TAXANE-BASED CHEMORADIATION FOR ORGAN PRESERVATION WITH LOCALLY ADVANCED HEAD AND NECK CANCER: RESULTS OF A PHASE II MULTI-INSTITUTIONAL TRIAL

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Abstract: Background. The optimal drug schedule and sequencing of chemotherapy and radiation for organ preservation in head and neck cancer has yet to be determined. We undertook a phase II trial of a taxane-based induction chemotherapy (ICT) followed by a taxane-based concurrent chemoradiation (CCR) regimen in patients with resectable stage III or IV disease to determine the feasibility, toxicity, and overall efficacy.

Methods. Forty-four patients with laryngeal or tongue base carcinomas were enrolled. All patients received 3 cycles of chemotherapy with paclitaxel 175 mg/m² and carboplatin AUC (area under the curve) 6–7.5 over 30 minutes on days 1, 22, and 43. Responding patients went on to receive radiation (70 Gy/7 weeks) with cisplatin 75 mg/m² IV on days 1, 22, and 43 and weekly paclitaxel 30 mg/m² IV (n = 22). Because of hematologic toxicity, the concurrent regimen was changed to weekly carboplatin AUC 1 plus weekly paclitaxel 30 mg/m² (n = 22).

Results. Twenty-three patients with stage III and 21 patients with stage IV disease were enrolled. Median follow-up was 3.7 years. Acute toxicity of concurrent cisplatin and paclitaxel was excessive, with significant hematologic toxicity and 2 toxic deaths. Acute toxicities of concurrent carboplatin and paclitaxel were tolerable. No patients required permanent percutaneous gastrostomy tubes. The organ preservation rate was 83% (toxic deaths considered failures). Of 42 evaluable patients, 20 patients had complete responses (48%), 17 partial responses (41%), 3 minor responses (11%), 1 stable disease (2%), and 1 progressive disease (2%). Two-year local control, relapse-free survival, and overall survival were 82%, 77%, and 71%, respectively.

Conclusion. There were no significant differences in relapse-free survival or organ preservation rates between concurrent regimens. Platinum and paclitaxel-based CCR is feasible after ICT and provides a high rate of organ preservation. Substitution of concurrent cisplatin to weekly carboplatin with paclitaxel and radiation has an improved toxicity profile. The ease of administration and low toxicity make this a regimen that is practical for use in the community setting.

Keywords: taxane; chemoradiation; larynx; oropharynx

The majority of patients with squamous cell carcinomas of the head and neck (SCCHN) region present with locally advanced (American Joint
Committee on Cancer [AJCC] stage III or IV) disease. Historically, patients with resectable disease underwent surgical resection followed by radiation therapy. Alternative treatment approaches have been investigated more recently. The initial results of the Veterans Affairs Larynx Cancer Study Group Trial, published in 1991, demonstrated equivalent survival for laryngeal cancer patients undergoing induction chemotherapy (ICT) when compared with immediate surgery with postoperative radiation. Analogous results were reported compared with immediate surgery with postoperative undergoing induction chemotherapy (ICT) when equivalent survival for laryngeal cancer patients Group Trial, published in 1991, demonstrated that CCR is associated with improved survival in the resectable and unresectable patient populations when compared with radiation therapy alone. The question has arisen as to whether ICT followed by radiation or CCR provides superior outcomes. The Radiation Therapy Oncology Group conducted a phase III trial comparing radiation alone versus 3 cycles of ICT with cisplatin and 5-fluorouracil followed by radiotherapy (RT) versus CCR with high-dose cisplatin. Organ preservation rates were 55% versus 65% versus 85%, respectively. Thus, CCR has become the standard of care for function preservation in locally advanced disease.

As local disease becomes better controlled with CCR, patients are living long enough to manifest underlying metastatic disease. Thus, the rate of local failure has diminished and distant failure has become a more common clinical issue. This has led to a new therapeutic dilemma: how should occult metastatic disease be treated? One potential approach is to combine ICT with CCR. Because patients with SCCHN often present with poor performance status, comorbid disease, and suboptimal nutritional status, concern has been expressed that this approach may result in excessive toxicity and decreased capacity to deliver concurrent chemotherapy. Thus, we decided to investigate the feasibility of sequential ICT followed by CCR with a focus on developing an effective treatment regimen with an acceptable toxicity profile.

