Paradigm Shift in the Treatment of Head and Neck Cancer: The Role of Neoadjuvant Chemotherapy

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Key Words. Head and neck cancer • Chemotherapy • Neoadjuvant • Docetaxel • Paclitaxel

Learning Objectives
After completing this course, the reader will be able to:
1. Explain the need for chemotherapeutic treatment for patients with squamous cell carcinoma of the head and neck.
2. Identify the role of neoadjuvant chemotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck.
3. Discuss results of randomized trials evaluating taxane-based neoadjuvant chemotherapy for patients with unresectable locally advanced squamous cell carcinoma of the head and neck.

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Abstract
Chemotherapy is an integral component of the management of patients with locally advanced head and neck cancer, though the optimal use of chemotherapy remains to be defined. The combination of a platinum agent and 5-fluorouracil has been used as the standard neoadjuvant treatment and has been shown to permit organ preservation in operable patients and improve long-term survival outcomes in operable and inoperable patients. Recently, the addition of a taxane, docetaxel or paclitaxel, to standard platinum plus 5-fluorouracil induction chemotherapy has been shown to further improve response rates and survival outcomes. Phase III data are emerging to support combinations of docetaxel or paclitaxel with a platinum plus 5-fluorouracil as a new, more effective and less toxic standard for neoadjuvant chemotherapy. Sequential treatment regimens, incorporating a combination of induction chemotherapy and chemoradiation, are also under study in efforts to further improve long-term survival outcomes. Induction regimens incorporating docetaxel or paclitaxel with a platinum plus 5-fluorouracil are under evaluation in this setting. Randomized trials comparing a sequential treatment approach with standard therapies are also being undertaken and will likely define a new treatment paradigm for patients with locally advanced head and neck cancer. The Oncologist 2005;10 (suppl 3):11–19

Introduction
The majority of patients with head and neck cancer present with locally advanced disease. While head and neck cancer, particularly early stage disease, is potentially curable with standard treatments of surgery and radiation, long-term disease-free and overall survival rates for patients with advanced disease are poor. Approximately 50%–60% of patients have local disease recurrence within 2 years, and 20%–30% of patients develop metastatic disease [1, 2]. In

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addition, a substantial proportion of patients endure significant functional and aesthetic consequences following definitive surgical management. In an effort to improve outcomes, chemotherapy has been integrated into a combined modality approach involving surgery and/or radiation therapy for locally advanced head and neck cancer. Effective strategies have incorporated chemotherapy as neoadjuvant (induction) therapy, delivered prior to definitive locoregional treatment, or concurrently with radiation therapy (chemoradiotherapy). Data from randomized trials have confirmed that the addition of chemotherapy to curative treatment improves clinical outcomes in patients with advanced disease, demonstrating significant benefits in terms of organ preservation [3–5], longer time to disease progression [3–11], better locoregional control [11], fewer distant metastases [5, 6], and longer overall survival times [6–12].

The optimal method of integrating chemotherapy into combined modality treatment remains an ongoing subject of debate and clinical study. Several meta-analyses evaluating clinical benefit with chemotherapy in head and neck cancer have suggested that concurrent chemoradiotherapy provides greater benefit than neoadjuvant chemotherapy followed by locoregional treatment [13–16]. However, subset analyses of platinum–5-fluorouracil chemotherapy regimens support a role for induction therapy [15, 17]. The largest and most detailed of these meta-analyses, performed by the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) Collaborative Group, evaluated data from more than 10,000 patients enrolled in 63 clinical trials. In that analysis, concomitant chemoradiotherapy was associated with an absolute survival benefit of 8% at 5 years (p < .0001), while the survival benefit with neoadjuvant chemotherapy, 2% at 5 years, was not significant [15]. A recent update of this analysis incorporated data from 24 additional studies, most of them chemoradiotherapy studies, bringing the total patient number to over 16,000. The update confirmed a survival benefit of 5% at 5 years with the addition of chemotherapy (p < .0001) and also significantly favored the use of concomitant chemoradiotherapy, 8% survival benefit at 5 years (p ≤ .0001) [16]. However, in these analyses, response to chemotherapy was not taken into account, and the modest benefit of neoadjuvant chemotherapy on survival could be partially attributed to the inclusion of suboptimal chemotherapy regimens with limited activity. In addition, induction regimens are complicated, and timing is more important for radiotherapy and surgery than for chemoradiotherapy regimens. The combination of cisplatin (Platinol®; Bristol-Myers Squibb, Princeton, NJ, http://www.bms.com) and 5-fluorouracil (PF) has established activity in head and neck cancer and is considered a standard induction regimen [3, 4, 6, 7, 8, 18]. Within the original MACH-NC meta-analysis, an overall evaluation of types of chemotherapy found PF chemotherapy to be associated with an overall 16% lower risk for death [15]. In a subset analysis including only PF induction regimens, there was a significant 5% absolute survival benefit at 5 years (p < .01), which underestimated the effect resulting from the inclusion of patients who underwent inappropriately timed surgical interventions or therapy containing carboplatin (Paraplatin®; Bristol-Myers Squibb) [17].

