Multicenter Randomized Phase II Study of Paclitaxel (1-Hour Infusion), Fluorouracil, Hydroxyurea, and Concomitant Twice Daily Radiation with or without Erythropoietin for Advanced Head and Neck Cancer

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ABSTRACT

Purpose: To expand on our experience with the combination of paclitaxel, fluorouracil, hydroxyurea, and twice daily irradiation (T-FHX) and to assess the impact of weekly administration of erythropoietin (r-HuEpo) on transfusion requirements, we conducted a Phase II multi-institutional trial with a simplified 1-h paclitaxel infusion schedule and randomized patients to receive weekly doses of r-HuEpo.

Patients and Methods: A total of 90 patients with locally advanced head and neck cancers (stage IV, 96%; N2/N3, 66%) were treated on a regimen of 1-h infusion of paclitaxel (100 mg/m2/day, day 1), 120-h infusion of 5-fluorouracil (600 mg/m2/day, days 0–5); hydroxyurea 500 mg p.o. every 12 h for 11 doses; and radiation 150cGy bid, days 1–5 of each 14-day cycle repeated for five cycles over 10 weeks (7200–7500 cGy). Before initiating therapy, patients were randomized to receive r-HuEpo 40,000 IU s.c. once weekly.

Results: At median follow-up of 40 months, 3-year progression-free survival is 62%, locoregional control is 84%, and systemic control is 79%. Overall survival is 59%. Anemia, leucopenia, dermatitis, and mucositis were the most frequent grade 3 or 4 toxicities. Patients randomized to erythropoietin experienced less grade 2/3 anemia (52 versus 77%; P = 0.02), but transfusion requirements were not significantly different.

Conclusions: T-FHX is an active and tolerable regimen inducing local tumor control and promising survival with organ preservation in high-risk patients. One h infusion of paclitaxel simplified the regimen without compromising efficacy. Addition of erythropoietin does not reduce the need for transfusion with this nonplatinum-containing regimen. T-FHX should be advanced to a randomized trial and compared with a cisplatin-based concomitant regimen.

INTRODUCTION

Concomitant chemoradiotherapy has proven superior to radiation therapy alone in recent meta-analyses and several recently published randomized studies in advanced, unresectable head and neck cancer (1–5). At the University of Chicago and subsequently in the Radiation Therapy Oncology Group, the combination of two radiopotentiating agents, FHX, given concomitantly on a week on/week off schedule with radiotherapy has succeeded in maximizing locoregional control and achieving organ preservation in advanced head and neck cancer (6, 7). The regimen has been intensified in subsequent trials by the addition of a third agent, C-FHX, or continuous infusion T-FHX (Taxol, Bristol, New Jersey) and the use of twice daily radiation, resulting in high locoregional control and survival rates with severe but manageable toxicity (8, 9).

There is evidence suggesting that cytotoxicity of radiation is dependent on good oxygenation of the target tumor tissue and that anemia before or during chemoradiotherapy could have a negative impact on response and survival (10). Treatment options for chemotherapy-related anemia are red cell transfusions and/or the administration of r-HuEpo (11). The current study builds on a previous Phase I trial (12) and replaces the 120-h continuous infusion paclitaxel in T-FHX with a 1-h infusion of paclitaxel.

Received 8/14/02; revised 12/26/02; accepted 12/31/02.

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1 This study was supported, in part, by the University of Chicago/Northwestern University Oral Cancer Research Center Grant P50 DE11921, University of Chicago Cancer Research Center Grant P30 CA14599, The Francis Lederer Foundation, The Geraldi Norton Memorial Corporation, The Robert and Valda Svendsen Memorial, Bristol-Myers Squibb, Princeton, New Jersey, and Ortho Biotech, Raritan, New Jersey.

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3 The abbreviations used are: FHX, fluorouracil, hydroxyurea, and radiotherapy; C-FHX, addition of cisplatin to FHX; T-FHX, addition of paclitaxel to FHX; r-HuEpo, recombinant human erythropoietin; CT, computed tomography; 5FU, 5-fluorouracil; G-CSF, granulocyte colony-stimulating factor; QOL, quality of life.
the same total dose on day 1 of each cycle in an attempt to ease its administration. The complete response rate, toxicity, and disease-free and overall survival were the primary objectives of this Phase II trial. Patients were also randomized to receive r-HuEpo with the objective of maintaining baseline hemoglobin levels or increase hemoglobin during chemoradiation and prevent or reduce transfusion requirements. To achieve this objective the number of transfusions required to maintain a hemoglobin of at least 10 throughout all treatment cycles, and mean hematocrit values were compared in each group.

