with chemotherapy</td>
</tr>
<tr>
<td>Domenge et al.</td>
<td>2000</td>
<td>318</td>
<td>OP</td>
<td>PF × 3</td>
<td>S + RT or RT</td>
<td>Median 5.1 vs. 3.3 years ( P = .03 )</td>
<td>( P = .11 )</td>
<td>No difference in locoregional or distant control</td>
</tr>
<tr>
<td>Lewin et al.</td>
<td>1997</td>
<td>461</td>
<td>OC, OP, HP, L</td>
<td>PF × 3</td>
<td>RT</td>
<td>( P = .59 )</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Dalley et al.</td>
<td>1995</td>
<td>280</td>
<td>All</td>
<td>PF × 3</td>
<td>S and/or RT</td>
<td>60% vs. 53% at 2 years ( P = .54 )</td>
<td>Median 24.7 vs. 20.6 months NS</td>
<td></td>
</tr>
<tr>
<td>Paccagnella et al.</td>
<td>1994</td>
<td>237</td>
<td>OC, OP, HP, PS</td>
<td>PF × 4</td>
<td>S + RT (resectable) RT (unresectable)</td>
<td>29% vs. 20% at 3 years ( P = .21 )</td>
<td>37% vs. 33% at 3 years ( P = 0.22 )</td>
<td>Distant control better with chemotherapy in unresectable group, OS better with chemotherapy</td>
</tr>
<tr>
<td>Depondt et al.</td>
<td>1993</td>
<td>300</td>
<td>OC, OP, HP, L</td>
<td>CbF × 3</td>
<td>S and/or RT</td>
<td>56% vs. 46% at 4 years NS</td>
<td>33% vs. 30% at 4 years NS</td>
<td>Locoregional control worse with chemotherapy</td>
</tr>
</tbody>
</table>

Abbreviations: PF, cisplatin and 5-FU; CbF, carboplatin and 5-FU; S, surgery; RT, radiation therapy; NS, nonsignificant; NR, not reported; OS, overall survival; DFS, disease-free survival; OC, oral cavity; HP, hypopharynx; OP, oropharynx; PS, paranasal sinuses; L, larynx.

*Postoperative radiation for high risk patients only
Nevertheless, concomitant chemoradiotherapy resulted in a clinically meaningful survival benefit of 8% at 5 years (HR, 0.81; 95% CI, 0.76–0.88). In addition, Pignon et al. analyzed 6 trials that compared induction chemotherapy followed by single-modality radiation therapy with concomitant or alternating chemoradiotherapy, for example, as in the studies by Taylor et al. and Adelstein et al. The hazard ratio (0.91, with 95% CI of 0.79–1.06) was in favor of concomitant or alternating chemoradiotherapy but did not reach statistical significance. Furthermore, sequencing induction and single-modality radiotherapy was proved inferior for organ preservation compared with concomitant therapy. This was shown in a randomized phase III trial in laryngeal cancer. Therefore, concurrent chemoradiotherapy has emerged as a standard for treatment of locally advanced head and neck cancer. Results may be further improved by the addition of induction chemotherapy to concurrent chemoradiotherapy.

### Current Treatment Approaches and the Potential Role of Induction Chemotherapy

Chemotherapy has an established role in the curative therapy of head and neck cancer. Site-specific randomized trials in nasopharyngeal and oropharyngeal cancers as well as a study in unresectable disease showed a survival advantage with concomitant chemotherapy and radiation versus radiation alone, whereas in laryngeal cancer, concurrent chemoradiotherapy resulted in a higher rate of organ preservation. In the postoperative setting, radiation plus cisplatin was superior to radiation alone. Despite these advances and the wide acceptance of concurrent chemoradiotherapy, patient outcomes remain suboptimal.

Two major therapeutic developments strongly support the reevaluation of induction chemotherapy for head and neck cancer. First, locoregional control has significantly improved in the era of chemoradiotherapy. In a number of randomized trials, the survival benefit derived from the addition of concurrent chemotherapy to radiation was predominantly a result of improved locoregional control. Many groups have reported high rates of locoregional control that approach 90% using intensive chemoradiotherapy regimens. In that setting, distant failure was predominant, surpassing locoregional failure. Therefore, eradication of micrometastases with effective systemic therapy becomes critical. Second, newer triplet chemotherapy regimens are more efficacious than the previously standard PF, as has been documented in randomized comparisons. With systemic disease being increasingly important and the development of better chemotherapies, the rationale for the incorporation of induction chemotherapy is appealing.
Laryngeal and Hypopharyngeal Cancers
The avoidance of laryngectomy is the best example of an organ preservation goal. Three randomized trials that included about 600 patients with locally advanced but resectable laryngeal or hypopharyngeal squamous cell carcinoma compared induction chemotherapy followed by radiation therapy with surgery that included laryngectomy followed by radiation therapy. A meta-analysis showed a non-significant trend toward worse local control (12% vs. 25%) and overall survival (39% vs. 45% at 5 years) with the non-surgical approach. Significant heterogeneity was seen among the 3 trials. In addition, one trial included a small sample size of less than 70. These factors limit the interpretation of the results.

