Long-term outcomes with concurrent carboplatin, paclitaxel and radiation therapy for locally advanced, inoperable head and neck cancer

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Received 25 September 2006; revised 7 February 2007; accepted 8 February 2007

Background: Our goal was to evaluate long-term efficacy outcomes of patients with squamous cell carcinoma of the head and neck (SCCHN) treated with carboplatin, paclitaxel (Taxol) and radiotherapy.

Patients and methods: We conducted a phase II trial in inoperable patients with locally advanced SCCHN. Carboplatin 100 mg/m² and paclitaxel 40 mg/m² were administered i.v. once a week during external beam radiation therapy (180 cGy per fraction) for 6–7 weeks. Interstitial brachytherapy was used as a boost in selected patients with primary malignancies of the oral cavity and the oropharynx.

Results: Fifty-five patients were enrolled. Fifty-two patients (95%) had stage IV and 51 (93%) had technically unresectable disease; 62% had an oropharyngeal primary site. Twenty-one patients underwent brachytherapy boost. Grade 3 or 4 mucositis occurred in 30% of patients. One death occurred during treatment that was related to complications of gastrostomy tube placement. Forty of 50 assessable patients (80%) had an objective response, with a complete response rate of 52%. With a median follow-up of 69 months for surviving patients, the 5-year progression-free survival was 36% and the 5-year overall survival was 35%. Two of the 18 long-term survivors of >50 months were gastrostomy tube feeding dependent. Patients undergoing brachytherapy boost (n = 21) had similar outcomes compared with the rest of the patients. In multivariate analysis, baseline hemoglobin levels and N stage were predictive of survival.

Conclusion: Treatment with concurrent carboplatin, paclitaxel and radiation is safe and offers curative potential for poor prognosis patients with locally advanced SCCHN.

Key words: brachytherapy, carboplatin, head and neck cancer, paclitaxel, radiation

introduction

Head and neck cancer is a worldwide health problem. In the United States alone, it afflicts ~40 000 people per year and accounts for 3% of all cancers [1]. More than 90% of these cancers are squamous cell carcinomas. The majority of patients with squamous cell carcinoma of the head and neck (SCCHN) present with locoregionally advanced disease and are managed with combined modality approaches. Newer treatment strategies that incorporate a combination of systemic agents and radiation are being widely investigated in this setting with the goal of improving both locoregional and distant disease control.

Several randomized phase III trials and meta-analyses have documented a survival and/or organ preservation benefit from the addition of chemotherapy to radiation as primary therapy for locally advanced SCCHN [2–6]. Multiple chemotherapeutic agents have been investigated in combination with concurrent radiation, the most commonly used of which is cisplatin. In patients with unresectable, locally advanced SCCHN, a subset of patients with a particularly poor outlook, a phase III trial showed that radiotherapy with cisplatin was superior to radiotherapy alone; the 3-year survival improved from 23% to 37% [2]. In the same three-arm study, however, a regimen of concurrent radiation, cisplatin and 5-fluorouracil (5-FU) with optional surgical salvage failed to show superiority over radiotherapy alone. Other phase II trials that included cisplatin-based combinations and radiation have shown promising results [7]. Whether two-drug combinations offer an advantage over monotherapy in the setting of concurrent chemoradiotherapy for SCCHN remains uncertain.

Carboplatin, a DNA-damaging platinum agent, is a potent radiosensitizer and has been shown to enhance the effect of radiation alone in a small number of randomized clinical trials...
in locally advanced SCCHN [8, 9]. As compared with cisplatin, carboplatin has the advantage of decreased incidence of out-of-field toxic effects, such as nephrotoxicity, ototoxicity and neurotoxicity. Paclitaxel, a taxane, is also considered a potent radiosensitizer [10], possibly due to its effect in inducing cell cycle arrest in G2/M phase. Both carboplatin and paclitaxel have demonstrated promising clinical activity as single agents and in combination regimens against recurrent or metastatic SCCHN [11–14]. Based on the activity of carboplatin and paclitaxel in SCCHN and emerging promising data from other groups [15, 16], we designed a phase II trial to test the combination of weekly carboplatin and paclitaxel administered concurrently with radiation therapy for patients with locally advanced, inoperable SCCHN. In addition, we incorporated brachytherapy as boost radiotherapy in selected patients in order to further improve locoregional control. We report an analysis of long-term outcomes of this study.