PATIENTS AND METHODS

The study opened in March 1997 and closed to patient accrual in March 1999. Patients were entered at five participating institutions: The University of Chicago; University of Illinois at Chicago; Northwestern University; Michael Reese Hospital; and Weiss Memorial Hospital. Eligible patients had locoregionally advanced stage IV carcinoma of the head and neck arising from the oral cavity, pharynx (including nasopharynx, oral pharynx, and hypopharynx), and larynx. Patients with stage III disease were eligible only if primary site included the base of tongue or hypopharynx. All therapy was given with curative intent. Before study entry patients were evaluated by a multidisciplinary team composed of the attending surgeon, a radiation oncologist, and medical oncologist. The timing and feasibility of surgery were determined on each patient before initiation of therapy. All patients were required to have histological or cytological confirmation of squamous cell carcinoma, mucoepidermoid carcinoma, or lymphoepithelioma. The presence of distant metastases (M1) conferred ineligibility. Measurability of surgery were determined on each patient before initiation of therapy. All patients were required to have histological or cytological confirmation of squamous cell carcinoma, mucoepidermoid carcinoma, or lymphoepithelioma. The presence of distant metastases (M1) conferred ineligibility. Measurable disease was not required but was carefully documented when present. Patients had not received prior chemotherapy or radiotherapy and had Karnofsky performance status ≥ 60%. Baseline laboratory requirements included an absolute neutrophil count ≥ 1500 cells/µl; platelet count ≥ 100,000/µl, and hemoglobin ≤ 16 g/dl. Initial staging procedures consisted of a history and physical, panendoscopy and biopsy with tumor measurements, dental evaluation, head and neck and chest CT scans, bone scan, barium swallow; quality of life; and speech and swallowing assessment. Placement of a feeding device was recommended. Patients with sensitivity to cremaphor EL, human albumin or mammalian, or Escherichia coli-derived proteins were excluded. All patients signed institutional review board-approved informed consent forms.

Surgery. Decisions as to the timing and advisability of surgery were made on an individual basis. A general goal of the protocol was to obtain organ preservation. Most often, patients underwent chemotherapy and radiation as planned primary therapy. Simple excision of the primary lesion was allowed as the initial treatment. The extent of surgery varied, and it ranged from laser resection or wide excisional biopsy to resection of an oral cavity or tonsillar primary. Modified neck dissection could also be performed. Salvage surgery was recommended for residual disease at the primary site or neck after completion of chemoradiotherapy. For patients initially staged as N2 or N3, modified neck resection also was recommended, even in the absence of overt residual tumor. Surgery at the primary site was omitted in patients who achieved complete remission confirmed by physical examination, radiographic imaging, and or a negative biopsy.

Chemotherapy and Radiation. Before initiating therapy, patients were randomized to receive or not receive r-HuEpo (Procrit; Ortho-Biotech, New York) during chemoradiotherapy. All patients were admitted to the inpatient unit and treatment started on day 0 (usually Sunday evenings) with hydroxyurea administered at 500 mg p.o. every 12 h for 11 doses. The first daily dose of hydroxyurea on days 1 through 5 was given 2 h before the first fraction of daily radiotherapy. Continuous infusion 5FU was also started day 0 in the evening at 600 mg/m² and continued for 5 days (120 h). Paclitaxel was administered i.v. over 1 h at 100 mg/m² on day 1 after the first dose of radiation. Premedication for paclitaxel included dexamethasone 10 mg p.o. at 12 h and 1 h before paclitaxel and benadryl 25 mg i.v. push 30 min before paclitaxel. Radiation therapy was administered twice daily with a minimum of 6 h between fractions at 1.5 Gy/fraction with concomitant chemoradiotherapy during days 1 through 5 (total dosage 15 Gy/cycle). No chemoradiotherapy was administered on days 6 through 13; cycles were administered every other week. For patients randomized to r-HuEpo (Procrit; Ortho Biotech) 40,000 IU was administered once weekly for 14 weeks, starting with the first treatment week of cycle 1 and continued for 4 weeks after treatment finished. Patients randomized to r-HuEpo also received concomitant oral iron therapy (ferrous sulfate 325 mg three times daily) beginning day 1 and continued throughout administration of Procrit (Fig. 1). All patients with a hemoglobin < 10 g/dl at baseline were transfused packed RBCs, generally 2 units (or more if necessary) to achieve a minimum hemoglobin of 10 g/dl before the start of therapy. Patients were also transfused packed RBCs if hemoglobin was < 10 on days 0–5 of any cycle of chemoradiotherapy.

