A PHASE II MULTI-INSTITUTIONAL TRIAL OF CHEMORADIATION USING WEEKLY DOCETAXEL AND ERYTHROPOIETIN FOR HIGH-RISK POSTOPERATIVE HEAD AND NECK CANCER PATIENTS

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Purpose: To determine efficacy and toxicities of postoperative concurrent chemoradiation using docetaxel in high-risk head and neck cancer. Methods and Materials: High-risk patients were enrolled 2–8 weeks after surgery. Treatment included 60 Gy for 6 weeks with weekly docetaxel 25 mg/m² and erythropoietin alpha 40,000 U for hemoglobin ≤12 g/dL. Primary endpoints included locoregional control (LC), disease-free survival (DFS), and patterns of failure (POF). Secondary endpoints were toxicity and quality of life. Results: Eighteen patients were enrolled (14 male, 4 female), aged 24–70 years (median, 55 years). Primary site included oropharynx = 7, oral cavity = 8, hypopharynx = 1, and larynx = 2. Pathologic American Joint Committee on Cancer Stage was III = 3 patients, IV = 15 patients. High-risk eligibility included ≥2 positive lymph nodes = 13, extracapsular extension = 10, positive margins = 8 (11 patients with two or more risk factors). Docetaxel was reduced to 20 mg/m²/week after 5 patients had prolonged Grade 3 or higher mucositis. Overall, number of doses delivered was 2 of 6 > 3 months) were seen, particularly at 25 mg/m²/week. Conclusion: Postoperative radiation therapy with weekly docetaxel 20 or 25 mg/m²/week for high-risk postoperative head and neck cancer caused intolerable mucosal toxicity, prompting early study termination. Further studies should consider 15 mg/m². Actuarial 3-year LC is 82%, similar to cisplatin-based chemoradiation regimens. Distant metastasis remains an important issue requiring additional systemic interventions. © 2007 Elsevier Inc.

Chemoradiation, Docetaxel, Postoperative, Head and neck cancer, Clinical trial.

INTRODUCTION

Postoperative radiation with concurrent cisplatin has shown improved efficacy over radiation alone within the Radiation Therapy Oncology Group (RTOG) for patients with high-risk head and neck cancer (HRHNC), defined as more than two involved nodes (N), extracapsular extension (EC), involved surgical margins (+M), and within the European Organisation for Research and Treatment of Cancer (EORTC) (for patients with +M, EC, perineural, or vascular spread) (1, 2). Concurrent chemoradiation (CCR) for high-risk postoperative patients is now considered standard of care. Unfortunately, many patients still succumb to both locally recurrent and distant metastasis, which has prompted investigation of other potential agents. The taxanes, in particular, have garnered significant attention as chemotherapeutics in this setting and may provide an alternative approach to cisplatin-based regimens with reduced renal toxicity and ototoxicity. Taxane enhances tubulin polymerization while inhibiting depolymerization leading to G2/M cell cycle arrest (3). This provides

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radiotherapy because cells in the G2/M phase appear to be 2.5 times more sensitive to radiation than cells in the G1/S phase (4–9). The very low concentrations (<5 nM) required for cell cycle arrest (10, 11) appear to be sustained in vivo (12).

Docetaxel has shown significant activity in squamous cell carcinoma of the head and neck with response rates of 34–45% as a single agent in patients with locally recurrent or metastatic disease, which is higher than what is achieved with cisplatin in a similar setting (13–15). In fact, three Phase II studies using docetaxel combinations for nonmetastatic disease have shown overall response rates that approach 100% (16–18), and one randomized trial (TAX 323) has shown an improvement in overall survival by adding docetaxel to cisplatin and 5-FU during induction (19, 20). Neutropenia occurs in more than 90% of patients when docetaxel is given every 3 weeks but at a much lower rate when given weekly (21). Comparison of weekly and every 3 weeks docetaxel has shown similar pharmacokinetics, which further supports this weekly regimen (12). This has been confirmed clinically in Phase II trials in which weekly and every 3 weeks docetaxel have been compared (22–24). Nonhematologic toxicities occur in a minority of patients and are often ameliorated with corticosteroid premedication. Because myelosuppression is also a major issue for cisplatin, weekly docetaxel appears to be a reasonable alternative (21).