patients and methods

patient selection

Eligible patients were adults (218 years) of good performance status (PS) (Karnofsky scale ≥70%) with stage III–IV (American Joint Committee on Cancer (AJCC), 5th edition, 1997), measurable or evaluable, locally advanced, pathologically proven SCCHN without evidence for distant metastases who had not been previously treated with chemotherapy or radiation therapy. Patients with tumors of unknown primary site were included, provided they met all other eligibility criteria. All patients were either deemed unresectable by the otolaryngologist or had refused surgical treatment by desiring an organ-sparing approach. Unresectability criteria included invasion of the carotid artery, base of skull, prevertebral fascia or cervical spine, or inability to achieve a functional reconstruction. A multidisciplinary team consisting of an otolaryngologist, a medical oncologist and a radiation oncologist evaluated each patient before protocol enrollment. Clinical staging was carried out by physical examination, endoscopy and examination under anesthesia and radiologic studies that included computed tomography (CT) or magnetic resonance imaging (MRI) of the neck and chest radiograph. All patients had dental evaluation at baseline. All but two patients received prophylactic gastroscope tubes for nutritional support either before or soon after initiation of chemoradiotherapy.

Adequate hematologic (white blood cell ≥3500/µl, platelets ≥100 000/µl, hemoglobin (Hb) ≥9 g/dl), renal (serum creatinine <1.5 g/dl, calculated creatinine clearance >50 ml/min) and hepatic (bilirubin <1.6 g/dl) function had to be demonstrated by appropriate laboratory testing before enrollment. Other eligibility criteria included the absence of concomitant or prior second malignancy (except for basal cell carcinoma of the skin, nonmelanoma skin cancer or carcinoma in situ of the cervix) or any concurrent medical illness that would potentially interfere with completion of protocol therapy. Pregnant or lactating females were excluded, as were patients of childbearing potential who did not use an adequate method of contraception while on therapy. All patients provided full, written informed consent.

treatment plan

chemotherapy. The chemotherapy regimen consisted of paclitaxel (Taxol) (40 mg/m²/week), administered as an i.v. infusion for 3 h followed by carboplatin (100 mg/m²/week) as 1-h infusion. Therapy was administered in the outpatient setting following i.v. hydration and appropriate premedications and antiemetics. Chemotherapy was initiated within 2 days of starting radiation therapy and was given for 6–7 weeks.

dose modifications. Hematology tests and serum chemistry was repeated every other week. Toxic effects were graded using National Cancer Institute Common Toxicity Criteria. If the absolute neutrophil count (ANC) was >2000/µl and the platelets were >100 000/µl, full doses of chemotherapy were administered. If the ANC was between 1000 and 1999/µl or the platelet count was between 75 000 and 100 000/µl, the dose of both chemotherapy drugs was reduced by 50%. If the ANC was <1000/µl or the platelet count was <75 000/µl, both chemotherapy drugs were held for 1 week and counts were repeated 1 week later. Radiation therapy was held only for grade 4 mucositis.

response evaluation

Patients were evaluated weekly with a history and physical examination, documentation of PS and toxicity evaluation. Laboratory testing (complete blood count, differential, platelet count) was carried out at least every other week and more often as indicated. CT scans and/or MRI scans of the neck and chest radiograph, and other radiographic evaluation as indicated, was carried out before and 4–6 weeks after completion of therapy. Complete response (CR) was defined as the disappearance of all known tumor masses lasting for at least 4 weeks, without the appearance of new lesions. Partial response (PR) was defined as a decrease in 50% or more in the sum of the products of the largest perpendicular diameters of all measurable lesions. Progressive disease was defined as an increase of >25% of the above measurements or the appearance of any new lesions. Measurements obtained that were between the definitions of PR and progressive disease were considered to be stable disease (SD).
This phase II study was designed to accrue in two stages. It was planned to accrue 25 patients in the first stage with the intention of accruing additional patients only if at least 12 responses were noted, i.e. the response rate was at least 48%. This end point was met, and the study went on to accrue a total of 55 patients. Patients' characteristics were summarized by descriptive statistics (median, range and frequency). The percentage of patients experiencing clinical response (CR or PR) was reported along with the corresponding exact 95% confidence intervals (CIs) [17]. The overall survival (OS) was calculated as the time difference between day 1 of treatment and death or last follow-up, if patient was still alive. The progression-free survival (PFS) was calculated as the time difference between day 1 of treatment and time of recurrence/progression or last follow-up. Kaplan–Meier curves [18] (with 95% CI) were plotted for OS and PFS. Log-rank tests [19] were used for the comparisons of survival outcomes stratified by different covariates, including baseline Hb level (low versus high), disease stage (T0–3 versus T4, N0–1 versus N2–3), brachytherapy (yes versus no), PS (0 versus 1) and disease site (oropharynx versus others). Cox regression models [20] were used to assess the effect of continuous baseline Hb level, together with other covariates found significant in log-rank tests, on PFS and OS.

