Phase II Trial of Dose-Dense Paclitaxel, Cisplatin, 5-Fluorouracil, and Leucovorin with Filgrastim Support in Patients with Squamous Cell Carcinoma of the Head and Neck

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Presented in part at the 36th Annual Meeting of the American Society of Clinical Oncology, New Orleans, Louisiana, May 20–23, 2000.

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Received February 12, 2004; revision received April 23, 2004; accepted May 18, 2004.

BACKGROUND. The current study evaluated the feasibility and clinical activity of a combination of paclitaxel, cisplatin, 5-fluorouracil (5-FU), and leucovorin administered on a biweekly schedule to patients with recurrent or unresectable squamous cell carcinoma of the head and neck (HNSCC).

METHODS. Patients with recurrent or unresectable HNSCC were eligible if they had received a previous regimen of neoadjuvant chemotherapy, concurrent chemoradiotherapy, or no previous systemic therapy. Patients received paclitaxel (175 mg/m^2 on Day 1), cisplatin (35 mg/m^2 on Days 1 and 2), leucovorin (200 mg/m^2 on Day 1), and 5-FU (1000 mg/m^2 per day as a 48-hour continuous intravenous infusion on Days 1 and 2) every 2 weeks. Patients received subcutaneous filgrastim (300 μg per day) on Days 3–9 of each cycle. Treatment was administered on an outpatient basis for a maximum of six cycles.

RESULTS. Thirty-five patients received a combined total of 194 treatment cycles. Eighteen complete responses (51%) and 12 partial responses (34%) were documented, for an overall response rate of 86% (30 of 35 patients). The median progression-free survival duration was 14 months, and the median overall survival duration was 18 months. Two toxicity-related deaths were documented (one due to neutropenic sepsis and the other due to catheter-related pulmonary embolism). Grade 4 neutropenia was observed in one patient. Other severe (Grade 3 or 4) toxic effects included mucositis (14%), anemia (6%), thrombosis (6%), thrombocytopenia (3%), and neuropathy (3%).

CONCLUSIONS. The current dose-dense, four-agent, taxane-containing biweekly schedule was feasible and effective in patients with recurrent or unresectable HNSCC. However, given the single-center nature of the current study and the highly selected study population, further validation of these findings is recommended. ***Cancer* 2004;101:768–75.** © *2004 American Cancer Society.*

KEYWORDS: head and neck, dose-dense, paclitaxel, filgrastim.

Squamous cell carcinoma of the head and neck (HNSCC) accounts for the majority of malignancies that arise in the head-and-neck region.[1] The prognosis for patients with early-stage HNSCC is favorable, and treatment with surgery or radiotherapy yields 5-year overall survival (OS) rates of 70–90%.[2] Occurrence of a second primary tumor is one of the major concerns for patients with this stage of disease.[3] However, two-thirds of patients present with advanced locoregional (Stage III/IV) disease. Despite combined-modality approaches involving chemotherapy and radiotherapy or surgery, locoregional and distant recurrence, respectively, are noted in up to 60% and 25% of

DOI 10.1002/cncr.20439
Published online 2 July 2004 in Wiley InterScience (www.interscience.wiley.com).

patients who receive this type of treatment, and the 3-year survival rate associated with such treatment is $< 30\%$.[2,4] After disease recurrence, the median survival period associated with standard treatment is 6 months.[5–8]

For patients with locally advanced or recurrent disease, the combination of cisplatin and infusional 5-fluorouracil (5FU) is accepted as standard chemotherapy. The response rates range from 60% to 80% in the neoadjuvant setting and from 30% to 40% for patients with recurrent disease.[5–9]

The taxanes, used as single agents or in combination with other cytotoxic agents, have demonstrated activity in patients with HNSCC.[10] Cisplatin + paclitaxel, with or without 5-FU, yielded response rates of 21–38% in patients with recurrent disease[11–14] and response rates of 60–88% in patients with unresectable disease.[15–17] The main side effect of paclitaxel in combination with cisplatin is peripheral neuropathy, and mucositis and diarrhea are observed when 5-FU is included in the regimen.