Anemia is a common presenting hematologic abnormality in patients with head and neck cancer and may worsen throughout the course of radiation or chemoradiation (25). Pretreatment or treatment-related anemia is correlated with tumor hypoxia, which is a predictor for radioresistance (26, 27). At the time of this trial design, some studies had shown improved outcomes with erythropoietin in the setting of radiation treatment (28–30). Therefore, we added erythropoietin treatment to patients who presented with hemoglobin (Hgb) <12 g/dL.

This Phase II trial evaluated the efficacy and toxicity of concomitant postoperative radiation therapy and docetaxel in HRHNC. The hypothesis tested was that the substitution of cisplatin by weekly docetaxel during radiation would not cause undue toxicity, would improve locoregional control, and would decrease the incidence of distant metastases. Erythropoietin alpha was used to keep hemoglobin optimal during radiation.

**METHODS AND MATERIALS**

**Patient selection**

Patients were entered in this prospective Phase II trial between July 2000 and June 2003 at three institutions (the Vanderbilt-Ingram Cancer Center, Nashville Veterans Affairs Medical Center, and University of Colorado Health Sciences Center). Eligibility required patients to be aged 18 years or older and have American Joint Committee on Cancer (AJCC) Stage III/IV tumors that were grossly resected and histologically proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. A minimum of one high-risk finding was required on clinical and pathologic review, which included two or more involved nodes, EC, +M. Also required was ECOG performance of 0 to 2, as was normal organ function, pretreatment blood tests (white blood cell count ≥3,500, platelets ≥100,000, serum glutamic-oxaloacetic transaminase [SGOT] ≥2.5 times normal limit, an alkaline phosphatase within normal limits if SGOT was elevated or ≤4 times the normal limit if SGOT is normal). Internal review board–approved informed consent was required for all patients, and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Exclusion criteria included gross disease following surgery, synchronous head and neck primary tumors, distant metastases, a preexisting peripheral neuropathy, prior chemotherapy, prior radiation therapy above the clavicles, or prior malignancy within the previous 3 years (except early stage nonmelanomatous skin cancers, carcinoma in situ of the cervix, or early-stage prostate cancer).

**Pretreatment evaluation**

Pretreatment evaluation included complete history and physical examination including assessment of performance and dental status; confirmed surgical pathology; preoperative CT, MRI, or both from the skull base to clavicles; chest X-ray; complete blood count with differential; comprehensive metabolic panel; electrocardiogram; and dental evaluation. All patients were evaluated by a multidisciplinary team consisting of radiation oncology, medical oncology, and otorhinolaryngology. After surgical resection, pathology was reviewed and patients with high-risk features entered into this trial began treatment 2–8 weeks following surgery.

**Surgery**

Eligible patients underwent curative intent primary surgery. The surgical resection extent depended on the tumor location and volume. The procedures followed accepted norms for adequate excision, with reconstruction as necessary to optimize function and cosmesis.