Certain patient groups, such as those with large-volume T4 tumors, have a substantial risk for failure when treated with sequential chemotherapy and radiation. In the VA laryngeal study, patients with bulky T4 tumors treated with induction chemotherapy followed by radiation required salvage laryngectomy in 56% of cases versus 29% when the tumors were smaller. Based on this observation, a subsequent randomized trial in laryngeal cancer (RTOG 91-11) excluded bulky laryngeal tumors with cartilage invasion or invasion greater than 1 cm into the base of tongue. Moreover, in the EORTC hypopharyngeal study only 5% of patients had T4 disease. Therefore, there are currently insufficient data on laryngeal preservation for resectable but bulky stage T4 tumors of the larynx or hypopharynx. The previously referenced RTOG 91-11 study was a 3-arm phase III randomized trial in laryngeal cancer that contained no surgical arm. It enrolled 547 patients with stage III/IV laryngeal cancer, excluding large-volume T4 tumors, as mentioned. The 3 treatment arms were: (1) the laryngeal preservation strategy used in the VA laryngeal study (cisplatin and 5-FU for 3 cycles followed by radiotherapy for responders); (2) radiation plus concurrent cisplatin administered every 3 weeks for 3 cycles; and (3) radiation alone. Locoregional control and laryngeal preservation rates were improved with concurrent chemoradiotherapy versus either radiation alone or sequential therapy. No overall survival differences were found among the three arms, probably reflecting the benefit from salvage surgery in this group of patients. Therefore, concurrent chemoradiotherapy emerged as the optimal strategy to achieve laryngeal preservation. Whether the addition of induction chemotherapy further improves outcomes warrants evaluation in future randomized trials.

Unresectable Head and Neck Cancer
For locally advanced, unresectable head and neck squamous cell carcinoma, concurrent chemoradiotherapy emerged as standard therapy after the results of a three-arm randomized phase III trial conducted by the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG). The treatment arms were: (1) conventional radiotherapy alone; (2) conventional radiotherapy plus single-agent cisplatin; and (3) split course radiotherapy with concurrent cisplatin and 5-FU. This trial enrolled 295 patients with unresectable squamous cell head and neck cancer, before closing because of slow accrual. At 3 years, overall survival was 23% in arm 1, compared with 37% in arm 2 (P = .014), and 27% for arm 3 (P > .05).

ECOG is currently conducting a phase II trial of concurrent cisplatin and cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, along with conventional fractionation radiotherapy in patients with unresectable tumors (E3303). Cetuximab is anticipated to receive FDA approval in the United States for use in conjunction with radiation therapy for head and neck cancer on the basis of the improvement in locoregional control and overall survival shown in a phase III randomized trial that compared radiation plus cetuximab with radiation alone for the treatment of patients with stage III/IV head and neck cancer. Cetuximab-based chemoradiotherapy may evolve into the new standard for the combined modality therapy of unresectable head and neck cancer.

Current Randomized Trials of Induction Chemotherapy
A number of studies have shown the feasibility of platinum-based induction chemotherapy followed by radiation plus concurrent chemotherapy (Table 4). Currently, 3 randomized trials of induction chemotherapy are either ongoing or planned (Table 5). In all 3 studies, the control treatment arm is concurrent chemoradiotherapy, induction chemotherapy is a variant of the TPF regimen, and primary endpoint is overall survival. Study populations and
choice of agents in the concurrent part of the treatment differ considerably though. The group from the University of Chicago is conducting a phase III randomized trial in patients with N2 or N3 disease who are at high risk for distant metastasis. Concurrent chemoradiotherapy in both arms consists of hyperfractionated radiotherapy plus docetaxel, hydroxyurea, and 5-FU, 1 week on and 1 week off.