Treatment cycles were not postponed for mucositis, dermatitis, or diarrhea. For grade 4 mucositis, dermatitis, or diarrhea exceeding 7 days duration or that persisted on day 1 of a subsequent cycle, 5FU was decreased to 500 mg/m²/day and paclitaxel decreased to 75% of the calculated dose. For WBC count of 1000–1999 cells/µl or platelet count of 50,000–74,999 cells/µl, paclitaxel was decreased 75% of the calculated dose.

<table>
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<th>Day</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>Cycles Repeated every 14 days for 5 cycles</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
<td>XX</td>
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<tr>
<td>Total Radiotherapy Dose: 65-75 Gy</td>
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<td></td>
<td></td>
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<tr>
<td>Erythropoietin given weekly for 14 weeks</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Fig. 1 Treatment regimen. T-FHX chemoradiotherapy regimen administered every other week.
and hydroxyurea was decreased to 50% of the full dose. For WBC count of <1000 cells/µl or platelet count < 50,000 platelet/µl on days 0 through 5 of any cycle, paclitaxel and oral hydroxyurea were withheld, whereas 5FU and radiotherapy were continued. In the presence of a persisting fever that exceeded 38°C or other clinically apparent infections, a cycle could be postponed for 1 week or interrupted if this was judged to be necessary in the opinion of treating medical and radiation oncologist. G-CSF was not routinely administered in between cycles, however, in patients who developed grade 3 neutropenia at any time or ≥ grade 2 neutropenia on day 0 of any cycle, G-CSF (5 µg/kg) was administered on days 6 through 12 at a minimum of 12 h after completion of 5FU. In these patients, G-CSF was used in all subsequent cycles.

Radiotherapy Guidelines. Patients underwent dental evaluation and treatment as soon as possible during the initial evaluation. Patients underwent CT-based simulation and field arrangements determined with plans to treat gross disease and areas of potential microscopic involvement. Opposed lateral fields were used initially to treat the primary site and neck lymph nodes. The anterior and posterior triangle nodes and the base of skull were included in the initial treatment volume in most cases. In selected cases, a three-field technique or wedged pair was used. Three-dimensional conformal planning and tissue compensators were used when appropriate. If indicated, a separate field was used to treat the supraclavicular fossa. Custom cerrobend blocks were used to shield areas that were not considered at risk of containing disease or to block critical structures such as spinal cord to avoid exceeding tissue tolerance. Each cycle of chemoradiation consisted of 5 consecutive days of concomitant chemoradiotherapy. Patients received 150 cGy twice daily (300 cGy/day and 1500 cGy/week) on the alternate week schedule. There was a minimum of 6 h between fractions. Total radiation dose for presumed microscopic disease was 4500–6300 cGy. Areas of gross disease were boosted after appropriate field reduction to total dose of 7000–7500 cGy.

Statistical Analysis. After completion of chemoradiotherapy, patients were evaluated for response status using bimodal measurements as described previously (8, 9). Data were summarized using frequencies, percentages, means, SDs, and ranges. Survival time, progression-free survival time, time to locoregional progression, and time to distant progression were analyzed using Kaplan-Meier product limit curves. The term locoregional is used to describe disease in the primary tumor region and/or neck. In the progression-free survival analysis, progression was defined to be the occurrence of at least one of the following events: locoregional progression; distant progression; treatment-related (including late toxicity at any time of follow-up) death; or death from disease. All deaths within 3 months of completion of treatment were reported as treatment related. The log-rank test was used to compare curves between subgroups, in particular, to compare groups receiving or not receiving r-HuEpo.