**Radiotherapy**

The treatment schema is detailed in Fig. 1. All patients were immobilized in thermoplastic head-and-shoulder masks with treatment-planning CT scans for defining target volumes. The target volumes and doses were determined from clinical information, operative findings, or CT/MRI. Three clinical target volumes (CTV) were defined: CTV60 (60-Gy dose) for high-risk target volumes (i.e., +M, EC, or nodal regions with ≥2 nodes involved), CTV44 (54-Gy dose) for intermediate-risk regions (i.e., entire surgical bed), and CTV60 (50-Gy dose) for low-risk regions (i.e., prophylactic nodes down to the clavicles). Planning target volume was defined as the CTV plus a 5- to 10-mm margin to compensate for variables of treatment setup and internal organ motion. The treatment fields varied with tumor site. Hypopharynx primaries required coverage of the level I to V nodal regions including the retropharyngeal nodes with a superior border at the base of skull. Larynx primaries require coverage of upper jugular nodal region, extending to the base of the skull in cases with pyriform sinus involvement. Both ipsilateral and contralateral posterior nodal regions were treated if there were histologically involved anterior chain nodes. Oral tongue and floor of mouth primaries had a posterior border lying anterior to the spinal cord and only required level V irradiation if there were histologically involved nodes. Tracheostomas, if present, were irradiated in patients with pyriform sinus lesions and in patients with T3 or T4 laryngeal prima-
<table>
<thead>
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<th>SCREENING</th>
<th>ENTRANCE CRITERIA</th>
<th>ENROLLMENT</th>
<th>TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stage III/IV SCCA Head/Neck s/p resection</td>
<td>2. Pathologic Findings</td>
<td>RT - 60 Gy in 6 weeks (2 Gy once a day, 5x a week) plus concomitant Docetaxel 25 (20) mg/m² IV over 30 minutes on days 1, 8, 15, 22, 29 and 36 with RT (premeds decadron 6 mg po 12 hours, and 20 mg IV 30 min before docetaxel) plus Erythropoietin alpha 40,000U s.q. weekly x 6 weeks (if Hgb ≤12g/dL)</td>
<td></td>
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<tr>
<td>2. Pathologic Findings</td>
<td>A. Positive margins B. ≥2 positive nodes C. extranodal capsular spread D. clinical or pathologic N3 nodal disease</td>
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</table>

Fig. 1. Treatment schema. Abbreviations: s/p = status/post; SCCA = squamous cell carcinoma; RT = radiation therapy; IV = intravenous; po = per oral; s.q. = subcutaneous; Hgb = hemoglobin.

Drug therapy

Docetaxel 25 mg/m² was given weekly intravenously (i.v.) over 30 min (Days 1, 8, 15, 22, 29, and 36 of radiotherapy) and held for radiation breaks. Premedication included dexamethasone 6 mg orally given 12 h before and 20 mg i.v. given 30 min before docetaxel. Docetaxel dose was modified based on toxicities according to CTC grading. If the absolute neutrophil count (ANC) was <1,000 or platelet count <75,000, docetaxel was held for the week while radiation continued. Docetaxel was held for Grade 4 mucositis or dermatitis. Chemotherapy restarted when toxicities reduced to Grade 2. If bilirubin was less than or equal to the upper limit of normal (ULN), alkaline phosphatase ≤5 times the ULN, and SGOT was ≤5 times the ULN, docetaxel was reduced to 15 mg/m²/week. However, if bilirubin was greater than ULN or alkaline phosphatase was >5 times ULN, or SGOT >5 times ULN, docetaxel was held up to 3 weeks pending recovery of laboratory values. If these returned to normal, docetaxel was reduced to 15 mg/m²/week, but if not, the patient was removed from the study. If docetaxel was held for 3 weeks in a row, the patient received no further docetaxel. Missed drug treatments were not made up. Nausea and vomiting were treated with antiemetics without dose modification. Prolonged (≥3 months) Grade 3 mucositis in four of the first five patients treated necessitated a decrease in docetaxel dose to 20 mg/m²/week.

If Hgb was <12 g/dL, erythropoietin alpha 40,000 U subcutaneous (s.c.) weekly starting Day 1 of treatment was given and continued until Hgb ≥14 g/dL. However, if the Hgb dropped by >1 g/dL within 1 week of receiving erythropoietin, then the dose was increased to 60,000 U weekly. If Hgb dropped below 10 g/dL, patients received a transfusion of packed red blood cells (PRBCs) until Hgb ≥12 g/dL with resumption of erythropoietin as well as iron supplementation until Hgb increased to ≥14 g/dL.