The concept of dose density refers to the administration of drugs with a shortened intertreatment interval. It is based on the observation in experimental models that a given dose kills a certain fraction, rather than a certain number, of exponentially growing neoplastic cells.[18] It has been hypothesized that more frequent administration of cytotoxic therapy would be more effective in minimizing residual tumor burden than would dose escalation.[19] On the basis of this experimental model, which has yielded a survival benefit for patients with breast carcinoma,[19,20] we hypothesized that a dose-dense schedule combining four active agents could be efficacious in terms of response rate in patients with unresectable HNSCC.

We anticipated that a biweekly 120-hour infusion of 5-FU in combination with cisplatin and paclitaxel would induce severe mucositis.[15] Therefore, we instead opted for a 48-hour infusion of 5-FU with leucovorin modulation, similar to the one used by De Gramont et al. to treat patients with colorectal carcinoma.[21] This combination of 5-FU and leucovorin allows the safe delivery of a high dose of modulated 5-FU on a biweekly basis.

The current study was designed to evaluate the feasibility and clinical activity of a dose-dense, four-agent, paclitaxel-containing biweekly schedule in patients with recurrent or unresectable HNSCC.

MATERIALS AND METHODS

Patient Eligibility

For inclusion in the study, patients were required to be older than 18 years and to have histologically documented, bidimensionally measurable HNSCC that was recurrent or deemed unresectable. All patients were required to have an Eastern Cooperative Oncology Group performance status (PS) of 0–1, life expectancy $\geq$ 12 weeks, and adequate bone marrow, hepatic, and renal function (i.e., absolute neutrophil count [ANC] $\geq 2.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, hemoglobin level $\geq$ 10.0 g/dL, aspartate aminotransferase or alanine aminotransferase levels $<$ 1.5 times the upper limit of normal, alkaline phosphatase level $<$ 5 times the upper limit of normal, normal bilirubin level, creatinine clearance $>$ 50 mL/min, and a normal serum calcium level).

Patients who had undergone previous chemotherapy for recurrent disease or received previous taxane therapy, systemic anticancer treatment in the previous 6 months, or irradiation to major bone marrow areas were excluded from the study. Patients with Grade $\geq$ 2 peripheral neuropathy or other serious medical or psychiatric conditions were also excluded. Patients were required to have received no previous therapy or only 1 previous regimen of neoadjuvant or adjuvant chemotherapy or chemotherapy administered concurrently with radiotherapy, provided that the regimen did not include taxanes and was terminated $>$ 6 months before disease recurrence. Patients with previous malignancies were eligible if they had been treated curatively and had been free of disease for $>$ 5 years. The scientific review board and the ethics committee of the University Hospital 12 de Octubre (Madrid, Spain) granted protocol approval. Patients were required to provide written informed consent before study enrollment.

Within 1 week of study entry, physical examination and acquisition of a complete clinical history were performed for all patients, as were complete blood counts, serum biochemistry tests (including liver and renal function tests and monitoring of electrolyte levels), urinalysis, and electrocardiography. Chest radiographs and computed tomography (CT) scans of the head and neck were obtained within 3 weeks before study entry.

Treatment Plan

The treatment regimen consisted of a 2-day course of paclitaxel (175 mg/m^2 as a 3-hour intravenous [i.v.] infusion on Day 1), followed by cisplatin (35 mg/m^2 as a 30-minute i.v. infusion on Days 1 and 2), leucovorin (200 mg/m^2 as a 1-hour i.v. infusion on Day 1), and, finally, 5-FU (1000 mg/m^2 per day as a 48-hour continuous i.v. infusion on Days 1–2), administered every 14 days. Chemotherapeutic agents were infused via an implantable subcutaneous device (Port-a-Cath, SIMS Deltec, Inc., St. Paul, MN). All patients were premedicated with i.v. dexamethasone (20 mg), diphenhydra-

mine (50 mg), and cimetidine (300 mg) 30 minutes before paclitaxel administration. Standard mannitol and i.v. hydration accompanied cisplatin administration. Prophylactic antiemetics included i.v. ondansetron (8 mg) before chemotherapy and oral ondansetron (8 mg) 3 times daily for 2 days. Patients received subcutaneous filgrastim (300 μg per day) on Days 3–9 of each cycle. No prophylactic antibiotics were administered. Treatment was administered on an outpatient basis for a maximum of six cycles.

