Rate of Pathologic Complete Responses to Docetaxel, Cisplatin, and Fluorouracil Induction Chemotherapy in Patients With Squamous Cell Carcinoma of the Head and Neck

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Objective: To report the rate of pathological complete response after induction chemotherapy with the docetaxel, cisplatin, and fluorouracil (TPF) combination.

Design: Retrospective cohort analysis.


Patients: Seventy-two patients with newly diagnosed squamous cell carcinoma of the head and neck; 68 (95%) of the patients had stage IV, locally advanced disease.

Interventions: Three cycles of induction chemotherapy followed by a biopsy of the primary site. All patients subsequently underwent chemotherapy with 3 cycles of TPF.

Main Outcome Measure: Rate of pathological complete response at the primary site after induction chemotherapy with 3 cycles of TPF.

Results: Biopsy results were negative for cancer in 64 patients (89%) and positive in 8 patients (11%). The median follow-up was 2 years. In the positive biopsy result group, 2 (25%) of 8 patients died of disease vs 3 (4%) of 64 patients in the negative biopsy result group. Twenty-nine neck dissections were performed; results were positive in 7 patients (all alive with no evidence of disease) and negative in 22 patients (21 alive with no evidence of disease). The overall 2- and 5-year progression-free survival is currently projected at 85% and 85%, respectively; the overall 2- and 5-year survival, at 95% and 90%, respectively. Importantly, T4 presentation did not predict a positive biopsy result at the primary site or a positive neck dissection result (P=.60 and P=.56, respectively). N3 presentation (12 patients) did not predict a positive biopsy result at the primary site (P=.87) but did correlate with positive neck dissection results in 6 of 12 patients (P<.001).

Conclusions: Induction chemotherapy with the TPF regimen results in a high pathological complete response rate (89%). This rate is higher than with the cisplatin plus fluorouracil combination therapy, which was reported to be between 25% and 50% in previous studies. Chemoradiotherapy is currently an accepted standard of care, but induction chemotherapy continues to be investigated. Based on recent phase 3 trial results and the data presented herein, we propose that the 3-drug combination be used as the new platform when administering induction chemotherapy.


Locally advanced squamous cell carcinoma of the head and neck (SCCHN) is usually managed by chemotherapy, radiation, and surgery.1 Organ preservation is a major goal in this cancer. Recent studies have shown that chemotherapy and radiation can replace surgery in selected sites when organ preservation is desired.2,3 Chemotherapy can be given concurrently with radiation (ie, chemoradiotherapy) or before radiation therapy (ie, induction chemotherapy). Induction chemotherapy, also known as neoadjuvant chemotherapy, continues to be aggressively investigated, and recently there has been a clear interest in this modality. The proponents of induction chemotherapy argue that it allows better delivery of drugs to “treatment naive” tumors with an intact blood supply and at the same time provides maximal treatment to eradicate micrometastasis. Induction chemotherapy also represents a great tool to investigate new drugs in head and neck cancer.

Combination chemotherapy with cisplatin and fluorouracil (PF), developed at Wayne State University, Detroit, Mich, has been the standard induction chemotherapy treatment for patients with locally advanced SCCHN.1 In treatment naive patients, the original PF chemotherapy results in a major response rate of 60% to 90%
and a clinical complete response (CR) rate of 20% to 50%.5-7 Despite the high overall response rates with PF induction chemotherapy, the moderate CR rates at the primary site and the poor CR rate in patients with extensive nodal disease, particularly with newer and more sensitive imaging techniques, are disappointing and are associated with low survival rates at 2 and 3 years, particularly in trials recruiting patients with advanced-stage disease.

These results have stimulated intensive investigations of new agents and combinations in an attempt to improve on clinical CRs and on primary site pathologic CR (pCR) rates achieved with induction chemotherapy. Docetaxel is an effective agent in SCCHN.8,9 As a single agent, it has produced response rates of 21% to 42% in patients with locally advanced, recurrent, and/or metastatic disease. The most significant toxic effect is febrile neutropenia. Neuprophath, a major adverse effect of cisplatin, is minimal with docetaxel use. Differences in mechanisms of action and relatively nonoverlapping toxic effects of taxanes, and in particular docetaxel, compared with PF and PF-related combination therapy have prompted investigators to examine the combination of these agents with PF-based regimens to increase the response rates and cure rates in patients with advanced SCCHN treated with a curative intent.