According to initial study design, 60 patients were to be enrolled with half assigned randomly to receive r-HuEPO based on an expected total response rate (complete response and partial response) among these patients to be ~90%. A 90% response rate among 60 patients would yield a 95% confidence interval for the true response rate of 79–96%. On the basis of data from prior Phase II study, the average change in hematocrit from baseline to end of treatment was −6.3 percentage points. On the basis of the assumption that the addition of r-HuEPO would reduce the mean change to −3.0, then 30 patients in each group would provide > 80% power to detect a difference significant at the 0.05 level. The investigators decided to accrue an additional 30 patients after the initial goal of 60 was met based on early data indicating favorable response and survival rates. These additional patients continued to be randomized to receive r-HuEPO.

RESULTS

Ninety eligible patients with previously untreated locoregionally advanced head and neck cancer were entered onto the study. Follow-up data from five institutions were available through March 2002. Pretreatment characteristics are listed in Tables 1 and 2. Staging information is listed in Table 3. Stage IV, T4, and N2/N3 were encountered in 96, 61, and 66% of patients, respectively.

Response. Twelve patients were not accessible for response; 10 had complete surgical resection (with organ preservation) before chemoradiotherapy, 1 patient withdrew after two cycles, and 1 patient expired before evaluation but after com-

<table>
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<th>Table 1 Pretreatment patient characteristics</th>
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<td>Pipe or cigar only</td>
</tr>
<tr>
<td>Cigarettes &lt;20 pack-yrs</td>
</tr>
<tr>
<td>Cigarettes 20–40 pack-yrs</td>
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<td>Cigarettes &gt;40 pack-yrs</td>
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<td>5–10% body weight</td>
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<tr>
<td>&gt;10% body weight</td>
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</table>
Multicenter Randomized Phase II Study of Drug Agents

Patients received four of five planned cycles. (All of these were intended to have five cycles, or some were postoperative and planned for only four cycles.)

Of the 49 surviving patients without evidence of disease, 11 remain feeding tube dependent, although one was able to have some oral intake. Three of these were unable to take anything p.o. at baseline; 1 patient was able to drink clear liquids only. Seven of these patients had oropharyngeal cancer (5 tonsil, 1 base of tongue, 1 oral pharynx). The remaining 4 had cancer of the oral tongue, pyriform sinus, and supraglottic larynx (2). All of these patients had a feeding support device placed before or during treatment, and all but 1 patient never had the tube removed.

Five patients died of treatment-related toxicity in the absence of documented disease progression. Only one of these, a pulmonary embolism, occurred before completion of therapy. Three events were from unknown causes at 2.5, 3 and 5.5 months after the start of therapy, respectively, and one was from bacterial endocarditis 4.5 months after the start of therapy. Two patients died of late toxicity after apparent hemorrhage from the head and neck region but without definitive evidence of local recurrence 7 and 20 months after the start of therapy.

**Surgery.** Nineteen patients underwent surgery before chemoradiotherapy, including a neck dissection in 14 patients and surgery at the primary site in 12 patients (Table 6). Primary site surgeries included 4 tonsillectomies, 2 base of tongue resections, 2 partial maxillectomies, 1 local excision of an anterior tongue primary, and 1 floor of mouth resection, respectively. Two patients underwent laser debulking of a base of tongue and a pyriform sinus primary. Two patients with unknown primary site underwent neck dissections as initial treatment before chemoradiotherapy, one of which also included an ipsilateral tonsillectomy. Of 32 patients who underwent neck dissection after completion of chemoradiotherapy, 10 were found to have pathologic evidence of residual disease. Radiographic response

### Table 2 Tumor characteristics

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<tr>
<th>Primary site</th>
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<th>Percentage</th>
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<tr>
<td>Oral cavity</td>
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<td>16</td>
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<tr>
<td>Nasopharynx</td>
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<td>2</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>39</td>
<td>43</td>
</tr>
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<td>Hypopharynx</td>
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<td>12</td>
</tr>
<tr>
<td>Supraglottic larynx</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Glottic larynx</td>
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<tr>
<td>Subglottic larynx</td>
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<td>1</td>
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<tr>
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<tr>
<td>4</td>
<td>86</td>
<td>96</td>
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<th>Histology</th>
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<tr>
<td>Squamous cell</td>
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<td>96</td>
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<tr>
<td>Mucoepidermoid</td>
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<th>Differentiation</th>
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<tr>
<td>Well</td>
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<td>13</td>
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<tr>
<td>Mod</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Undifferentiated</td>
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<tr>
<td>Poor</td>
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<td>30</td>
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<tr>
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### Table 4 Acute toxicity T-FHX (n = 90)

The most severe grade for each patient is recorded. The median hemoglobin nadir was 9.4 gm/dl. Grade 4 leucopenia was defined as nadir <1,000/μl; grade 4 thrombocytopenia was <25,000/μl.