Endpoints

The primary objective of this study was to evaluate the effectiveness of concurrent radiochemotherapy given postoperatively. The primary endpoints were locoregional control rate (LC), overall survival (OS), disease-free survival (DFS), and patterns of failure (POF). Toxicities and quality of life (QOL) were secondary endpoints. Follow-up assessments were performed 2–4 weeks after treatment, then every 2 months for the first year and every 4 months for the subsequent 2 years. Patients were evaluated every 6 months thereafter. The primary tumor and regional disease were assessed by physical examination (with endoscopy) and/or CT/MRI scan at 3 months and thereafter, if clinically warranted. Metastatic evaluation required chest X-rays or CT scans.

Statistical methods

For planning purposes, we assumed that all locoregional failures would occur in the first 2 years in this protocol because the percentage of failures after 2 years is exceedingly low. For sample size estimation, a binomial distribution was used in which failure was defined as local or regional recurrence. In addition, the treatment was also compared with respect to NED survival and overall survival. These two endpoints, however, were considered secondary endpoints. The required sample size of 30 patients was estimated based on review of similar high-risk postoperative head and neck cancer patients from previous intergroup studies (RTOG 88-24, INT 0034). Analyses of study results focused on estimating the overall survival, DFS, and POF. The Kaplan-Meier estimates method was applied to estimate the overall survival and DFS for the study subjects. The SAS version 9.1.3 was used for all analyses.
RESULTS

Patient disease characteristics

Between July 2000 and June 2003, 18 patients were enrolled. The pretreatment patient characteristics are illustrated in Table 1. The median age was 55 years, and 14 of the 18 patients were men (78%). The AJCC staging characteristics are shown in Table 2. The majority had primary tumors within the oral cavity or oropharynx. Of the 18 patients, 13 had advanced nodal disease (N2b or greater), 10 had EC, and 8 had high-risk features. All patients had an ECOG performance status of 0 to 1 at time of enrollment. At the time of analysis, 10 of the 18 patients (56%) were alive; the median follow-up for surviving patients was 34 months (range, 14–66 months) and 30 months (range, 5–66 months) for all patients.

Treatment administration

All 18 patients completed radiation (60 Gy). Mean number of days of break during radiation (for toxicity) was 1 day. Median weekly docetaxel doses delivered was five doses. Weight loss during treatment was 5% (median). Only one transfusion was given for Hgb <10 g/dL. Four of 18 patients required percutaneous endoscopic gastrostomy (PEG) tube placement (one long term). Prolonged mucositis (>3 months) and taste loss (>3 months) in four of five initial patients prompted dose reduction of docetaxel to 20 mg/m²/week.

Toxicity

Acute toxicity outcome is detailed in Table 3. The most severe acute toxicity was mucositis that occurred in all patients reaching Grade 3 or 4 in 14 of 18 patients (78%). Grade 3 dermatitis, dysphagia, and xerostomia were noted in smaller numbers of patients, whereas the remainder of toxicities was only Grade 1 or 2. Figure 2 illustrates a patient with prolonged mucositis. There was no increase in late toxicities.

Patient outcomes

Four patients have died of disease: one with local recurrence and distant metastasis; one with local and regional recurrence; one with local, regional, and distant metastasis; and one with distant metastasis only. Four patients died disease-free: two from second primary cancers (colon and melanocytoma), one from myocardial infarction, and one from suicide. In terms of primary endpoints, the estimated

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Table 1. Patient characteristics (n = 18)

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<tr>
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<td>Age (range, 24–70 years; median, 55 years)</td>
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<tr>
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<td>50</td>
</tr>
<tr>
<td>≥60 years</td>
<td>9</td>
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<td>≥2 nodes</td>
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<td>2</td>
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Abbreviation: ECOG = Eastern Cooperative Oncology Group.