The taxoids, a class of tubulin-binding agents that promote polymerization and the formation of stable microtubules, have demonstrated efficacy in the treatment of locally recurrent and metastatic SCCHN. In vitro data demonstrate a radiosensitization effect of paclitaxel in squamous cancer cell lines. Our prior single-institution experience utilizing paclitaxel 175 mg/m² with carboplatin AUC (area under the curve) 6–7.5 as 3 cycles of induction therapy in locally advanced head and neck cancer showed complete response rates of 53% and partial responses of 40% (overall response 93%) with minimal toxicity. Building on this work, we designed a phase II trial of induction therapy with carboplatin and paclitaxel followed by a concomitant taxane-based regimen in patients with surgically resectable American Joint Committee on Cancer (AJCC) stage III or IV squamous cell carcinomas of the larynx or tongue base. The objectives of this trial were to assess: (1) the feasibility of induction therapy followed by concomitant chemoradiation, (2) toxicity, and (3) efficacy.

PATIENTS AND METHODS

Patients. Patients were entered on trial between September 1997 and December 1999 among 6 institutions in the Vanderbilt-Ingram Cancer Center Affiliated Network: the Vanderbilt-Ingram Cancer Center, Saint Thomas Hospital, Erlanger Health System, and Wellmont Holston Valley Medical Center, Providence Hospital, and the Veteran's Administration Hospital in Nashville. Eligibility criteria included the following: previously untreated patients, histologically confirmed squamous carcinoma, and AJCC stage III or IV tumors that were surgically resectable but would have required a total laryngectomy. Patients with evidence of cartilage or bone invasion (T4) were eligible if considered surgically resectable. Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1 was a requirement, as was normal organ function. Pregnant or lactating patients or those with prior malignancies ≤5 years (except early-stage nonmelanomatous skin and early-stage prostate cancer) were not eligible. Institutional review board approval was obtained prior to study enrollment. All patients signed informed consent.

Pretreatment evaluation included history, physical examination, biopat and endoscopic tumor staging by an otolaryngologist, CT or MRI from the skull base to clavicles, chest X-ray, complete blood count with differential, comprehensive metabolic panel, electrocardiogram, and dental evaluation.
Treatment Plan.

**Induction Chemotherapy.** All patients were treated with ICT utilizing paclitaxel 175 mg/m² IV over 3 hours and carboplatin AUC 7–7.5 IV every 21 days for 3 cycles. Doses were calculated using actual body weight. Standard premedications were given to prevent anaphylaxis to Cremaphor. Patients with less than a partial tumor response (PR) ≥50% after the completion of 3 cycles of induction therapy were referred for surgical resection and postoperative radiation. Those that experienced a PR or complete tumor response (CR) went on to concurrent chemotherapy with radiation.

**Concurrent Chemotherapy.** The first 22 patients were treated with concurrent chemotherapy consisting of paclitaxel 30 mg/m² over 30 minutes weekly × 7 starting on day 1 of radiation plus cisplatin 75 mg/m² over 1 hour on days 1, 22, and 43 (regimen 1). Because of excessive hematologic toxicity, the protocol was amended and all subsequent patients were treated with concurrent chemotherapy consisting of weekly × 7 paclitaxel 30 mg/m² over 30 minutes and weekly × 7 carboplatin AUC 1 starting on day 1 of radiation (regimen 2).

**Radiation Therapy Guidelines.** All patients underwent CT-based treatment for 3-dimensional treatment planning before ICT. Patients received 70 Gy at 2 Gy daily to the primary tumor and involved nodes in 35 fractions over 7 weeks. Spinal cord dose was limited to 45 Gy. Initial fields usually involved opposed lateral fields using either 4 MV or 6 MV X-rays to the primary tumor and upper neck nodes to 50 Gy with a 2- to 3-cm margin, followed by a boost of 20 Gy using 1- to 2-cm margins. No intensity-modulated radiation was used. Posterior cervical chain nodes were treated after 40 Gy using 9 to 12 MeV electrons to protect the spinal cord. Clinically uninvolved lower nodal sites down to the clavicles were treated to 50 Gy in 5 weeks using an anterior field with dose calculated at 3- to 4-cm depth. When lower cervical nodes were clinically involved, anterior–posterior lower neck fields were used, with dose calculated at the midplane to 50 Gy, followed by a boost to all clinically involved nodes to 70 Gy using a 1- to 2-cm margin.