Chemotherapy, either induction therapy or concurrent chemoradiotherapy, is now routinely integrated into the treatment of patients with locally advanced head and neck cancer. For induction therapy, the PF regimen remains a standard, though results of recent studies evaluating the addition of a taxane to PF induction therapy may change this standard of care. In addition, sequential treatment approaches, involving the use of both induction chemotherapy and chemoradiotherapy, may further improve the clinical benefit of chemotherapy in patients with locally advanced head and neck cancer. Sequential treatment approaches are currently being evaluated in several large, randomized trials. This article reviews the current developments in neoadjuvant chemotherapy and discusses early results from randomized studies that are defining the optimal use of chemotherapy for patients with locally advanced head and neck cancer.

**Neoadjuvant Chemotherapy**

Induction chemotherapy with PF (cisplatin, 100 mg/m² on day 1 and 5-fluorouracil, 1,000 mg/m² by continuous infusion on days 1–5) has become a standard regimen for patients with locally advanced head and neck cancer, producing overall response rates of 60%–90%, with complete responses in up to 50% of patients [17, 18]. In patients with intermediate or advanced tumors of the larynx and hypopharynx, induction PF chemotherapy has been effectively used in place of surgery, allowing organ preservation in a large proportion of patients without compromising survival [3, 4]. In patients with more advanced or unresectable head and neck tumors, the use of induction PF chemotherapy has been associated with direct long-term survival benefits [6–8]. Benefit with respect to organ preservation with PF induction chemotherapy was demonstrated in two large, randomized trials. In a phase III randomized trial conducted by the Veterans Affairs Laryngeal Cancer Study Group, patients with previously untreated advanced laryngeal cancer were randomized to receive either induction PF chemotherapy and radiation or surgery and radiation therapy [3]. Laryngeal preservation was achieved in 64% of patients in the chemotherapy arm, and fewer distant metastases occurred in these patients. Overall survival rates for
the two groups were similar, suggesting that chemotherapy could be used effectively for organ preservation without compromising overall survival.

The second randomized phase III trial, conducted by the European Organization for Research and Treatment of Cancer (EORTC), evaluated PF induction chemotherapy with definitive radiation versus standard surgery and radiation in patients with operable pyriform sinus cancer [4]. With induction chemotherapy, preservation of the larynx was possible in 42% of patients. In addition, chemotherapy was associated with fewer failures at distant sites, though overall survival rates between the two study arms were not different.

More recently, the three-arm Intergroup 91-11 study compared induction chemotherapy, concurrent chemoradiotherapy, and radiation therapy alone in patients with operable, intermediate-stage laryngeal cancer [5]. The rate of laryngeal preservation was highest with concurrent chemoradiotherapy, followed by induction chemotherapy and then radiation alone; however, overall survival rates were similar for all three groups. Local disease control was better with chemoradiotherapy, and both arms involving chemotherapy had better control of distant disease and better overall disease-free survival than radiation alone.

