Intensification Regimen 2 for Advanced Head and Neck Squamous Cell Carcinomas

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Objective: To determine the feasibility, toxicity, and compliance of an intense treatment regimen for patients with advanced, previously untreated, resectable head and neck squamous cell carcinomas.

Design: Prospective, nonrandomized, controlled (phase 1 or 2) clinical trial; median time at risk, 25 months (range, 7 days to 36 months).

Setting: Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University, Columbus.

Patients: Forty-three patients (median age, 59 years; range, 32-76 years) with resectable, previously untreated stage III or IV squamous cell carcinomas of the oral cavity, oropharynx, or hypopharynx or stage II squamous cell carcinomas of the hypopharynx (referred sample of patients).

Interventions: Days 1 to 4, perioperative, slightly accelerated, hyperfractionated radiotherapy (9.1 Gy) to off cord fields; days 1 to 3, cisplatin, 30 mg/m² per day; day 4, surgical resection and intraoperative radiotherapy boost (7.5 Gy); days 45 to 52, postoperative radiotherapy (40 Gy to the primary site and upper neck and 45 Gy to the supraclavicular areas); days 24, 45, and 66, paclitaxel, 135 mg/m² per 24 hours, with routine granulocyte colony-stimulating factor support; and days 25 and 46, cisplatin, 100 mg/m².

Main Outcome Measures: Toxicity, compliance, local control, and distant metastatic rates.

Results: Patient compliance was 91% (39 of 43 patients), but protocol compliance was only 58% (25 of 43 patients), reflecting increased toxicity of the systemic regimen (2 [5%] of the 43 patients experienced grade 5 hematologic toxicity due to the regimen; 16 [37%], grade 4; and 10 [23%], grade 3). Local-regional control was 92% (23 of 25 patients), and the distant metastatic rate was 8% (2 of 25) in patients completing treatment per protocol. One patient had surgical salvage of a second primary tumor.

Conclusions: Local control and patient compliance were encouraging, but systemic toxicity was unacceptable. Thus, the paclitaxel was changed to a weekly regimen.


From the Divisions of Radiation Oncology (Drs Grecula, Nag, Bauer, Martinez-Monge, and Gahbauer) and Medical Oncology (Dr Rhoades), the Department of Otolaryngology (Drs Schuller and Agrawal), the College of Pharmacy (Drs Au and Johnson), and the Biostatistics Unit (Dr Young), Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, The Ohio State University Comprehensive Cancer Center, Columbus.
PATIENTS AND METHODS

The patients all originated from the Department of Otolaryngology, The Ohio State University, Columbus. The investigational protocol was reviewed and approved by the Scientific Review Committee of The Ohio State University’s Comprehensive Cancer Center and the Institutional Review Board. Eligible patients had previously untreated resectable squamous cell carcinomas (SCCs) of the oral cavity, oropharynx, or hypopharynx. The patients must have had clinically stage III or IV disease according to the American Joint Committee on Cancer (1992) and no distant metastases. Stage II hypopharyngeal carcinomas were also eligible. A Karmofsky performance index of 60 or greater, adequate bone marrow function (platelet count ≥ 100 × 10⁹/L, and absolute neutrophil count ≥ 2.0 × 10⁹/L), creatinine clearance greater than 1.0 mL/s (> 60 mL/min), and adequate hepatic function (bilirubin level, < 31 µmol/L [< 1.8 mg/dL], serum transaminases, < 4 times the upper limit) were required. Written informed consent was obtained from all patients before the initiation of therapy. Patients with prior malignant neoplasms were excluded unless they were disease free for 5 years, had adequately treated basal or squamous cell skin cancers, or had in situ cervical cancer (because of the excellent prognosis associated with these limited cancers). All patients were examined by a multimodality team consisting of a head and neck surgeon (D.E.S.), a dentist, a medical oncologist (C.A.R.), and a radiation oncologist (J.C.G., S.N., C.J.B., or R.A.G.). Patients with a history of cardiac disease were cleared for treatment by the medical oncologist. In general, patients with prior bradyarrhythmias, atrioventricular conduction defects, or marginal cardiac function were eligible but underwent cardiac monitoring during treatment. Forty-three patients were registered into the trial from January 20, 1996, through July 14, 1997.