Table 4  Selected Trials of Induction Chemotherapy Followed by Concurrent Chemoradiotherapy in Head and Neck Cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of publication</th>
<th>Patient population</th>
<th>N of evaluable patients</th>
<th>Induction regimen</th>
<th>ORR (%)</th>
<th>Concurrent chemoradiotherapy regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urba et al.</td>
<td>2005</td>
<td>Resectable BOT or HP</td>
<td>59</td>
<td>Cisplatin 100 d1 5-FU CI 1000 d1-5 x 2 cycles</td>
<td>78</td>
<td>Cisplatin Conventional fractionation</td>
</tr>
<tr>
<td>Haraf et al./Vokes et al.</td>
<td>2003</td>
<td>OC, OP, L, HP, NP, U, O</td>
<td>64/69</td>
<td>Pt 135 Cb AUC 2 Weekly 6/8 w x 1 cycle</td>
<td>82/87</td>
<td>Paclitaxel/5-FU/hydroxyurea Hyperfractionated radiation Week on, week off</td>
</tr>
<tr>
<td>Hitt et al.</td>
<td>2003</td>
<td>OC, OP, HP, L</td>
<td>387</td>
<td>Cisplatin 100 d2 5-FU CI 500 d1-5 Paclitaxel 175 d1 vs. PF</td>
<td>80 vs. 68</td>
<td>Cisplatin d1,2,2,43 Conventional fractionation</td>
</tr>
<tr>
<td>Cmelak et al.</td>
<td>2003</td>
<td>Resectable base of tongue, L</td>
<td>42</td>
<td>Pt 175 d1 Cb 6-7.5 d1 Q 21 d x 3 cycles</td>
<td>89</td>
<td>Carboplatin/ paclitaxel weekly Conventional fractionation</td>
</tr>
<tr>
<td>Hainsworth et al.</td>
<td>2002</td>
<td>OC,OP,HP,L,NP,S, U</td>
<td>123</td>
<td>Carboplatin AUC 6 Paclitaxel 200 d1 5-FU 225 CI d1-43 x 1 cycle</td>
<td>70</td>
<td>Carboplatin/ paclitaxel weekly Conventional fractionation</td>
</tr>
<tr>
<td>Machtay et al.</td>
<td>2002</td>
<td>Resectable OP</td>
<td>53</td>
<td>Pt 200 d1 Cb 6 d 1 Q 21 d x 2 cycles</td>
<td>89</td>
<td>Paclitaxel weekly Conventional fractionation</td>
</tr>
</tbody>
</table>

Doses are in mg/m². Paclitaxel doses are in mg/m²; carboplatin dose is in AUC.

Abbreviations: Pt, paclitaxel; Cb, carboplatin; d, day; w, week; PF, cisplatin/5-FU; ORR, overall response rate; OC, oral cavity; OP, oropharynx; BOT, base of tongue; HP, hypopharynx; L, larynx; NP, nasopharynx; N, nasal cavity; S, sinuses; U, unknown; O, other.

Table 5  Planned or Ongoing Randomized Trials of Induction Chemotherapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Eligibility</th>
<th>Induction regimen</th>
<th>Chemoradiotherapy</th>
<th>Endpoint/ sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td>Resectable oropharyngeal only</td>
<td>TPF x 3</td>
<td>Conventional radiation plus cisplatin</td>
<td>Survival/ n = 398</td>
</tr>
<tr>
<td>Dana-Farber Cancer Institute</td>
<td>Stage III/IV (oral cavity, oropharynx, hypopharynx,larynx)</td>
<td>TPF x 3</td>
<td>CONTROL ARM: Accelerated fractionation plus cisplatin INDUCTION ARM: radiation plus weekly carboplatin, if CR to induction; radiation plus docetaxel, if less than CR</td>
<td>Survival/ n = 300</td>
</tr>
<tr>
<td>University of Chicago</td>
<td>N2-N3 All sites</td>
<td>TPF x 2</td>
<td>Docetaxel, hydroxyurea, 5-FU, hyperfractionated radiation (week on, week off)</td>
<td>Survival/ n = 400</td>
</tr>
</tbody>
</table>

Abbreviations: T, docetaxel; P, cisplatin; F, 5-FU; CR, complete response; SWOG, Southwest Oncology Group.
off. Posner and colleagues from Dana-Farber Cancer Institute and collaborating institutions followed a different approach and customized the concurrent regimen to the response obtained after induction with TPF: conventional radiotherapy plus weekly carboplatin for patients with CR or accelerated boost radiotherapy plus docetaxel for patients with stable disease or partial response (the Paradigm Trial). The concurrent chemoradiotherapy alone treatment arm is accelerated boost radiotherapy plus cisplatin.

Finally, SWOG is planning a study in locally advanced resectable oropharyngeal cancer using standard cisplatin and radiation as concurrent chemoradiotherapy (Fig. 1). Other randomized studies in other groups of patients are under consideration. Patients with unresectable tumors who are at high risk for failure and in whom surgical salvage may not mask a positive effect of chemotherapy are an appropriate study population for trying to show a survival advantage with the addition of induction chemotherapy. The future will tell whether the selection of patients and therapeutic agents was the best to definitely answer the scientific question at hand.

Conclusions

Despite the introduction of concurrent chemoradiotherapy as an effective method of combining radiation and chemotherapy, patient outcome is far from optimal. The evidence reviewed indicates that revisiting the role of induction chemotherapy in head and neck cancer is a worthy goal of investigation. Randomized trials of chemoradiotherapy with or without induction chemotherapy are currently ongoing or planned, with various study designs. A second verdict on induction chemotherapy for head and neck cancer is expected to be reached by the end of this decade.

References