We have been using docetaxel, cisplatin, and fluorouracil (TPF) induction chemotherapy for almost a decade now and have reported extensively on its efficacy in head and neck cancer. The most recent incorporation of aggressive chemoradiotherapy and selected surgery.10-12 This treatment regimen, called sequential chemoradiotherapy, includes induction chemotheraphy, followed by chemoradiotherapy, followed by selective surgery to the neck in the form of a neck dissection. The main toxic effects of this regimen have been previously reported in detail13 and include mucositis, which typically occurs on days 7 to 10 and lasts for 3 to 5 days, and febrile neutropenia, which occurs in less than 10% of patients. Nausea and vomiting are common and manageable with an aggressive antiemetic regimen. The pCR rate to TPF induction chemotherapy administered before radiation and its significance is unknown. It has been shown in previous studies that patients who achieved a pCR after PF-based induction chemotherapy have an overall better prognosis and better locoregional control.13-15 It has been our standard practice to obtain a biopsy specimen from the primary site after induction chemotherapy and before starting chemoradiotherapy. To our knowledge, this is the first report of the rate of primary site pCR to TPF induction chemotherapy in head and neck cancer.

### RESULTS

Between June 1999 and May 2004, 72 patients underwent a biopsy of the primary site after TPF induction chemotherapy and before starting chemoradiotherapy. The median follow-up for this group was 2 years. Patient characteristics are given in Table 1 and Table 2. Of the 72 patients, 68 (95%) had stage IV disease. The most common primary site was the oropharynx in 54 patients.

### METHODS

This is a retrospective analysis of the pCR rate to TPF induction chemotherapy. All patients had newly diagnosed SCCHN and had not received prior chemotherapy, radiation, or surgery. They had a performance status of 0 or 1. Treatment included 3 cycles of TPF induction chemotherapy, followed by chemoradiotherapy. Taxotere and cisplatin were both administered on day 1 at a dose of 75 mg/m² and 100 mg/m², respectively; fluorouracil was administered as a continuous infusion for 96 hours at 1000 mg/m² per day, also starting on day 1. Supportive care measures included aggressive hydration on days 1 and 2 of chemotherapy. This is done in the clinic with 2 liters of normal saline with electrolyte replacement. Patients are given an aggressive antiemetic regimen with ondansetron hydrochloride, dexamethasone, metoclopramide hydrochloride, and lorazepam for 5 days. Ciprofloxacin therapy is started on day 5 for a total of 10 days. Chemoradiotherapy consisted of weekly carboplatin plus paclitaxel or docetaxel with standard or concomitant boost radiation therapy.16,17 A biopsy was performed in all patients in the operating room after induction chemotherapy and before starting chemoradiotherapy. Neck dissection was performed 6 to 12 weeks after chemoradiotherapy for patients with N3 disease and for those who had an incomplete response to chemoradiotherapy.

**Table 1. Baseline Characteristics of Patients Who Underwent a Biopsy of the Primary Site After TPF Induction Chemotherapy**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (83)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (17)</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>53 (29-71)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>54 (75)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Larynx</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4 (5)</td>
</tr>
<tr>
<td>IV</td>
<td>68 (95)</td>
</tr>
<tr>
<td>Radiation regimen</td>
<td></td>
</tr>
<tr>
<td>SFX</td>
<td>46 (64)</td>
</tr>
<tr>
<td>AFX-CB</td>
<td>26 (36)</td>
</tr>
</tbody>
</table>

Abbreviations: AFX-CB, accelerated radiation with concomitant boost; SFX, standard fractionation radiation; TPF, docetaxel, cisplatin, and fluorouracil.

*Data are given as number (percentage) of patients unless otherwise specified.

**Table 2. TNM Stage in Patients Who Underwent a Biopsy of the Primary Site After TPF Induction Chemotherapy**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>N1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>N2</td>
<td>6</td>
<td>26</td>
<td>9</td>
<td>5</td>
<td>46</td>
</tr>
<tr>
<td>N3</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>31</td>
<td>15</td>
<td>18</td>
<td>72</td>
</tr>
</tbody>
</table>

Abbreviation: TPF, docetaxel, cisplatin, and fluorouracil.