**Surgery.** Patients who did not have a PR to induction therapy or did not achieve a CR at the primary site after completion of chemoradiation underwent salvage surgery. Salvage neck dissections were performed in all patients with palpable residual adenopathy but was optional for patients with a clinical CR after treatment for N1–N3 nodal disease.

**Follow-up.** Patients had follow-up examinations with fiberoptic endoscopy every 6 to 8 weeks for the first year, every 3 months for the second year, and every 4 to 6 months thereafter until 5 years. Post-treatment CT was required at 6 to 12 weeks, at 1 year, and if clinically indicated.

**Dose Modifications.**

**Induction Therapy.** Patients experiencing grade 4 neutropenia for more than 7 days or febrile neutropenia were dose reduced to paclitaxel 135 mg/m² plus carboplatin AUC 5. If prolonged neutropenia or febrile neutropenia recurred with the subsequent cycle, granulocyte-colony stimulating factor was added. For patient with grade 4 thrombocytopenia, carboplatin was reduced to an AUC of 6 and 5 for first and second episodes, respectively. Patients developing grade 3 neurotoxicity had a dose reduction in both paclitaxel (135 mg/m²) and carboplatin (AUC of 6). For any other clinically significant grade 3 or 4 toxicity, chemotherapy was withheld until resolution to grade 1 status, at which time treatment resumed as a reduced dose of paclitaxel 135 mg/m².

**Concomitant Therapy.** Blood counts were checked weekly during CCR. For patients receiving regimen 1, cisplatin treatment was held for a creatinine clearance of <50 or a Cr of >1.5. Weekly paclitaxel was held if absolute neutrophil count (ANC) was <1000 cm⁻³ or platelets were <75,000 uL⁻¹. For patients on regimen 2, both carboplatin and paclitaxel were held for an ANC <1000 cm⁻³ or platelets <75,000 µL⁻¹. Treatment resumed when counts returned above these values. For patients experiencing grade 4 mucositis or grade 3 dermatitis, chemotherapy was held at the discretion of the treating physician.

**Function Assessment.** After the first 10 patients were treated, substantial speech and swallowing toxicity was noted. The protocol was amended to further evaluate these parameters using the Performance Status Scale-Head and Neck Cancer (PSS-HN). The PSS-HN contains 3 subscales, which are unique to head and neck cancer: normalcy of diet, eating in public, and understandability of speech. The normalcy of diet subscale assesses the degree to which patients are able to swallow a normal diet. The eating in public subscale is based on subject report of with whom they...
eat and in what settings they eat. The understand-
ability of speech subscale contains a list of items
ranked hierarchically and numbered accordingly,
with normal functioning at the high end (100
points) and total dysfunction at the opposite end (0
points). The PSS-HN was administered at base-
line, postinduction, within 4 weeks posttreatment,
and at months 3 and 6 posttreatment.

**Statistical Design.** The endpoints of this study
were to assess the following: (1) feasibility of induc-
tion therapy followed by concomitant chemoradia-
tion as measured by the ability to deliver drug and
radiation therapy as scheduled, (2) toxicity, and
(3) efficacy as defined by tumor response rates and
organ preservation rate (freedom from salvage surgery). A 2-stage accrual design described by
Simon and colleagues was utilized to ensure that
the number of patients undergoing this treatment
was minimized if at least a 65% rate of organ
preservation was achieved. Initially, 17 eligible
patients were entered into the study. At least 8
complete responses were required, or the phase II
trial would be terminated. The probability of early
termination was calculated to be 0.038 (type 1
error) if the true organ preservation rate was 0.65.
It was calculated that a minimum of 35 total patients would need to be enrolled to provide a
statistical power to detect differences of 85% with
a significance of 0.05 (α). Chi-square (2-sided) and
log-rank tests were used to evaluate differences
between groups for toxicity and survival.