<table>
<thead>
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<th>% grade</th>
<th>% grade</th>
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<table>
<thead>
<tr>
<th>Toxicity</th>
<th>% grade</th>
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<tr>
<td>Hemoglobin</td>
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<tr>
<td>Leukopenia</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
</tr>
<tr>
<td>Dermatitis (in-field)</td>
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<tr>
<td>Pain</td>
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### Table 5 Chemotherapy dose intensity (no. of patients)

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<th>Intended (mg/m²/wk)</th>
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<tr>
<td></td>
<td>&lt;60%</td>
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<tr>
<td></td>
<td>60–79%</td>
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<tr>
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<td>80–99%</td>
</tr>
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<td>100%</td>
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<table>
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<td>Paclitaxel</td>
<td>50</td>
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### Table 3 T and N stage (n = 90)

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<th>N₁</th>
<th>N₂a</th>
<th>N₂b</th>
<th>N₂c</th>
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<td>T₄</td>
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<td>27</td>
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before neck dissection correlated poorly to pathologic response (Fig. 2). Two patients with partial responses at the primary site successfully underwent salvage total laryngectomies. In a third patient, salvage surgery was unsuccessful because of unresectable disease.

**Survival.** With a median follow-up time of 40 months (range, 1.5–58.7 months), the median survival has not yet been attained. Three-year progression free and overall survival rates are 62 and 59%, respectively (Figs. 3 and 4). Twenty-eight patients (31%) have progressed locoregionally and/or distantly (Fig. 5). Eleven patients (12%) progressed locoregionally and 15 patients (17%) distantly. In 2 patients (2%), initial progression was simultaneously locoregional and distant. Fourteen of 17 patients progressing with distant disease were initially staged N2 (9 patients) or N3 (5 patients). Three of 10 patients with positive neck dissections eventually developed disease progression, 1 with local progression and 2 with distant progression. Of the 22 patients with negative neck dissections, 7 eventually progressed, 6 progressed distantly, and 1 progressed locally and distantly. There was no difference in survival between patients with negative and positive neck dissections. There have been 41 deaths, including 26 (64%) related to disease, 5 (12%) related to toxicities, 2 (5%) from possible late complication, 6 (15%) from unrelated illnesses, and 1 from a second primary (lung cancer). The cause of death in 1 patient could not be determined.

**Erythropoietin.** Forty-seven (52%) patients were randomized to receive erythropoietin with the objective of maintaining a minimum hemoglobin level of at least 10 g/dl throughout the treatment, whereas 43 patients received no rHuEpo. Only patients randomized to rHuEpo actually received it. Transfusions before the start of chemoradiotherapy needed to achieve a baseline hemoglobin of at least 10 g/dl were not counted in the erythropoietin analysis. Grade 2/3 hemoglobin toxicity was less common in patients receiving erythropoietin than in those not receiving erythropoietin [24 (52%) versus 33 (77%); \( P = 0.02 \); Fig. 6]. However, randomization to erythropoietin did not statistically significantly alter the number of patients requiring transfusion [19 (40%) versus

### Table 6  Surgery

<table>
<thead>
<tr>
<th>Initial surgery</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary +/− ND*</td>
<td>12</td>
</tr>
<tr>
<td>ND Only</td>
<td>7</td>
</tr>
<tr>
<td>Surgery after T-FHX</td>
<td></td>
</tr>
<tr>
<td>Primaryb</td>
<td>2</td>
</tr>
<tr>
<td>ND only</td>
<td>32</td>
</tr>
</tbody>
</table>

* ND, neck dissection.  
b All salvage procedures (2 laryngectomies).

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Fig. 2 Correlation of radiographic and pathologic response in 32 patients with N2 or N3 disease who underwent neck dissection.

Fig. 3 Progression-free survival of 90 patients entered on protocol 8626.

Fig. 4 Overall survival of 90 patients entered on protocol 8626.