In patients with more advanced or unresectable tumors, PF induction chemotherapy has been associated with long-term survival benefits. In a phase III trial conducted by the Italian Gruppo di Studio sui Tumori della Testa e del Colla, patients with advanced squamous cell head and neck cancer were randomized to receive either PF induction chemotherapy followed by locoregional treatment or locoregional treatment alone [6]. In patients with operable tumors, the development of distant disease was lower with chemotherapy, but there were no differences in overall survival between treatment arms. However, in patients with inoperable tumors, induction chemotherapy led to better local and distant disease control as well as overall survival. With long-term follow-up, overall survival times in the subset of inoperable patients receiving chemotherapy were 21% at 5 years and 16% at 10 years, compared with 5- and 10-year survival rates of 8% and 6%, respectively, in patients not receiving chemotherapy ($p = .04$) [7].

Survival benefits in both resectable and unresectable patients with PF induction chemotherapy were observed in a randomized phase III trial conducted by the French Groupe d’Etude des Tumors de la Tete et du Cou (GETTEC). The median overall survival time in patients with advanced oropharyngeal cancer receiving induction PF chemotherapy followed by locoregional therapy was 5.1 years, compared with 3.3 years for patients who did not receive chemotherapy ($p = .03$) [8].

These modern studies clearly demonstrate that PF induction chemotherapy can contribute substantial clinical benefit to the management of patients with locally advanced head and neck cancer. However, there remains considerable room for improvement, particularly in terms of long-term survival outcomes. The taxanes docetaxel (Taxotere®; Aventis Pharmaceuticals Inc., Bridgewater, NJ, http://www.aventispharma-us.com) and paclitaxel (Taxol®; Bristol-Myers Squibb) are active in squamous cell head and neck cancer. Several phase II studies have indicated that adding a taxane improves responsiveness to PF-based induction chemotherapy. More recently, preliminary results of a randomized phase III trial comparing induction chemotherapy using docetaxel and PF with PF alone indicate that incorporation of a taxane substantially improves clinical response and survival in locally advanced head and neck cancer.

The clinical activity and safety of single-agent docetaxel have been established in several phase II studies in patients with advanced or recurrent head and neck cancer [19–21]. Overall response rates were in the range of 21%–42%, and grade 3–4 neutropenia predictably was the most common toxicity. In patients with locally advanced head and neck cancer, the addition of docetaxel to PF-based induction therapy has resulted in consistently high overall response rates, in the range of 71%–100%, and very encouraging long-term survival rates (Table 1) [22–30].

Investigators at the Dana Farber Cancer Institute have conducted a series of four phase II studies evaluating the addition of docetaxel to PF-based chemotherapy [22–26]. Those trials were built, in part, on their institutional experience using the combination of cisplatin, 5-fluorouracil, and leucovorin as induction therapy for head and neck cancer [31–33]. Consistently high complete (42%–61%) and overall (93%–100%) response rates were reported in this series of studies, with 3-year overall survival rates of 62%–78% [22–26]. The high-dose trials required growth factor support. Common toxicities included grade 4 neutropenia, mucositis, fatigue, nausea, and vomiting. Long-term follow-up of patients enrolled in these studies showed that recurrent locoregional disease was the most common site of treatment failure, occurring in 25% of patients for whom data were available [34]. Appearance of distant metastases alone occurred in 6% of patients, while 5% of patients had both locoregional and distant disease failure.

High response rates with docetaxel, cisplatin, and 5-fluorouracil (TPF) induction chemotherapy were also seen in studies conducted in Europe and Japan, which reported overall response rates of 64%–94%. Again, grade 3–4 neutropenia was the most common serious adverse event, with
nausea and vomiting, stomatitis, and other gastrointestinal toxicities occurring with some frequency [27–30].