The treatment schema is as follows. Perioperatively (days 1–4), the patients were given a slightly accelerated hyperfractionated boost of external beam radiotherapy consisting of 9.1 Gy with 6-MV x-rays delivered to the primary tumor and clinically involved nodes (excluding the spinal cord). The external beam radiotherapy was divided into 7 twice-daily treatments of 1.3 Gy with an interfraction interval of at least 6 hours. Concurrent cisplatin chemotherapy, 30 mg/m² per day, was delivered intravenously on days 1 to 3. Patients were hydrated intravenously with 1 L of 0.45% sodium chloride in 5% dextrose with 10 mEq of potassium chloride, 2 g of magnesium sulfate, and 40 g of mannitol for 2 hours before cisplatin therapy. Surgical resection and intraoperative radiotherapy to the site of closest surgical margin were performed on day 4. For patients with surgical margins negative for tumor (as determined by frozen section pathologic analysis), a modest intraoperative dose of 7.5 Gy was delivered with 6-MeV electrons (prescribed to the 90% isodose) or iridium 192 high-dose rate brachytherapy (prescribed at a depth of 0.5 cm). For 1 patient with microscopic tumor at the surgical margins at the base of the skull, a dose of 10 Gy was delivered with 6-MeV electrons. On day 24, the patients began a 24-hour intravenous infusion of paclitaxel, 135 mg/m² (the first 2 patients received their first dose at 175 mg/m²; the protocol was then amended secondary to grade 4 neutropenia). All patients were premedicated with dexamethasone, 20 mg orally at 12 and 6 hours before the beginning of paclitaxel infusion or 20 mg intravenously 30 minutes before paclitaxel infusion. The patients received 300 mg of cimetidine hydrochloride intravenously and 50 mg of diphenhydramine hydrochloride intravenously 30 minutes before paclitaxel therapy. On day 25, after intravenous hydration (as previously discussed), patients received a second course (bolus intravenous infusion) of cisplatin, 100 mg/m², over 2 hours and underwent postoperative external beam radiotherapy with 6-MV x-rays (an additional 40 Gy delivered in 20 treatments to the primary tumor site and regional draining lymph nodes and 45 Gy delivered in 20 treatments to the lower neck and bilateral supraclavicular areas). Parallel opposed upper neck fields were prescribed to midline, and the lower neck/bilateral posterior neck electron boosts of 10 Gy (at 100% isodose) were delivered in 5 treatments. The electron energy was chosen to limit the spinal cord dose to less than 45 Gy (total dose). On days 45 and 66, the second and third courses of paclitaxel, 135 mg/m², were infused over 24 hours. The third course of cisplatin, 100 mg/m², was delivered on day 46 (also with prehydration as previously described). All patients received subcutaneous injections of recombinant human granulocyte-colony stimulating factor (G-CSF) beginning 24 hours after the completion of each paclitaxel infusion at 300 µg/d for 10 days or until the absolute granulocyte count was greater than 10,000, at least 1 week after the paclitaxel treatment. Prophylactic antibiotic and antifungal coverage with oral ciprofloxacin hydrochloride, 500 mg twice daily, and oral fluconazole, 100 mg daily, was administered to all patients who developed an absolute neutrophil count of less than 0.5 × 10⁹/L. The medications were continued until the absolute neutrophil count was above 1.5 × 10⁹/L. Radiotherapy was delayed for an absolute neutrophil count of less than 0.5 × 10⁹/L and continued when it was greater than 0.5 × 10⁹/L. If the absolute neutrophil count was less than 1.5 × 10⁹/L, chemotherapy was delayed until it rose above 1.5 × 10⁹/L. If the delay in granulocyte recovery was 7 days or longer, the next dose of paclitaxel was reduced to 100 mg/m², and the cisplatin dose was decreased to 80 mg/m². The same dose reductions were performed for Radiation Therapy Oncology Group (RTOG) grade 2 or higher thrombocytopenia (platelet count < 75 × 10⁹/L) on the day paclitaxel was to be administered. If the patient had neutropenic fever, the second paclitaxel dose was reduced to 100 mg/m²; if neutropenic fever persisted, the third dose was reduced to 75 mg/m².