**RESULTS**

**Patient Characteristics.** Forty-four patients were
enrolled between September 1997 and December
1999. Patient characteristics are listed in Table 1.
The median age was 60 years, the majority of
patients were male, and the majority of patients
had a performance status of 0. Twenty-three pa-
tients had AJCC stage III and 21 had stage IV dis-
ease (Table 2).

**Table 1.** Patient characteristics (N = 44).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;60 y</td>
<td>22 (50)</td>
</tr>
<tr>
<td>≥60 y</td>
<td>22 (50)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (84)</td>
</tr>
<tr>
<td>Female</td>
<td>7 (16)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Larynx</td>
<td>32 (72)</td>
</tr>
<tr>
<td>Base of tongue</td>
<td>12 (28)</td>
</tr>
<tr>
<td>ECOCG performance</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35 (79)</td>
</tr>
<tr>
<td>1</td>
<td>8 (18)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Abbreviation: ECOCG, Eastern Cooperative Oncology Group.

**Table 2.** Distribution by AJCC classification.

<table>
<thead>
<tr>
<th>T classification</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>T4</td>
<td>1</td>
<td>6</td>
<td></td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>9</td>
<td>17</td>
<td>3</td>
<td>44</td>
</tr>
</tbody>
</table>

**Feasibility.**

**Induction Therapy.** Thirty-seven patients (84%) com-
pleted all 3 cycles of ICT without prolonged delays.
Three patients (7%) received 2 cycles and 4 (9%) received only 1 cycle. Thirty-nine patients went on
to receive full-dose definitive RT. Of the 6 patients
who did not receive radiation therapy, 3 under-
went laryngectomy for failure to achieve an
adequate response to chemotherapy, 1 died of na-
dir sepsis after refusing hospital admission, and 2
refused further treatment after induction therapy.

**Concurrent Chemoradiation.** Of the 39 patients who
went on to receive full-dose definitive RT, 2 pa-
tients did not receive any concomitant chemother-
apy: 1 with a recent dermatologic infection and the
second due to renal failure. One patient on regi-
men 1 received cisplatin only due to possible aller-
gic reaction to paclitaxel. Eighteen patients were
treated on the concurrent cisplatin arm. For regi-
men 1, dose delivery was 72% for cisplatin and
81% for paclitaxel. However, 6 patients failed to
receive at least 5 weekly doses of paclitaxel due to
decreased counts. For regimen 2, dose delivery was
86%, with only 2 patients receiving less than 5
doses of concurrent chemotherapy.

Fifteen of 39 patients who underwent irradiation
required no treatment breaks, completing 70 Gy in 7
weeks. Twenty patients required a 1- to 5-day break in radiation, most commonly for per-
cutaneous gastrostomy tube (PEG) placement.
Three patients required more than a 5-day break.

PEGs were not mandated unless patients had
significant weight loss due to dysphagia at the
time of initial presentation. PEGs also were placed
if patients developed weight loss despite nutritional counseling. A total of 16 patients required PEGs at some point before completion of treatment. All patients were able to have PEGs removed by 1 year after treatment completion.

**Toxicity.**

**Induction Chemotherapy.** All 44 patients were eligible for assessment of toxicity. ICT was generally very well tolerated. Grade 3 and 4 toxicities are noted in Table 3. As expected, hematologic toxicity with neutropenia and thrombocytopenia predominated. Four patients experienced severe complications while on induction therapy. One patient died of nadir fever after refusing hospitalization with a known febrile episode. One patient developed an unusual dermatologic infection that necessitated protracted antibiotic therapy and removal from study. Both events were deemed to be related to treatment. One patient developed a severe drug eruption. Although the drug rash was not felt to be due to chemotherapy, all medications were discontinued due to the severity of the reaction. One patient developed cardiopulmonary toxicity secondary to an overdose of narcotics. The patient developed renal failure due to cholesterol embolization after undergoing cardiac catheterization. The toxicity was not felt to be related to treatment. No patients developed dose-limiting neurotoxicity.