Table 2. Patients’ pathologic AJCC Stage

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<th>N3</th>
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<td>7</td>
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<tr>
<td>T2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
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<tr>
<td>T3</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>T4</td>
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<td>4</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Total</td>
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<td>2</td>
<td>14</td>
<td>0</td>
<td>18</td>
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Abbreviation: AJCC = American Joint Committee on Cancer.

Table 3. Acute toxicity scoring according to NCI CTC Version 3.0

<table>
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<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
<td>Nausea/vomiting</td>
<td>7</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Mucositis</td>
<td>—</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>3</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>4</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CTC = Common Toxicity Criteria; NCI = National Cancer Institute.

Fig. 2. A patient with prolonged mucositis.
LC at 3 years is 82% (Fig. 3a). The estimated 3-year DFS is 78% (Fig. 3b). Finally, OS is 76% at 1 year and 55% at 2 years with a median OS over 3 years (Fig. 3c).

**DISCUSSION**

The primary objective of this study was to determine efficacy and toxicity of concurrent docetaxel with postoperative radiation. Our results show that although feasible, postoperative concurrent docetaxel with radiation is associated with a high rate of acute treatment related side effects. Numerous randomized trials (31–36) as well as three meta-analyses (37–41) have shown superior LC and OS with the addition of concurrent chemotherapy to local treatment alone. In particular, RTOG 95-01, a randomized Phase III trial, corroborated these findings. Patients with HRHNC were randomized to postoperative irradiation with or without concurrent 100 mg/m² cisplatin on Days 1, 22, and 43 (2). The concomitant arm showed 82% LC compared with 72% for radiation alone at 2 years. A similar Phase III trial, EORTC 22931, was published simultaneously with RTOG 95-01 (1). This trial randomized 167 high-risk postoperative patients to radiation versus radiation with cisplatin 100 mg/m² on Days 1, 22, and 43. Similar to the RTOG trial, this EORTC study also showed that cisplatin/radiation was superior to radiation alone in terms of LC and DFS. The EORTC trial also showed an OS advantage in the chemoradiation group. The improvement in disease control in these two trials was counterbalanced by the increase in acute toxicities, which occurred twice as often with the addition of cisplatin. Interestingly, there were no differences in late toxicities in both trials, although the follow-up may be too short at this time. These trials have changed the standard of care for postoperative treatment in patients with high-risk features.

Despite the improvements in outcome with concurrent cisplatin, the rate of distant metastases or second primaries is unaltered (1, 2), suggesting that the effect of cisplatin on OS derives from radiosensitization (42). However, even LC needs to be improved because more than 20% of patients will fail locally (42). Furthermore, cisplatin delivered at 100 mg/m² has significant renal and hematologic toxicity. Therefore, the use of taxanes as both radiosensitizers and as systemic chemotherapeutics may be an alternative approach with radiation. Clin-
ical data regarding taxanes, both paclitaxel and docetaxel, with radiation have come from thoracic tumors, particularly non–small cell lung cancer, esophageal cancer, and breast cancer (43–49). Neoadjuvant trials with taxanes have shown response rates of 41–100% (16, 17, 50–57). Several groups have examined docetaxel in combination with radiation in locally advanced head and neck cancers when used as definitive treatment both before and during radiotherapy (21, 36, 58–60). More recently, a few studies examining concurrent docetaxel and radiation have been published for patients in a postoperative setting (61–64). Highly selected patients appeared to do well with this regimen (64), although unselected patients fared worse (61). The hope was that this regimen would provide superior results to cisplatin-based regimens. Whether concurrent docetaxel can decrease the rate of distant metastases remains to be seen.