The pathologic stage and outcome are given in Table 1. This population included 29 men and 14 women; 2 men and 1 woman were African American. The age of the patients ranged from 32 to 76 years (median, 59 years). Of the 43 patients, 11 (26%) had oral cavity primary cancer, 20 (47%) had oropharyngeal primary cancer, 11 (26%) had hypopharyngeal primary cancer, and 1 (2%) had a supraglottic carcinoma with hypopharyngeal extension. Table 2 shows the clinical and pathologic stages of the patients. In 29 (67%) of the 43 patients, the clinical and pathologic stages coincided. Ten patients (23%) had a higher pathologic stage, secondary to nodal status. Two patients (5%) with mandibular gingival carcinomas had evidence of mandibular involvement clinically but not pathologically. Thus, the stage of their cancer was decreased from cIV to pII. Two patients (5%) had pathologic stage III (T3 N0 M0) carcinomas of the tonsil and clinical stage IV disease (T4 N2b M0 and T4 NX M0, respectively).

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cisplatin chemotherapy and radiotherapy, have previously been published. They demonstrated excellent patient compliance (92%) and excellent local-regional control. Two of the 37 patients developed second primary tumors, but there were no local tumor recurrences at median time at risk (18.6 months). An unpublished update at a median time at risk of 40 months upholds the excellent local control (J.C.G., D.E.S., Roy Smith, MD, et al, 1999). Since distant metastases developed in 5 (17%) of the 29 patients who received treatment per protocol, paclitaxel was added to the postoperative regimen in the intensification 2 protocol (IRII). Also, the dosage of the perioperative cisplatin was changed, from 80 mg/m² per 80-hour continuous infusion to 30 mg/m² per day for 3 days, to allow outpatient administration. Considering the excellent local control in the IRI, the radiotherapy schema was not changed.

**RESULTS**

At the time of analysis, the time at risk (length of follow-up or survival) for the 43 patients ranged from 7 days to 36 months (median, 25 months). As this was a phase 1 or 2 trial, the primary objectives were to assess compliance, toxic effects of the new intensified regimen, local control, and incidence of distant metastases. Comparative analysis of survival with historical controls was not an objective.

**COMPLIANCE**

Patient noncompliance (defined as the patient deciding against continuing treatment per protocol) was 9% (4 of 43 patients). One patient refused postoperative chemotherapy, 1 refused his last radiation treatment due to RTOG grade 2 mucositis, 1 refused further chemo-

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**Table 1. Patient Outcome**

<table>
<thead>
<tr>
<th>Affected Area</th>
<th>Pathologic Stage</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>T1</td>
<td>.</td>
<td>.</td>
<td>.</td>
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<td>.</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>14 and 19</td>
<td>.</td>
<td>41†</td>
<td>39</td>
<td>14, 19, 39, and 41, NED</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>.</td>
<td>26†</td>
<td>32† and 40†</td>
<td>.</td>
<td>26, 32, and 40, DwD</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>.</td>
<td>11 and 20</td>
<td>36†</td>
<td>8†</td>
<td>8, DwD (lr); 11, NED; 20, NED (surgical salvage of a second gingival primary tumor); and 36, DwD (lr, rnd, dm)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>T1</td>
<td>.</td>
<td>34</td>
<td>12,† 21,† and 37†</td>
<td>.</td>
<td>12, DwoD; and 21, 34, and 37, NED</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>.</td>
<td>.</td>
<td>4, 10, 15, 23, 25†</td>
<td>.</td>
<td>4, 10, 17, and 22, NED; 15, DwD (dm); 23, DwD (lr); and 25, DwD</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>38 and 42†</td>
<td>7</td>
<td>1,† 16, 24,† and 29</td>
<td>.</td>
<td>1, DwD (lr); 7, 29, 38, and 42, NED; 16, DwD (lr, dm); and 24, DwD</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>T4</td>
<td>.</td>
<td>.</td>
<td>18 and 35</td>
<td>.</td>
<td>18, NED; and 35, DwD</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
<td>.</td>
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<tr>
<td></td>
<td>T2</td>
<td>13,† 28, and 31</td>
<td>2, 3,† 5, 9,† 33, and 43</td>
<td>.</td>
<td>2 and 3, DwoD; and 5, 9,† 13, 28, 31, 33, and 43, NED</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>.</td>
<td>.</td>
<td>6</td>
<td>.</td>
<td>6, NED</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>.</td>
<td>27†</td>
<td>30†</td>
<td>.</td>
<td>27 and 30, NED</td>
</tr>
</tbody>
</table>

* The numbers indicate patient reference number; NED, alive with no evidence of disease; DwoD, dead without disease; DwD, dead with disease; lr, local recurrence; rnd, regional nodal disease; dm, distant metastases; and ellipses, data not applicable.
† Protocol noncompliance.
‡ Supraglottic.