**Concurrent Chemoradiation.** Toxicity is noted in Table 4. Five of the first 9 patients (55%) experienced anemia (hemoglobin ≤ 10 g/dL), requiring red blood cell transfusion, and median end-treatment hemoglobin dropped to 10.6 g/dL. Thereafter, all patients received prophylactic human recombinant erythropoetin 40,000 units/week, resulting in only 6 of 33 (18%) requiring transfusions, and median end-treatment hemoglobin was higher than median pretreatment levels (13.6 g/dL from 13.2 g/dL). No erythropoietin-related toxicities were noted.

Hematologic toxicity differed significantly between the 2 concurrent chemotherapy regimens.

**Table 3.** Induction therapy: worse grade toxicity.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10</td>
<td>20</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>3</td>
<td>–</td>
</tr>
<tr>
<td>Fever/infection</td>
<td>1</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>–</td>
<td>4</td>
<td>–</td>
</tr>
</tbody>
</table>

**Table 4.** Acute toxicities of concurrent chemoradiation regimens.

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>CCR regimen 1 (n = 20)</th>
<th>CCR regimen 2 (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Xerostimia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transfusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red cells</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CCR, concurrent chemoradiation
Note. One patient died early during concurrent chemoradiation from acute upper gastrointestinal bleed secondary to esophageal variceal bleed, which was considered unrelated to therapy.
Three of 18 (16%) patients receiving the concurrent cisplatin/paclitaxel/radiation (regimen 1) experienced grade 3 or 4 anemia (Hgb ≤ 10 g/dL), whereas only 1 of 20 patients (5%) experienced grade 2 or higher with carboplatin/paclitaxel/radiation (regimen 2) \((p = .01)\). Likewise, 50% of patients on regimen 1 and 15% on regimen 2 experienced grade 3 or 4 neutropenia \((p = .01)\), and 40% of patients getting regimen 1 developed grade 3 or 4 thrombocytopenia compared with 5% on regimen 2 \((p = .03; \text{Table 4})\). Two toxic deaths occurred with treatment: 1 from nadir sepsis, and the second died 8 days after completion of treatment due to aspiration pneumonia. Both patients had been treated with concurrent cisplatin/paclitaxel.

**Response to Induction Therapy.** Per protocol, patients must have completed induction therapy to be considered eligible for response assessment. Thirty-nine patients were eligible for response to induction therapy. Response among the 39 eligible patients included the following: CR, 20 (51%); PR, 15 (38%); MR, 3 (7.7%); and SD, 1 (2.6%).

**Locoregional Control.** Three patients underwent laryngectomy after ICT per protocol for poor tumor response. In 1 patient, the surgical specimen had microscopic nests of residual tumor and was determined to be a near pathologic CR. All 3 patients are without evidence of tumor recurrence. Two patients with suboptimal response refused laryngectomy and proceeded to CCR. One patient had no evidence of disease, and 1 died of pneumonia shortly after completing therapy. Seven patients died of disease: 3 with local recurrence only and 4 with local or distant recurrence \((\text{Figures 1A and 1B})\). Six patients had a neck dissection, 3 of these with initial N3 disease and 3 others with N1 or N2 disease who had an incomplete nodal response to chemoradiation. Four of these 6 were histologically free of residual tumor.

**Organ Preservation.** Three patients underwent surgery at the primary tumor site for a poor response to ICT. All 3 remain free of tumor recurrence. Four patients had an incomplete response after CCR or experienced a recurrence at the primary tumor site and required salvage surgery. Two of the 4 are currently free of disease after salvage surgery.