To assess the potential for a survival benefit from the addition of docetaxel to PF-based chemotherapy, results from a study evaluating data from six of the above phase II studies of TPF-based chemotherapy were compared with data from patients receiving PF induction chemotherapy in randomized phase III trials. To account for possible differences in the distribution of prognostic factors in patients enrolled in the phase II and phase III trials, a patient selection standardization method and Cox model were used to adjust for potential selection bias. Adjusting for prognostic differences, the addition of docetaxel to PF-based chemotherapy resulted in an estimated 2-year survival benefit of 20% (p < .0001) [35]. This improvement in survival was robust, irrespective of the distribution of evaluated prognostic factors.

Recently, a survival benefit for TPF over PF induction chemotherapy was demonstrated in a direct comparison in a randomized phase III trial (TAX 323) conducted by the EORTC. A total of 358 patients with locally advanced and unresectable squamous cell head and neck cancer was randomized to receive induction therapy with either PF (cisplatin, 100 mg/m² on day 1; and 5-fluorouracil, 1,000 mg/m² on days 1–5) every 3 weeks for four cycles or TPF (docetaxel, 75 mg/m², cisplatin, 75 mg/m² on day 1; and 5-fluorouracil, 750 mg/m² on days 1–5) every 3 weeks for four cycles. Following induction chemotherapy, all patients received radiotherapy according to investigator/institutional choice (conventional, accelerated, or hyperfractionated). Surgery was permitted prior to radiation therapy (neck dissection) or 3 months following radiation. Preliminary results were presented in 2004 (Table 2) [36]. The overall response rate with TPF was significantly higher than that with PF, 68% versus 54% (p = .007). At a median follow-up time of 32 months, both progression-free and overall survival times were significantly longer with TPF than with PF, with a progression-free survival hazard ratio

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>No. of evaluable patients</th>
<th>Response rate Complete</th>
<th>Overall</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colevas et al. [22], Haddad et al. [26]</td>
<td>Docetaxel, 25–60 mg/m², day 1; cisplatin, 25 mg/m², days 1–5; 5-fluorouracil, 700–800 mg/m², day 1–5; leucovorin, 500 mg/m², days 1–5</td>
<td>23</td>
<td>61%</td>
<td>100%</td>
<td>100% at 1 year; 83% at 2 years; 78% at 3 years</td>
</tr>
<tr>
<td>Colevas et al. [23], Haddad et al. [26]</td>
<td>Docetaxel, 60 mg/m², day 1; cisplatin, 31.25 mg/m², days 1–4; 5-fluorouracil, 700 mg/m², days 1–4; leucovorin, 500 mg/m², days 1–4</td>
<td>30</td>
<td>63%</td>
<td>93%</td>
<td>83% at 1 year; 80% at 2 years; 77% at 3 years</td>
</tr>
<tr>
<td>Colevas et al. [24], Haddad et al. [26]</td>
<td>Docetaxel, 60–95 mg/m², day 1; cisplatin, 100 mg/m², day 1; 5-fluorouracil, 700 mg/m², days 1–4; leucovorin, 500 mg/m², days 1–4</td>
<td>34</td>
<td>44%</td>
<td>94%</td>
<td>82% at 1 year; 68% at 2 years; 62% at 3 years</td>
</tr>
<tr>
<td>Posner et al. [25], Haddad et al. [26]</td>
<td>Docetaxel, 75 mg/m², day 1; cisplatin, 100 mg/m², day 1; 5-fluorouracil, 700 mg/m², days 1–4</td>
<td>43</td>
<td>40%</td>
<td>93%</td>
<td>98% at 1 year; 79% at 2 years; 77% at 3 years</td>
</tr>
<tr>
<td>Janinis et al. [27]</td>
<td>Docetaxel, 80 mg/m², day 1; cisplatin, 40 mg/m², days 2–3; 5-fluorouracil, 1,000 mg/m², days 1–3</td>
<td>0</td>
<td>20%</td>
<td>90%</td>
<td>85% at 1 year; 60% at 2 years</td>
</tr>
<tr>
<td>Schrijvers et al. [28]</td>
<td>Docetaxel, 75 mg/m², day 1; cisplatin, 75–100 mg/m², day 1; 5-fluorouracil, 750 mg/m², days 1–5</td>
<td>48</td>
<td>0%</td>
<td>71%</td>
<td>69% at 1 year; 41% at 2 years</td>
</tr>
<tr>
<td>Tsukuda et al. [29]</td>
<td>Docetaxel, 60–70 mg/m², day 1; cisplatin, 60–70 mg/m², day 4; 5-fluorouracil, 600–750 mg/m², days 1–5</td>
<td>18</td>
<td>22%</td>
<td>94%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Watanabe et al. [30]</td>
<td>Docetaxel, 48 mg/m², day 1; cisplatin, 24 mg/m², days 1–4; 5-fluorouracil, 560 mg/m², days 1–5; leucovorin, 500 mg/m², days 1–4</td>
<td>34</td>
<td>59%</td>
<td>88%</td>
<td>93% at 2 years</td>
</tr>
</tbody>
</table>
of 0.72 (95% confidence interval [CI], 0.56–0.91; \( p = .006 \)) and overall survival hazard ratio of 0.73 (95% CI, 0.57–0.94; \( p = .016 \)). Final mature survival results are pending. Overall tolerability was better with TPF than with PF. Although the incidence of grade 3–4 neutropenia was higher with TPF, the PF arm had a higher incidence of grade 3–4 nausea, vomiting, stomatitis, and toxic deaths.