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**Table 2. AJCC (1992) Clinical Stage vs Pathologic Stage**

<table>
<thead>
<tr>
<th>Stage</th>
<th>pII</th>
<th>pIII</th>
<th>pIV</th>
<th>No. of Patients per Clinical Stage</th>
</tr>
</thead>
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<tr>
<td>cII</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
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<td>cIII</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>cIV</td>
<td>2</td>
<td>25</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>No. of patients per pathologic stage</td>
<td>2</td>
<td>34</td>
<td>43</td>
<td>43</td>
</tr>
</tbody>
</table>

*AJCC indicates American Joint Committee on Cancer; p, pathologic stage; and c, clinical stage.

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**Table 3. Toxity**

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**TOXICITY**

Toxicity (Table 3) was graded primarily using the RTOG Criteria for Acute and Late Effects. (The Southwest Oncology Group/National Cancer Institute Common Toxicity Criteria were used for categories not covered by RTOG.)

Acute morbidity was defined as adverse results that occurred within the first 90 days after initiating the perioperative treatment. During treatment, 5 (12%) of the 43 patients died. One of the patients, a 75-year-old woman with a clinical stage IV carcinoma of the palate, died on day 7 of a postoperative myocardial infarction. Two pa-
tients, a 67-year-old woman with a stage IV carcinoma of the piriform fossa and a 44-year-old man with a stage IV carcinoma of the tonsil, died of treatment-related sepsis on day 33 (after 2 courses of cisplatin and 1 course of paclitaxel at full doses) and day 53 (after 3 courses of cisplatin and 1 course of paclitaxel at full dose and 1 course of paclitaxel at reduced dose per protocol), respectively. The 67-year-old patient also required an angioplasty of the proximal anastomosis of a prior femoral-popliteal bypass graft and plasminogen activator thrombolytic therapy. A 67-year-old man with a clinical stage III carcinoma of the base of the tongue died on day 50 at a nursing home; he had been hospitalized 1 week before death for neutropenic fevers, sepsis, pneumonia, and patchy colitis. He had received 2 courses of cisplatin and 1 course of paclitaxel at full doses. He was admitted, treated, and discharged from a local hospital after a diagnosis of dehydration. He later died at home on day 50.

Despite receiving routine G-CSF after paclitaxel infusion, patients experienced notable neutropenia or leukopenia (10 [23%] experienced RTOG grade 3; 16 [37%], grade 4; and 2 [5%], grade 5). Of the 43 patients, 18 (42%) required hospitalization for infection-related complications, 3 (7%) developed abscesses, and 1 (2%) developed peritonitis (after G tube insertion). Only 5 (12%) of the 43 patients developed RTOG grade 3 mucositis. Granulocyte colony-stimulating factor might have served as a mucosal protectant. One patient (2%) developed an RTOG grade 3 skin reaction and received only 32 Gy of the planned 40 Gy of postoperative radiotherapy. Of the 43 patients, 3 (7%) experienced cardiac complications. Two patients developed myocardial infarctions during treatment (1 fatal), and 1 patient developed atrial fibrillation, requiring cardioversion. Of the 43 patients, 4 (9%) developed thrombosis (1 deep venous thrombosis, 1 pulmonary embolus, and 2 occlusions of vascular grafts); 7 (16%), fistulae; 4 (9%), exposed bone; and 1 (2%), optic neuropathy (after carotid resection for a nonhealing wound).

Late toxicity was defined as occurring more than 90 days after the initiation of treatment. Radiation Therapy Oncology Group grade 3 xerostomia developed in 4 (9%) of the 43 patients; esophageal stricture, 1 (2%); hypopharyngeal stricture, 1 (2%); and chronic aspiration requiring a completion laryngectomy after primary treatment for a stage III hypopharyngeal carcinoma, 1 (2%).