results

patient characteristics

From January 1997 to December 2001, a total of 55 patients were entered in this protocol. One patient withdrew consent less than a month after initiation of therapy, and was not assessable for toxicity or clinical response. A total of 54 patients were assessable for toxicity and 50 for response. Baseline characteristics are depicted in Table 1. Fifty-two patients (95%) had stage IV disease. The T and N stage distribution, using the AJCC staging classification, 4th edition, 1992, is shown in Table 2. All but four patients (93%) were deemed unresectable by the treating otolaryngologist; the remaining four patients were technically resectable but opted for nonsurgical therapy, including one patient with nasopharyngeal primary. The most common primary site of tumor was the oropharynx (62%), followed by the larynx (15%). In all, 21 of 55 patients (38%) underwent brachytherapy as a post-EBRT boost; selection criteria are outlined in the Patients and methods section. Three patients underwent elective neck dissection after chemoradiotherapy for residual lymphadenopathy.

treatment delivery and toxic effects

Seven patients (13%) required either a dose reduction or treatment delay during therapy. At least 6 weeks of concurrent chemotherapy with carboplatin and paclitaxel was successfully administered to 48 of 55 patients (87%). The most common toxic effects experienced were gastrointestinal and hematologic. Table 3 provides details regarding toxicity grading for all assessable patients (n = 54). Most of these were grade 1–2. Grade 3 and 4 toxic effects were less common and included both systemic and in-radiation field events. Grade 3–4 in-field radiation mucositis occurred in 30% of patients and grade 3–4 in-field radiation dermatitis in 11%. One patient died of a perforated intestine following the placement of a gastrostomy tube while on treatment. As noted above, 53 of 55 patients (96%) had prophylactic gastrostomy tubes placed for nutritional support. Only two of 18 long-term survivors (11%), however, had ongoing severe dysphagia and remained gastrostomy tube feeding dependent. Other significant late

Table 1. Patient characteristics, N = 55

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Age in years, median (range)</th>
<th>Gender, No. (%)</th>
<th>Race, No. (%)</th>
<th>ECOG performance status, No. (%)</th>
<th>Primary site, No. (%)</th>
<th>Base of tongue</th>
<th>Oropharynx, other</th>
<th>Oral cavity</th>
<th>Larynx</th>
<th>Nasopharynx, T3N0</th>
<th>Hypopharynx</th>
<th>Unknown primary site</th>
<th>Other</th>
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<tr>
<td>Age in years, median (range)</td>
<td>58 (44–80)</td>
<td>Male</td>
<td>42 (76)</td>
<td>Caucasian</td>
<td>48 (87)</td>
<td>0</td>
<td>19 (34)</td>
<td>15 (27)</td>
<td>2 (4)</td>
<td>8 (15)</td>
<td>1 (2)</td>
<td>3 (5)</td>
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<td>Gender, No. (%)</td>
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<td>Female</td>
<td>13 (24)</td>
<td>African-American</td>
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<td>Race, No. (%)</td>
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<td>ECOG performance status, No. (%)</td>
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Table 2. T stage/N stage pairings

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<th>Tx</th>
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<th>T3</th>
<th>T4</th>
<th>Total</th>
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<td>–</td>
<td>–</td>
<td>1</td>
<td>12</td>
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<tr>
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<td>7</td>
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<td>3</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Total</td>
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<td>0</td>
<td>6</td>
<td>6</td>
<td>39</td>
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Table 3. Treatment-related toxic effects

<table>
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<th>Toxicity (%) of 54 patients</th>
<th>Grade</th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<tr>
<td>In-field mucositis</td>
<td>9</td>
<td>57</td>
<td>28</td>
<td>2</td>
<td></td>
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<tr>
<td>In-field dermatitis</td>
<td>44</td>
<td>24</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20</td>
<td>15</td>
<td>0</td>
<td>2</td>
<td></td>
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<tr>
<td>Vomiting</td>
<td>11</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7</td>
<td>9</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Other gastrointestinal</td>
<td>72</td>
<td>6</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Weight loss</td>
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<td>17</td>
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<tr>
<td>Fatigue</td>
<td>53</td>
<td>18</td>
<td>2</td>
<td>2</td>
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<tr>
<td>Dehydration</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Anemia</td>
<td>52</td>
<td>26</td>
<td>6</td>
<td>0</td>
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</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
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<td>Leukopenia</td>
<td>41</td>
<td>31</td>
<td>4</td>
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<tr>
<td>Neutropenia</td>
<td>17</td>
<td>11</td>
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</table>
toxic effects recorded in these 18 patients with a median follow-up of 69 months were as follows: dysphagia (n = 5, including two patients with gastrostomy tube), neck fibrosis (4), xerostomia (6), chronic leukopenia (1), pharyngeal stenosis (1) and hoarseness (1).