The dose of docetaxel used initially in our patients (25 mg/m²) was based on studies by Tishler and colleagues (59). However, significant acute and subacute mucositis required a dose reduction to 20 mg/m². Since initiating the trial, several groups have published Phase I and II trials examining the use of docetaxel with concurrent radiation for head and neck cancers (21, 36, 58–60, 63, 64). Grade 3 or worse mucositis was almost invariably the dose-limiting toxicity. Furthermore, the maximum tolerated dose ranged from 10 mg/m² to 25 mg/m². Most recently, a Phase I/II trial by Tishler (65) using induction plus concurrent docetaxel and concomitant boost radiation therapy recommended a dose of 20 mg/m² postinduction. Therefore, our experience in this trial is consistent with other groups. The impact of this reduced dose on efficacy is uncertain. It is possible that this lower dose is sufficient for radiosensitization but not for distant control of micrometastases. This appears to be the case based on the patients’ outcomes in our study that do not seem to show an obvious advantage over what can be achieved with cisplatin (1, 2). The subacute toxicity is also a concern for us. Several patients had prolonged mucositis and loss of taste, although only one patient remained PEG-dependent. Our attempts at using intensity modulated radiation therapy for 3 of the 18 patients did not appear to ameliorate the acute toxicity. Some of this high toxicity may be related to the large proportion of oral cavity primaries in our study (44%), which is almost twice that of RTOG 95-01 and the EORTC trial (24% and 25%, respectively) (1, 2). However, the high rate of acute toxicity suggests that docetaxel may be better used at lower doses as a radiosensitizer. Docetaxel may also offer benefits in the induction setting and appears safer than cisplatin in terms of renal toxicity and myelosuppression (50–53, 66, 67). Weekly docetaxel at 30 mg/m² has been used successfully for patients with recurrent and metastatic head and neck cancers without causing Grade 3 and 4 toxicities (68). Recently published results by Kovacs (61) achieved better survival than that in the RTOG and EORTC Phase III trials using a four-modality approach of induction intra-arterial high-dose cisplatin followed by surgery, followed by docetaxel (25 mg/m²/week) with radiation (51.3 Gy). This approach takes advantage of the ability of taxanes to treat resistant tumors more effectively (69), although this particular report did not elaborate on toxicity to make a direct comparison.

Anemia rates are high in patients with head and neck tumors, and this correlates with hypoxic radiosensitivity (26, 27). Efforts have been made to address this issue of hypoxia by raising hemoglobin, either by transfusion or by exogenous erythropoietic agents. In RTOG 85-27, patients with Stage III/IV squamous cell carcinoma of the head and neck were randomly assigned to radiation alone or radiation plus etanidazole. Primary analysis demonstrated no survival advantage for concomitant etanidazole (70). However, a second analysis evaluating the association between pretreatment anemia and outcomes indicated that patients with a normal Hgb (≧14.5 gm/dL in men and >13 gm/dL in women) had a statistically significant improvement in OS and LC (71). Additional studies have confirmed the predictive value of hemoglobin on outcome (72, 73), but attempts to use erythropoietin and its analogs as a means to maintain normal hemoglobin have shown conflicting results (28, 74–82). Therefore, the RTOG initiated a prospective randomized trial to determine whether concurrent erythropoietin with radiation could improve LC. RTOG 99-03 has only been presented in abstract form, but despite significant improvements in Hgb levels, they found no improvement in outcome (83). Whether the use of erythropoietin in our patients confounded the results is unknown. No thrombovascular events occurred, but the potential for tumor protective mechanisms by erythropoietin may have obscured the effectiveness of the docetaxel–radiation interaction. It is unlikely, based on published data, that the erythropoietin contributed to the high mucositis rates observed.

The major limitation of this trial is the relatively small number of patients treated, which may have precluded seeing an improvement in LC or DFS, particularly with actuarial reporting. However, toxicities seen in these 18 patients warranted docetaxel dose reduction before larger numbers of patients were enrolled. Currently, the RTOG is conducting a Phase II trial of postoperative concurrent docetaxel and cetuximab with radiation versus concurrent cisplatin and cetuximab with radiation. It is important to note that this trial (RTOG 02-34) limits the dose of docetaxel to only 15 mg/m².

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