**EFS and Overall Survival.** Median follow-up for all patients was 3.7 years. Two-year and 3-year survival was 71% and 67%, respectively. Nine patients (23%) died of disease, including 2 patients who were taken off of study for failure to comply with or complete therapy. Two patients died during or within 30 days of treatment, and these were considered treatment-related deaths: 1 due to nadir sepsis with refusal of medical care, and 1 with pneumonia after completion of treatment. Another patient died of an esophageal bleed during treatment, which was unrelated to therapy. Four patients died of intercurrent disease without tumor relapse \((1 \text{ from myocardial infarction at 9 months, 1 from a secondary lung cancer at 36 months, and 2 from strokes at 25 months and 24 months})\). Actuarial overall survival \((\text{OS})\) at 36 months was 66%, and relapse-free survival \((\text{RFS})\) at 36 months was 80% \((\text{Figures 2A and 2B})\). Univariate analysis was performed to determine factors possibly related to RFS or OS. These included local failure, primary tumor stage, nodal stage, overall AJCC stage \((3 \text{ vs } 4)\), age \((< 60 \text{ vs } \geq 60)\), sex, primary site \((\text{larynx vs base of tongue})\), ECOG performance \((1 \text{ vs } 2)\), ICT response \((\text{CR or } \text{PR})\), and patient age at diagnosis. The analysis showed that age, primary tumor stage, and ECOG performance were significant predictors of RFS and OS.
PR vs <PR), need for neck dissection, and need for salvage surgery at the primary site. No factors reached statistical significance using either log-rank or Wilcoxon tests except AJCC stage (log-rank \( p = .01 \)) and ICT response (log rank \( p < .001 \)). Carboplatin/paclitaxel concurrent chemotherapy approached statistical significance (\( p = .08 \)).

**Patterns of Failure.** Patterns of first failure are presented in Table 5. Six patients who completed therapy eventually died of disease: 2 with local recurrence, one with locoregional recurrence, and 3 with metastatic disease (with or without locoregional recurrence; Table 5).

One patient had a recurrence solely in regional lymph nodes and had a successful salvage nodal dissection. A total of 7 patients (17%) developed distant metastases. Three of these were either associated with or following a primary tumor recurrence. All patients have succumbed to disease. Four patients experienced distant metastases without evidence of either local or regional recurrence. Three died from disease, and 1 died of intercurrent disease (myocardial infarction). Four additional patients died of intercurrent disease at a median of 24 months.

An analysis of possible risk factors for recurrence was performed. Tumor stage, tumor primary site, nodal status, induction response, age, and overall AJCC stage were considered; only tumor response to ICT (<CR) met statistical significance (\( p = .05 \)). An analysis of possible risk factors for distant metastatic disease was also performed. Local recurrence was the only statistically significant factor for development of distant metastases. Primary tumor stage, overall AJCC stage, nodal stage, induction response, number of cycles of induction, and age did not meet statistical significance.

**Symptom Assessment.** Results of the PSS-HN are presented in Table 6. Thirty-two patients were enrolled on study after the study was amended to include the PSS-HN as an outcome parameter. Patients failing to complete the baseline questionnaire and at least 50% of scheduled assessments were excluded from the analysis. Patients who were taken off study due to inadequate response to induction therapy, toxicity, or death were included in the analysis in order to avoid bias. Patients who were lost to follow-up or transferred care to a community hospital after completion of therapy were included in the analysis for the number of time points for which data were available. As noted, there is a marked decline in all 3 parameters at completion of CCR, with a return to baseline by month 6.

**DISCUSSION**

Results of this study demonstrate the feasibility and efficacy of ICT with carboplatin and paclitaxel followed by CCR with a taxane-based regimen.

<table>
<thead>
<tr>
<th>Table 5. Patterns of failure.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
</tr>
<tr>
<td>No failure</td>
</tr>
<tr>
<td>Local (with/without regional or distant metastases)</td>
</tr>
<tr>
<td>Distant metastases only</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Note. Two of 44 patients were considered unevaluable. Of the remaining 42, two patients who died within 30 days of treatment (neutropenic fever, pneumonia). One patient with simultaneous recurrences locally, regionally, and distantly, and the patient who had laryngectomy after induction chemotherapy were included in the local failure category. Two other patients died with local and regional failure without distant metastases.
The dose delivery of induction therapy with carboplatin and paclitaxel was high with 83% of patients receiving the scheduled treatment. The response rates were high at 89%, and toxicity was modest. CCR with every 3 week cisplatin plus weekly paclitaxel resulted in an excellent local control rate; however, the hematologic toxicity was significant. After the first 9 patients, erythropoietin was added to the regimen to ameliorate the severe anemia and excessive transfusion requirements. Although the addition of erythropoietin ameliorated the anemia, thrombocytopenia and neutropenia remained problematic. After the first 20 patients, weekly carboplatin was substituted for every 3 week cisplatin. This decision was based on emerging data showing comparable survival outcomes with carboplatin to cisplatin-based regimens for recurrent or metastatic patients but with lower toxicity. This change resulted in an effective, easy to administer, and tolerable treatment regimen. Function preservation rates were good with 7 patients undergoing surgical salvage: 3 per protocol for less than a partial response to induction therapy and 4 for persistent or recurrent disease. Only 2 patients died of local failure. A comparison between the 2 treatment arms failed to demonstrate a significant difference in overall survival. Functional outcome assessed using the PSS-HN demonstrated a return to baseline at 6 months.