response
Of 50 patients assessable for response, 26 (52%) had a CR, 14 (28%) PR, three (6%) SD and seven (14%) progressed. Thus, 80% of patients achieved an objective response (95% CI, 66%–90%). Of seven patients who progressed at first evaluation, one patient progressed in the primary, one developed bony metastasis (vertebrae) and five developed lung metastasis.

PFS and OS
With a median duration of follow-up of 69 months for surviving patients (29 months for all patients), the median PFS was 16 months (95% CI, 7–24), and the 3- and 5-year PFS were both 36% (95% CI, 23%–49%). At the time of analysis, 18 of 55 patients (33%) were alive and without evidence of disease. The median follow-up for these 18 patients was 69 months (range: 50–108 months). The median OS was 31 months (95% CI, 15–44 months). The 3- and 5-year OS was 45% (95% CI, 31%–57%) and 35% (95% CI, 23%–48%), respectively. All 37 deaths, except five, were due to disease progression. One patient died during treatment from intestinal perforation after gastrostomy tube placement, one patient died of second primary pancreatic cancer and three died of unknown causes.

Of 40 patients who achieved an objective response, 23 have recurred or progressed at a median of 9 months (range: 3–24 months), whereas in the subset of the 26 patients with a CR, 13 recurred at a median of 10 months (range: 4–22 months). Two of three patients with SD eventually progressed at 6 and 11 months. One patient with SD has not progressed at 108+ months of follow-up. This patient had a primary tumor involving the middle ear and a biopsy or surgical resection was never carried out post-treatment completion. One patient who recurred underwent salvage surgery and was still alive and disease free at last follow-up. Of 34 patients who progressed or recurred, 16 (47%) failed in locoregional sites only, 12 (35%) in distant sites only, five (15%) in both locoregional and distant sites; in one additional case, the site of recurrence was unknown.

univariate analysis for survival outcomes
We carried out univariate analysis of PFS and OS related to T stage (T4 versus others), N stage (N0–1 versus N2–3), disease site (oropharyngeal versus others), patient’s PS (0 versus 1), brachytherapy (yes versus no) and baseline Hb (≤11 g/dl versus >11 g/dl). Patients with PS of zero had a trend toward better PFS (log-rank test, P = 0.06) and better OS (log-rank test, P = 0.11) than patients with PS of one. HB values were predictive of PFS and OS as shown below. All other analyses yielded nonsignificant associations.

outcomes related to baseline Hb
Among patients with low baseline Hb (≤11 g/dl), only two of five (40%) patients achieved a response, whereas among those with normal baseline Hb (>11.0 g/dl), 38 of 45 (84%) patients achieved a clinical response (P = 0.04, Fisher’s exact test). Although the number of patients with Hb ≤11 g/dl was small (n = 5), these patients were found to have inferior PFS (log-rank test, P = 0.0002) and OS (log-rank test, P < 0.0001) compared with the rest of the patients. A Cox regression model relating PFS and OS to baseline Hb entered as a continuous variable yielded P = 0.04 and P = 0.02, respectively.

multivariate Cox regression model for OS and PFS
We included covariates with P value ≤0.25 in univariate analysis (log-rank test or univariate Cox regression model) into multivariate Cox regression model. After removing nonsignificant covariates in multivariate analysis, we found that continuous baseline Hb level (P = 0.004) was significantly associated with OS and N stage (N0–1 versus N2–3) (P = 0.06) was of borderline significance. Predictors of PFS on multivariate analysis were the continuous baseline Hb level (P = 0.003) and N stage (N0–1 versus N2–3) (P = 0.04) (see Table 4). For patients with the same N stage category, the progression hazard ratio decreases by 34% (1–exp(−0.416)) with every 1 g/dl increase in baseline Hb levels.

discussion
We report long-term efficacy results with a median follow-up of >5 years with concurrent chemoradiotherapy employing weekly carboplatin and paclitaxel in inoperable patients with locally advanced SCCHN. Almost all of our patients had stage IV, unresectable disease, even though we recognize that the definition of resectability in SCCHN lacks uniform definition between surgeons. We observed a 5-year PFS of 36% and a 5-year OS of 35% which demonstrate the curative potential of our approach. Our data are added to a large body of evidence supporting the use of concurrent chemotherapy and radiation that has accumulated over the last decade. This approach has been superior to radiation alone in terms of