Fig. 5 Locoregional and distant progression rates for all patients entered on protocol 8626.
P = 0.20) nor the mean (median) number of transfusions required [1.28 (0) versus 1.79 (1); P = 0.25] to maintain a hemoglobin of 10. Lack of benefit was independent of baseline hemoglobin. As expected, the addition of erythropoietin had no effect on other hematological toxicities such as leukopenia or thrombocytopenia, and the groups did not differ on any QOL, side effect, or performance parameter. The addition of erythropoietin had no significant effect on disease progression, overall survival or response rates (Figs. 7 and 8). The number of transfusions required to maintain a hemoglobin of 10 had no effect on overall survival. However, a baseline hemoglobin level of ≥14 g/dl in 16 patients (18%) was associated with improved overall survival (P = 0.05). No patients maintained hemoglobin levels > 14 during treatment (only 2 patients maintained hemoglobin > 12 during treatment). There was no survival benefit at any other hemoglobin level either before or during treatment.

DISCUSSION
This is the third consecutive Phase II trial from our group investigating intensive concomitant chemoradiotherapy in a curative and organ preserving intent in advanced head and neck cancer (8, 9). We demonstrate that paclitaxel in T-FHX can be administered over 1 h rather than over 120 h, easing the administration of that regimen and allowing for the elimination of routine G-CSF support between treatment cycles with no evidence of reduced efficacy (9). Toxicity and 3-year survival data from the two previously completed studies from our group (continuous infusion T-FHX and C-FHX) are summarized and compared with the current trial in Table 7. Despite the elimination of routine administration of G-CSF between cycles of 1-h T-FHX, grade 3/4 leukopenia was nearly identical to that seen with T-FHX using 120-h infusion, implying that the 1-h schedule is less myelosuppressive. The addition of paclitaxel to FHX had less hematological toxicity and similar nonhematological toxicity compared with the addition of cisplatin to FHX. Although mucositis appears increased in the latter trials, this toxicity is difficult to quantify, and interobserver differences may be partially responsible for this observation. A recent trial by Adelstein et al. (13) using a more traditional cisplatin/5FU regimen with hyperfractionated radiotherapy schedule and a trial by Sunwoo et al. (14) using three cycles of 120-h continuous infusion paclitaxel, and standard fractionated radiotherapy are also included in Table 7. Given the similar outcome data and consistent failure rates and patterns, it appears that paclitaxel can be substituted for cisplatin as a systemically active, radiation-enhancing agent without the subjective side effects and with less myelosuppression associated with cisplatin. Although the Sunwoo trial, using a less intensive chemoradiotherapy schedule, achieves similar overall survival with arguably less toxicity, it is a small trial (n = 33) with a higher percentage of stage 3 patients (15%) than the other trials.

The Meta-Analysis of Chemotherapy in Head and Neck Cancer showed a significant survival benefit when chemotherapy was added to definitive radiotherapy. Although cisplatin containing induction therapy demonstrated a small significant benefit, the great majority of survival benefit was realized when chemotherapy was given concomitantly with radiotherapy (4). Recent randomized trials using platinum-based combination chemoradiotherapy resulted in 3-year survival rates of 51, 55, and 49%, respectively, all significantly superior to survival with radiotherapy alone, with acceptable toxicity (1–3). The 3-year overall survival rates with T-FHX in our two large Phase II trials
appear to be superior to those achieved in each of these three randomized trials. Thus, treatment intensification as pursued here may lead to higher tumor control rates. This question should be pursued further in a definitive Phase III trial comparing TFHX or a similarly active regimen (13) against more traditional chemoradiotherapy regimens. There has been debate concerning the surgical management of the neck after completing chemoradiotherapy. In this multicenter study, there was some variance from one site to another, but in general, neck dissection was encouraged for N2 or N3 disease regardless of clinical or radiographic response to TFHX. Approximately one-third of patients (10 of 32) who underwent neck dissection after chemoradiotherapy had residual disease. This percentage is consistent with that found in our two previous studies and by other investigators (13, 15, 16). Post-treatment CT scan was not a reliable way to access for residual disease with 50% of patients with negative neck dissections having positive CT scans and 40% of patients with positive neck dissections having negative CT scans.

Restaging was done within a 4–6-week window after treatment during which time treatment-related edema could interfere with CT scan interpretation. Of interest, the rate of residual disease in the neck is much lower in our more recent trial that added two cycles of induction chemotherapy to the TFHX regimen (17).