There is little consensus as to which concomitant regimen provides the “optimal outcome.” Optimal outcome implies a balance between efficacy as measured by response and survival, and toxicity as measured by both acute and late effects, quality of life, and functional status. To complicate clinical decision-making further, the question as to which, if any, setting induction therapy improves survival when added to CCR has not been answered fully. Certainly subpopulations of patients would benefit more from an aggressive induction regimen than others (eg, patients with unresectable disease or those with a high risk of distant failure).

Investigators have taken several different approaches to identify the “optimal regimen.” The first approach is to use high doses of chemotherapy (either induction or concurrent) in the hopes of increasing efficacy. Unfortunately, in the head and neck patient population, more may not be better. Intensive chemoradiation regimens are associated with markedly increased acute toxicities and a mortality rate as high as 8%. Chemoradiation regimens have hit a “maximum tolerated toxicity”; indeed, some reported regimens may have passed that point. In addition, intense chemoradiation regimens require a highly coordinated team of experts accustomed to dealing with the sequelae of head and neck cancer therapy, which are unavailable to many community oncologists.

As presented in this paper, every 3 week induction carboplatin and paclitaxel followed by weekly carboplatin and paclitaxel with radiation was tolerable, effective, and easy to administer. During induction therapy, 46% of patients gained weight while 15% of patients lost weight, and 77% of patients had an increase in performance status, while 8% experienced a decrease in performance status. Concurrent carboplatin/paclitaxel/radiation was associated with high rates of oral mucositis; however, the mucositis was no more prolonged or severe than anticipated. Hematologic toxicity was limited, particularly after addition of erythropoietin. Furthermore, avoiding cisplatin in patients for whom adequate hydration is a challenge may ameliorate renal toxicity. The tolerable toxicity profile and ease of administration make this a regimen that can be exported to the general medical community.

Other investigators have reported similar promising results of induction carboplatin and paclitaxel. These provided the motivation to conduct a large confirmatory phase II trial through the ECOG (E2399). Preliminary results using this regimen show acceptable toxicity and high treatment delivery and tumor response rates in a multi-institutional setting.

To further diminish toxicity, investigators at Vanderbilt have been utilizing a weekly induction regimen with carboplatin AUC 2 and paclitaxel 60 mg/m². Preliminary results from 83 patients...
patients treated with concurrent carboplatin AUC 1–2 and paclitaxel 30 to 45 mg/m² and IMRT with or without induction carboplatin and paclitaxel were reported. This regimen was well tolerated, and early results demonstrate an excellent tumor control and 1- and 2-year overall and disease-free survival rates.

**CONCLUSIONS**

Concurrent chemotherapy plus radiation therapy is now standard treatment for patients with unresectable disease, in the organ preservation setting, and in postoperative patients with a high risk for disease recurrence. Whether the addition of induction therapy can improve CCR outcome in selected patients has yet to be definitively determined. Randomized trials using triplet taxane-based induction regimens appear promising. In the meantime, investigators continue to try to identify regimens that are feasible, have acceptable toxicity, and enhance survival and function outcome.

The results of this study demonstrate induction carboplatin and paclitaxel followed by every 3 week cisplatin with weekly paclitaxel was associated with undue toxicity. However, the substitution of weekly carboplatin and paclitaxel concurrent with radiation was feasible, had an acceptable toxicity profile, and was associated with a high rate of organ preservation. The ease of administration and low toxicity make this a regimen that is practical for use in the community setting. The value of ICT for organ preservation is currently an area of clinical investigation.

**REFERENCES**