SURVIVAL

In this study, the 2-year disease-specific survival rate was 86% (37 of 43 patients), and the overall survival rate was 65% (28 of 43 patients) (Figure). There have been 15 deaths (33%) (median time at risk, 25 months). Five deaths (12%) occurred during treatment as previously described. Four patients (9%) died without disease (1 of

<table>
<thead>
<tr>
<th>Type of Toxicity</th>
<th>Acute 3</th>
<th>Acute 4</th>
<th>Acute 5</th>
<th>Late 3</th>
<th>Late 4</th>
<th>Late 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic†‡</td>
<td>10 (23)</td>
<td>16 (37)</td>
<td>2 (5)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Infections requiring hospitalization‡</td>
<td>13 (30)</td>
<td>3 (7)</td>
<td>2 (5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis†‡</td>
<td>5 (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Skin†</td>
<td>1 (2)</td>
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<td></td>
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<tr>
<td>Fistula†</td>
<td></td>
<td>7 (16)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Thromboembolic‡</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac‡</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (2)</td>
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<tr>
<td>Optic neuropathy‡</td>
<td>1 (2)</td>
<td></td>
<td></td>
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<tr>
<td>Xerostomia†</td>
<td></td>
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<td>1 (2)</td>
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<tr>
<td>Hypopharyngeal stenosis‡</td>
<td></td>
<td></td>
<td></td>
<td>1 (2)</td>
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<td></td>
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<tr>
<td>Esophageal stenosis‡</td>
<td></td>
<td></td>
<td></td>
<td>1 (2)</td>
<td></td>
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<tr>
<td>Laryngeal dysfunction, requiring laryngectomy‡</td>
<td></td>
<td></td>
<td></td>
<td>1 (2)</td>
<td></td>
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</tbody>
</table>

*Data are given as the number (percentage) of patients. Acute toxicity occurred from day 1 to day 90; later, after day 90. The numbers (3, 4, and 5) indicate the grade; ellipses, data not applicable.
†Grade according to Radiation Therapy Oncology Group Criteria.
‡Grade according to Southwest Oncology Group/National Cancer Institute Common Toxicity Criteria.

Survival rate of the 43 patients studied.
a cerebral aneurysm, 1 of respiratory tract failure, and 2 of unknown causes. Six patients (14%) died with disease (3 with local failure only; 1 with local failure and distant metastases [lung]; 1 with local failure, regional nodal failure, and distant metastases [lung]; and 1 with only distant metastases [liver]). Three of these 6 patients received all treatments per protocol and had longer disease-free intervals (20, 21, and 21 months) than the 3 patients who did not (1, 6, and 11 months). The patient who developed an intracranial relapse at 1 month had microscopic residual tumor at the surgical margins of the vagus nerve at the base of the skull. His tumor classification was a clinical stage IV (T4 N2c M0) floor of the mouth carcinoma.

**LOCAL-REGIONAL CONTROL/DISTANT METASTASIS FREE RATE**

The overall local-regional control rate was 88% (38/43), and the distant metastasis free rate was 93% (40/43). In the 25 (58%) of the 43 patients who received all treatments per protocol, local-regional control was 92% (23 patients), and the distant metastases free rate was also 92%. Eight (32%) of these 25 patients required dose reductions per protocol guidelines for hematologic toxicity. One patient with a clinical stage III (T1 N1 M0) carcinoma of the anterior gingiva developed a second primary gingival carcinoma (stage I [T1 N0 M0]) away from the site of her original primary lesion 23 months after the initiation of therapy. The area was, however, in her prior radiotherapy fields. She underwent surgical salvage and has been disease free for an additional 9 months.

**COMMENT**

The IRI provided evidence that a multimodality regimen with perioperative cisplatin chemotherapy and radiotherapy, surgical resection, intraoperative radiotherapy, and postoperative cisplatin chemotherapy and radiotherapy was not only feasible but achieved excellent local-regional control and compliance. The distant metastases rate, however, was 17% in the 29 patients who received all of their treatment per protocol (ie, 5 patients had distant metastases). One of the goals of the IRII was thus to further intensify the systemic component of treatment.

During the IRI, laboratory studies with human tumor samples were carried out concurrently to address the issues of drug treatment duration and sequencing. In vitro pharmacodynamic studies demonstrated an immediate effect and a delayed effect of paclitaxel on human epithelial cancer cells, including the pharynx FaDu cell line. The immediate effect increased with treatment duration and drug concentration. For the delayed effect, treatments for 12 hours or less were less effective and required higher drug concentrations to produce 50% inhibition of cell growth than treatments for 24 hours or longer; treatments 24 hours or longer were equally effective. Thus, a 24-hour infusion of paclitaxel was chosen for the IRII.