There was no clear benefit derived from erythropoietin as used in this study. Although there was a significant decrease in grade 2/3 hemoglobin toxicity, this did not translate clinically to a decreased need for supplemental transfusion of RBCs to maintain hemoglobin of 10 g/dl. Similarly, there was no survival benefit associated with the use of erythropoietin. A hemoglobin level of >14 at baseline, observed in only 16 patients enrolled in the study, was associated with improved survival (P = 0.05). The lack of a benefit from r-HuEpo may be attributable to the short overall treatment duration (9 weeks) and the absence of a platinating agent in our regimen. For these reasons, the study may have been underpowered to detect a small but statistically significant difference.

There have been several recent trials that report pretreatment hemoglobin associated with improved response to chemoradiation in head and neck cancer. Dubray, in a prospective study, demonstrated that anemia was associated with lower locoregional control and survival after radiation therapy for head and neck cancer (18). Haddad et al. (19) and Budach et al. (20) reported that hemoglobin levels >12 and 14, respectively, were associated with improved locoregional control and overall survival. Staar et al. (21) have also reported on initial hemoglobin level as a significant factor for survival in patients treated with hyperfractionated radiotherapy with or without chemotherapy. Contrary to our findings Dunphy et al. (22) report in a study, which included induction chemotherapy, that the addition of erythropoietin significantly reduced anemia and the need for transfusions. Glaser et al. (23) report both correction of anemia and improved efficacy in patients receiving erythropoietin during neoadjuvant chemoradiotherapy. On the basis of these trials, a hemoglobin between 12 and 14 g/dl rather than 10 g/dl may be necessary to significantly improve response, survival, and decrease need for transfusion.

One-h TFHX has a high complete response rate, and overall survival is as good as or better than regimens currently being evaluated in randomized trials. Toxicity remains severe but manageable, and although patients report significant functional and QOL declines during treatment, the majority of these resolve to pretreatment levels by 12 months. On the other hand, even 2–4 years posttreatment completion, a subgroup of patients continue to have significant problems eating with up to 22% remaining tube dependent (24). Clearly QOL and functional parameters must be included in the design and analysis of aggressive chemoradiotherapy regimens, with the additional goal of identifying baseline parameters that might place patients at risk for long-term impairment. Treatment strategies such as alternating weeks of chemotherapy and radiotherapy or single agent chemoradiotherapy in the recently reported Head and Neck Intergroup Trial have generally proved less toxic but with lower survival in comparison to the intensified multitantient chemoradiotherapy regimens (25, 26).

As in prior trials from our group, as well as others using intensified chemoradiotherapy regimens, a reversal of the usual pattern of disease progression has emerged (8, 9, 13). With locoregional control rate of 83%, distant disease failure has become more common than locoregional failure (Fig. 5). Although trials of induction chemotherapy have failed to consistently demonstrate a survival benefit over radiation alone in advanced head and neck cancer, several trials have demonstrated a survival benefit over radiation alone.
stratified a decrease in distant metastases (27–30). Neoadjuvant chemotherapy significantly improved survival in the Groupe d’Etude de Tumeurs de la Tete et du Cou trial, although 73% of patients had stage II and III disease, as well as in subgroup analysis of patients with resectable disease in the Paccagnella trial (29, 31). Posner et al. (32) in a recent series of Phase II trials has achieved high complete response rates with intensive induction chemotherapy followed by chemoradiotherapy. Therefore, the current focus of our group is to integrate a brief, active induction regimen to precede 1-h T-FHX with the expectation of maintaining a high rate of locoregional control and decreasing distant disease failure. A secondary objective will be to select patients, based on their local response to induction chemotherapy, who might be safely treated with a lower total dose of radiotherapy and thus decrease toxicity from the regimen (17).

ACKNOWLEDGMENTS

We thank Michelle Scheuer for assistance with the preparation of the manuscript and Delores Watts, Gemetta Wallace, Jan-Marie McEvilly, Mary Jesse, Rosalyn Williams, Dr. Theodore Chung, Dr. Rod Humerekhouse, Dr. Henry Briele and Bing Bing Fung for assistance with data management, statistical analysis, and patient care.

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Multicenter Randomized Phase II Study of Paclitaxel (1-Hour Infusion), Fluorouracil, Hydroxyurea, and Concomitant Twice Daily Radiation with or without Erythropoietin for Advanced Head and Neck Cancer