Paclitaxel is also active in squamous cell head and neck cancer, with a single-agent response rate of approximately 40% \([37, 38]\). The dose-limiting toxicity of paclitaxel is generally neutropenia. Paclitaxel-associated neurotoxicity can also be problematic, particularly when used in combination with other neurotoxic agents such as cisplatin.

The addition of paclitaxel to PF-based chemotherapy has been evaluated in phase II trials in patients with advanced head and neck cancer, producing high overall response rates (86%–88%) and promising long-term survival times (Table 3) \([39, 40]\). The combination was generally well tolerated, with neutropenia and peripheral neuropathy being the most common serious adverse events. These phase II data have supported the evaluation of paclitaxel, cisplatin, and 5-fluorouracil (PPF) induction therapy in a phase III randomized trial using a sequential treatment approach in patients with head and neck cancer that is discussed below.

A recent Intergroup randomized phase III trial evaluated the effect of using paclitaxel in the place of 5-fluorouracil, as is typically used in PF induction therapy. Patients with locally advanced, recurrent, or metastatic head and neck cancer were randomized to receive either cisplatin (100 mg/m\(^2\)) on day 1 and 5-fluorouracil (1,000 mg/m\(^2\)) on days 1–4 or paclitaxel (175 mg/m\(^2\)) with cisplatin (75 mg/m\(^2\)) on day 1 \([41]\). No significant difference in response rate or overall survival was seen between the study arms, although PF was associated with a greater response rate, longer survival time, and greater 1-year survival rate.

Paclitaxel is frequently used in combination with carboplatin for the treatment of solid tumors, given that the toxicity profiles of these two agents are more compatible. Compared with cisplatin, carboplatin is less neurotoxic, nephrotoxic, and emetogenic, and the feasibility of paclitaxel–carboplatin combinations has been established in numerous studies. When used in platinum-based therapies for squamous cell cancer of the head and neck, however, carboplatin is less effective than cisplatin \([42, 43]\). Nonetheless, the advantage in tolerability with carboplatin versus cisplatin when used in combination with paclitaxel may, in part, offset differences in efficacy between these two platinums. In phase II evaluation, the combination of a relatively high dose of paclitaxel and carboplatin produced an overall response rate of 66% in patients with advanced squamous cell head and neck cancer \([44]\). A phase II study of a three-drug induction regimen incorporating ifosfamide with

### Table 2. TAX 323: a randomized phase II study of docetaxel, cisplatin, and 5-fluorouracil versus platinum plus 5-fluorouracil as induction chemotherapy in patients with locally advanced unresectable squamous cell head and neck cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>No. of evaluable patients</th>
<th>Overall response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermorken et al. [36]</td>
<td>Docetaxel, 75 mg/m(^2), day 1;</td>
<td>177</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>cisplatin, 75 mg/m(^2), day 1;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil, 750 mg/m(^2), days 1–5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cisplatin, 100 mg/m(^2), day 1;</td>
<td>181</td>
<td>54%</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil, 1,000 mg/m(^2), days 1–5</td>
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</tbody>
</table>