Table 4. Multivariate Cox regression analysis for PFS

<table>
<thead>
<tr>
<th>Parameter estimate</th>
<th>P value</th>
<th>Relative change in disease progression hazard ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline hemoglobin as a continuous variable</td>
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</tr>
<tr>
<td>−0.416</td>
<td>0.003</td>
<td>1−exp(−0.416)=34% (decrease corresponding to every increase by 1 mg/dl in baseline hemoglobin)</td>
</tr>
<tr>
<td>N stage (N2–3 versus N0–1)</td>
<td>0.871</td>
<td>0.04</td>
</tr>
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</table>

PFS, progression-free survival.
The 5-year PFS was 36% (95% CI, 23%–49%).

(PFS) with 95% confidence intervals (CIs) based on Greenwood’s method.

100 mg/m² and paclitaxel 45 mg/m² concurrently with

from the University of Maryland studied carboplatin

concurrent radiotherapy [16, 23]. Suntharalingam et al. [16]

experience with the use of carboplatin and paclitaxel with

Similar to our approach, two other groups have published

et al. [2] is comparable to the CR rate we observed (52%).

(a 3-year OS of 45%). Also, the CR rate of 40%–49% seen in

a 3-year OS of 37% which is comparable to our findings

follow-up of 41 months. In this study by Adelstein et al. [2],

patients treated with radiation plus high-dose cisplatin had

a 3-year OS of 37% which is comparable to our findings

(3-year OS of 45%). Also, the CR rate of 40%–49% seen in

the two chemoradiotherapy arms in the study by Adelstein et al. [2] is comparable to the CR rate we observed (52%).

Similar to our approach, two other groups have published experience with the use of carboplatin and paclitaxel with concurrent radiotherapy [16, 23]. Suntharalingam et al. [16] from the University of Maryland studied carboplatin 100 mg/m² and paclitaxel 45 mg/m² concurrently with radiotherapy for locally advanced SCCHN and reported a 3-year disease-free survival and OS of 48%, with median follow-up of 30 months. Moreover, investigators from Brown University have evaluated the combination of weekly carboplatin at an area under the curve (AUC) of one and paclitaxel both in inoperable [23] and resectable patients [24] with locally advanced SCCHN. The inoperable group is comparable with our patient population. In 33 patients, 67% of whom with stage IV disease, and with a short median follow-up of 14 months, they reported a clinical CR of 60% and an overall response rate of 90%.

The concurrent chemoradiotherapy regimen with weekly carboplatin and paclitaxel we employed was tolerated well and associated with a low potential for emetogenicity, nephrotoxicity and in-field dermatitis and mucositis. Only 13% of patients experienced a treatment delay or interruption.

Grade 3–4 stomatitis/mucositis was observed in only 30% of patients compared with a 90% incidence of grade

3–4 mucositis that Choungue et al. [23] observed, but using a higher paclitaxel dose of 60 mg/m². The same group observed lower toxicity when the dose of paclitaxel was reduced to 40 mg/m² and was given as preoperative therapy [25]. As noted, the majority of patients entered into the trial underwent prophylactic placement of gastrostomy tubes for nutritional support. Only two of 18 long-term survivors were, however, still dependent upon gastrostomy tube feeding.

Finally, although we employed carboplatin dosing in mg/m², carboplatin dosing based on the AUC is currently standard and it is recommended in future trials.

The use of interstitial brachytherapy to enhance local control is sometimes advocated depending upon institutional preference and expertise [26]. This protocol was not designed to test the role of this treatment modality, and we were unable to discern any added benefit for this procedure for the patients who underwent this additional therapy. Our study also evaluated the outcomes related to baseline Hb. Other studies found that anemia is an adverse independent prognostic factor in SCCHN [27]. Our analyses indicated that low baseline Hb was associated with poor response, PFS and OS after chemoradiotherapy.

Treatment with radiation and concurrent weekly carboplatin and paclitaxel with optional brachytherapy is an efficacious chemoradiotherapy regimen with acceptable toxic effects. Although this and other reports demonstrate the curability of unresectable SCCHN, results to date remain suboptimal and more effective treatments will need to be explored. Upcoming directions in the management of locally advanced SCCHN include the incorporation of neo-adjuvant chemotherapy and/or novel targeted agents, including the epidermal growth factor receptor inhibitors, in concurrent chemoradiotherapy regimens.

references