*Data are given as number of patients (N = 72).
The role of induction chemotherapy is still to be defined in locally advanced SCCHN, but it is clear that patients who receive induction chemotherapy and achieve complete CR and pCR have a better chance to respond to radiation therapy and hence have a better prognosis. Therefore, it is imperative that we continue to look both for the "best" induction regimen and the prognostic factors to gauge the importance of more or less additional therapy.

The PF combination has been the "traditional" induction regimen. Over the last few years there has been considerable interest in adding a third drug to the PF combination to try and improve its results. Three large phase 3 trials have been performed looking at combining a taxane (paclitaxel or docetaxel) to the PF regimen. The first study compared the PF combination plus paclitaxel with the PF combination only. This study showed that the 3-drug combination resulted in a better CR and overall response rate compared with the 2-drug combination: 33% vs 14% and 80% vs 68%, respectively. The rate of pCR was significantly improved with the 3-drug combination: 42% vs 23%.

A second large phase 3 study was presented in 2004, comparing the TPF with the PF regimen in patients with unresectable SCCHN. This study, still in an abstract form, showed that the 3-drug combination is better than 2 drugs for the response rate end point (after TPF induction chemotherapy, before starting chemoradiotherapy): 68% vs 54%. Both progression-free survival and overall survival were better with the 3-drug combination: 12.7 months vs 8.4 months and 18.6 months vs 14.5 months, respectively.

The rate of pCR in this study is not known. Another large phase 3 study comparing the TPF to the PF regimen has recently been completed, with more than 500 patients enrolled. Results are expected in early 2007.

Sequential chemoradiotherapy, using induction chemotherapy followed by chemoradiotherapy and selective surgery is an effective therapy in head and neck cancer. Phase 2 studies clearly support the notion that there is an improvement over traditional induction chemotherapy followed by radiation therapy. It has become clear that patients with head and neck cancer benefit from chemoradiotherapy compared with radiation therapy alone. These results and those of the reported phase 3 trials support the notion that when using induction chemotherapy as a primary modality in treating these patients, the definitive therapy should include chemoradiotherapy and not be limited solely to radiation therapy.

In the present study, we demonstrate that the rate of pCR after TPF induction chemotherapy is very high at 89% and that pCR at the primary site is associated with a significantly higher rate of local failure. In the present study, we demonstrate that the rate of pCR after TPF induction chemotherapy is very high at 89% and that pCR at the primary site is associated with a significantly higher rate of local failure. In the present study, we demonstrate that the rate of pCR after TPF induction chemotherapy is very high at 89% and that pCR at the primary site is associated with a significantly higher rate of local failure.

We have looked at some predictors of a positive biopsy result at the primary site, notably an N3 presentation in the neck or a T4 presentation. These patients (with T4 and/or N3 disease) are believed to represent a very high-risk patient population when it comes to local failure. Those 2 parameters were found not to predict a posi-
tive biopsy result at the primary site. We would like to also point out that the number of patients with a positive biopsy result after induction chemotherapy was extremely small (only 8 patients) in our patient population, making it difficult statistically to predict the patients who will have a positive biopsy result at the primary site and to compare positive and negative biopsy results.

We think it is useful to obtain a biopsy specimen from the primary site after induction chemotherapy. This might reveal a patient population at high risk of local recurrence that might deserve a more aggressive definitive approach. This issue is currently being looked at in our newly initiated phase 3 trial, the Paradigm Trial.23 In this trial, patients are stratified after induction chemotherapy to a different chemoradiation therapy based on whether they have a positive or negative biopsy result at the primary site.

At the University of Michigan, Detroit, larynx preservation trials have adopted a strategy of performing a laryngectomy on patients who have less than a 75% response after 1 cycle of induction chemotherapy. Those investigators, like us, believe that a “less than ideal” response to induction chemotherapy "selects" a high-risk patient population that deserves a more aggressive definitive therapy.23

The data also indicate that, although neck dissections should be mandatory in patients presenting with N3 neck disease, pathologic positivity in the neck dissection does not add prognostic significance for local or distant control. Finally, we recommend that investigators using induction chemotherapy to treat patients with head and neck cancer choose a 3-drug combination instead of the traditional PF regimen.

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REFERENCES