\( p = .007. \)

### Table 3. Paclitaxel and platinum plus 5-fluorouracil induction chemotherapy in head and neck cancer, phase II studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>No. of evaluable patients</th>
<th>Response rate</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitt et al. [39]</td>
<td>Paclitaxel, 175 mg/m(^2), day 1;</td>
<td>69</td>
<td>59%</td>
<td>44% at 5 years</td>
</tr>
<tr>
<td></td>
<td>cisplatin, 100 mg/m(^2), day 2;</td>
<td></td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil, 500–750 mg/m(^2), days 2–6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hitt et al. [40]</td>
<td>Paclitaxel, 175 mg/m(^2), day 1;</td>
<td>35</td>
<td>51%</td>
<td>Median, 18 months</td>
</tr>
<tr>
<td></td>
<td>cisplatin, 35 mg/m(^2), days 1–2;</td>
<td></td>
<td>86%</td>
<td>(relapsed/refractory disease)</td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil, 1,000 mg/m(^2), days 1–2;</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>leucovorin, 200 mg/m(^2), day 1;</td>
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<td></td>
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<tr>
<td></td>
<td>leucovorin, 500 mg/m(^2), days 1–4</td>
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</tbody>
</table>
paclitaxel and carboplatin produced an overall response rate of 81%, with overall survival rates of 88% and 82% at 1 and 2 years, respectively [45].

**Rationale for Sequential Therapy**

Both induction chemotherapy and chemoradiotherapy provide clinical benefit in the treatment of locally advanced head and neck cancer. Induction chemotherapy can significantly reduce local disease prior to definitive radiation and/or surgery, potentially permitting preservation of organ function and appearance. Induction therapy is also effective in controlling distant disease [6, 7, 34]. With the use of chemotherapeutic agents as radiation sensitizers, chemoradiotherapy increases locoregional treatment intensity and disease control but ostensibly is not as effective as induction therapy in managing distant disease [5, 8–11].

The use of both induction chemotherapy and chemoradiotherapy in a sequential approach may provide optimal benefit for patients with locally advanced head and neck cancer [46, 47]. A variety of induction and concurrent chemoradiotherapy regimens has been evaluated in phase II studies, and more recently, randomized comparative trials involving sequential therapy approaches have been conducted.

Investigators at the University of Michigan administered a single course of PF induction therapy to select laryngeal cancer patients for organ preservation [48]. Nonresponding patients proceeded to immediate surgery, while patients with a responding tumor received concurrent cisplatin and radiation therapy. Patients achieving complete responses following chemoradiotherapy went on to receive two cycles of adjuvant PF chemotherapy. Organ preservation and overall survival rates are promising, with 62% of patients alive, disease-free, and with an intact larynx at 2 years.

Investigators at Yale University evaluated a sequential regimen of PF/leucovorin induction chemotherapy followed by concurrent cisplatin and radiation therapy for organ preservation in patients with advanced head and neck and nasopharyngeal tumors [49]. Complete responses were seen in 67% of patients, with an impressive 5-year progression-free survival rate of 60%.

At the University of Pennsylvania, an induction regimen of high-dose paclitaxel and carboplatin with G-CSF followed by weekly chemoradiotherapy with low-dose paclitaxel was administered to patients with resectable oropharyngeal tumors [50]. Following chemoradiotherapy, 90% of patients had complete responses, and actuarial survival at 3 years was estimated to be 70%. However, the median follow-up time for that study was relatively short at 31 months.