Phase 2 studies of paclitaxel demonstrated that this agent was effective clinically in head and neck carcinomas. At our institution, paclitaxel, 250 mg/m² per 24-hour infusion, was used in previously treated and untreated patients with clinical stage II SCCs of the hypopharynx or clinical stage III and IV SCCs of the oral cavity, oropharynx, hypopharynx, or larynx. An objective response rate of 36% (12% complete responses and 24% partial responses) was observed in the initial patients. Only 3 (13%) of the initial 23 patients developed grade 4 granulocytopenia with routine G-CSF support. The Eastern Cooperative Oncology Group also completed a phase 2 trial of paclitaxel, 250 mg/m² per 24-hour infusion, and G-CSF in patients with advanced SCCs of the head and neck. Their patients had recurrent disease, newly diagnosed incurable local-regional disease, or distant metastases. The overall response rate (complete responses and partial responses) was 40%, and 91% developed grade 3 or 4 neutropenia.

Phase 1 trials with the combination of cisplatin and paclitaxel were completed by Rowinsky and colleagues and thus gave some assurance that the proposed chemotherapy treatment schedule in the IRII was reasonable. The interaction of paclitaxel, radiation therapy, and cisplatin was studied in human FaDu head and neck SCC cells in our concurrent translational laboratory study, and we found that the extent of synergy was dependent on the sequence of drugs. Paclitaxel followed by cisplatin produced a 7.5-fold synergy, whereas the reverse sequence produced only a 2.4-fold synergy. Thus, the former sequence was incorporated into the IRII.

Steinberg et al subsequently published a phase 1 study in 1997 of radiotherapy and 24-hour infusion of paclitaxel without G-CSF support in patients with locally advanced head and neck SCCs. They demonstrated that the maximum tolerated dose was 75 mg/m². This earlier study showed that 65% of patients developed grade 3 mucositis, in contrast to the 12% in our study. This difference may be due to the fact that a split course of radiotherapy was delivered in the IRII and perhaps also due to the mucosal protectant effect of G-CSF.

Intraoperative radiation therapy has the advantages of (1) a directly visualized boost to the areas of close surgical margin, (2) sparing of a portion of the normal surrounding tissues, and (3) treatment acceleration. However, potential drawbacks include the radiobiological disadvantages of a single large fraction, namely, increased late effects and the lack of tumor reoxygenation effect. The purposes of the slightly accelerated hyperfractionated perioperative boost radiosensitized with cisplatin were (1) to allow a more modest dose of intraoperative radiotherapy to be delivered (since late effects or complications are directly dependent on the size of the radiation fraction) while still delivering a clinically notable dose in this split-course regimen and (2) to condense the overall treatment time to improve local control and compliance. The goal was not to study altered fractionation per se. In this IRII, there were no treatment-related deaths due to radiotherapy, and the radiation morbidity was not unusual for this patient population.

The preliminary survival data reported in this study (Figure) are only intended to provide an initial assessment of this regimen, not to make a comparative statement about survival differences with other larger trials.
This IRII uses a combination of surgery, radiotherapy, and chemotherapy to attempt to decrease local-regional and distant disease, while increasing compliance. The IRII did decrease distant disease compared with the IRI (8% vs 17% in patients completing treatment per protocol). Also, the ultimate local control with the complete IRII, plus 1 surgical salvage for a second primary tumor, was excellent (92%). However, the short-term hematologic toxicity of the regimen was unacceptable (2 patients [5%] experienced grade 5; 16 [37%], grade 4; and 10 [23%], grade 3) and may have been related to the 24-hour exposure to paclitaxel.

We have initiated a new protocol, intensification 3, that uses weekly paclitaxel, $45 \text{ mg/m}^2$ per 3-hour infusion, for 9 courses beginning on day 10; 1 perioperative and 2 postoperative courses of cisplatin, $30 \text{ mg/m}^2$ per day for 3 days; and the same radiotherapy and surgery schedule with the exception that the postoperative radiotherapy begins on day 32 rather than day 25. If the toxicity of this new regimen is acceptable, a multi-institutional trial will be planned.

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