Induction chemotherapy with paclitaxel and carboplatin followed by chemoradiotherapy has also been evaluated in trials conducted at the University of Chicago [51], the Sarah Cannon Cancer Center [52], and the Vanderbilt-Ingram Cancer Center [53]. Toxicities, particularly during chemoradiotherapy, were high, but overall survival rates appear promising. At Brown University, an outpatient weekly induction regimen of paclitaxel, carboplatin, and ifosfamide (Ifex®; Bristol-Myers Squibb) followed by chemoradiotherapy produced very high response rates, though longer follow-up is needed to determine survival [54].

The benefits of the addition of a taxane to PF induction chemotherapy when used in sequential treatment are under evaluation in two randomized phase III studies (Table 4). Investigators in Madrid compared an induction treatment regimen of paclitaxel, cisplatin, and 5-fluorouracil with standard PF induction; both regimens were followed by concurrent chemoradiotherapy with cisplatin [55]. A total of 384 patients with locally advanced disease was randomized. In the preliminary results, the addition of paclitaxel to PF induction therapy resulted in a significantly higher complete response rate, 33% versus 14% ($p = .000007$), and organ

<table>
<thead>
<tr>
<th>Study</th>
<th>Induction chemotherapy</th>
<th>Chemoradiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitt et al. [55]</td>
<td>Paclitaxel, 175 mg/m², day 1; cisplatin, 100 mg/m², day 2; 5-fluorouracil, 500 mg/m², days 2–6</td>
<td>Cisplatin, 100 mg/m²; radiotherapy, 66–70 Gy (2 Gy/fraction)</td>
</tr>
<tr>
<td></td>
<td>vs. cisplatin, 100 mg/m², day 1; 5-fluorouracil, 1,000 mg/m², days 1–2</td>
<td>Cisplatin, 100 mg/m²; radiotherapy, 66–70 Gy (2 Gy/fraction)</td>
</tr>
<tr>
<td>TAX 324 [2]</td>
<td>Docetaxel, 75 mg/m², day 1; cisplatin, 100 mg/m², day 1; 5-fluorouracil, 1,000 mg/m², days 1–4</td>
<td>Carboplatin, AUC 1.5, weekly; radiotherapy, 70 Gy (2 Gy/fraction)</td>
</tr>
<tr>
<td></td>
<td>vs. cisplatin, 100 mg/m², day 1; 5-fluorouracil, 1,000 mg/m², days 1–5</td>
<td>Carboplatin, AUC 1.5, weekly; radiotherapy, 70 Gy (2 Gy/fraction)</td>
</tr>
</tbody>
</table>

Abbreviation: AUC, area under the concentration–time curve.
preservation rate, 86% versus 75% (p = .06), than with PF induction. In the early report, time to treatment failure and overall survival also favored the paclitaxel–PF arm.

The TAX 324 study compares sequential treatment regimens of TPF versus PF induction chemotherapy followed by concomitant chemoradiotherapy with weekly carboplatin. That trial is ongoing and has accrued more than 500 patients.

**Conclusion**

Evidence supporting the benefit of induction chemotherapy for the treatment of locally advanced head and neck cancer has been strengthened. The addition of a taxane to PF-based induction chemotherapy appears to substantially improve complete response rates and survival outcomes. As a component of sequential therapy, preliminary data from one randomized phase III trial support a benefit for the addition of paclitaxel to PF induction chemotherapy, and data from the TAX324 phase III trial, evaluating the addition of docetaxel to induction chemotherapy, are awaited.

Sequential therapy incorporating both induction chemotherapy and chemoradiation is a feasible approach and has the potential to further improve survival outcomes. Randomized trials comparing sequential treatment with induction and/or chemoradiotherapy are currently under way, and these trials will likely define a new paradigm for the role of chemotherapy in the management of patients with locally advanced head and neck cancer.

**Disclosure of Potential Conflicts of Interest**

Dr. Posner has acted as a consultant for Amgen, Pfizer, Millenix, GlaxoSmithKline, and NCI and has conducted clinical research for MedImmune, Lilly, Roche, Gentz, Genentech, sanofi-aventis, AstraZeneca, Bristol-Myers Squibb, Daiichi, OSI, Amgen, NCI, NIAID, and Eisai.

**References**