Retreatment on Day 15 required an ANC count $\geq 1.5 \times 10^9$/L, a platelet count $\geq 100 \times 10^9$/L, a creatinine clearance rate > 50 mL/min, and resolution of all nonhematologic toxicities (except alopecia and fatigue) to baseline or less than Grade 1. In case of a delay > 14 days, the patient was removed from the study. Predetermined dose adjustments (dose reduction or delay in administration) were permitted for all drugs after the occurrence of specific toxic effects. The doses of all 4 agents were reduced by 25% after any episode of febrile neutropenia, Grade 4 neutropenia lasting > 5 days, or Grade 4 thrombocytopenia. Doses of 5-FU and leucovorin were reduced by 25% after episodes of Grade 4 mucositis or diarrhea, Grade 3 mucositis, or diarrhea lasting > 5 days. Toxic events were recorded on a continuous basis and followed until they resolved to baseline or $<$ Grade 1.

Follow-up history and physical examination, complete blood cell counts, and serum biochemistry tests were performed at weekly intervals during treatment. Restaging CT scans, chest radiographs, and upper respiratory tract examinations were performed every 3 cycles (6 weeks) or when disease progression was clinically suspected.

Follow-Up

After therapy, patients were followed every 3 months for the first year, every 6 months from the second year through the fifth year, and once yearly thereafter. Follow-up visits included physical examination, endoscopic evaluation, blood tests, chest radiography, CT scanning of the head and neck, and other tests when clinically indicated.

Study Endpoints

The primary endpoint of the current study was tumor response. The criteria used to define response (complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) were based on standard World Health Organization definitions. Patients were considered evaluable for response once therapy was initiated. Secondary efficacy parameters included progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from diagnosis of recurrent or advanced disease to last contact or disease progression (either clinical or radiologic). Patients who died of causes other that HNSCC were censored in the analysis of PFS. OS was defined as the time from diagnosis of recurrent or advanced disease to last contact or death. Adverse events were classified and graded according to the National Cancer Institute Common Toxicity Criteria. Patients were considered evaluable for toxicity once therapy was initiated.

Statistical Analysis

The trial followed a two-stage Simon minimax design,[22] allowing early closure in case of treatment failure. The null hypothesis, which stated that the true response rate was $\leq 60\%$, was evaluated against the alternative hypothesis, which stated that the true response rate was $\geq 80\%$ (alpha error, 0.05; beta error, 0.20). Nine responses were required from the first 13 patients to continue accrual, and 26 responses were required from 35 patients for the regimen to be considered promising enough to warrant a comparative trial. Ninety-five percent confidence intervals (CIs) were calculated using the exact method. In addition, survival was estimated using the Kaplan–Meier product-limit method.[23] All tests were two sided at the 0.05 level of significance. The SPSS statistical package (Version 10.0; SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Patients

Between March 1999 and November 2000, 35 patients with locally advanced HNSCC were enrolled in the study. All patients were assessable for toxicity and survival, and response could be evaluated in 34 patients (1 patient died of neutropenic sepsis before response assessment). Demographic and clinical characteristics of the study cohort are summarized in Table 1. Twenty-four patients presented with recurrence of a previously diagnosed and treated HNSCC, and the remaining 11 patients presented with unresectable disease at diagnosis and received the study regimen as induction therapy. Five patients had received previous chemotherapy. Of these 5 patients, 4 (80%) had been treated with a combination of cisplatin and 5-FU as neoadjuvant chemotherapy (resulting in 1 CR and 3 PRs), and 1 (20%) had received cisplatin alone as concurrent chemotherapy. Fourteen patients had received radiotherapy. The median interval between initial diagnosis and disease recurrence was 18 months (range, 6–97 months).

TABLE 1
Patient Characteristics (n = 35)

Characteristic	No. of patients (%)
Gender	
Male	34 (97)
Female	1 (3)
Median age in yrs (range)	58 (29–77)
ECOG performance status	
0	22 (63)
1	13 (27)
Initial disease stage at diagnosis	
II	8 (23)
III	6 (17)
IV	21 (60)
Primary tumor site	
Oral cavity	9 (26)
Oropharynx	6 (17)
Hypopharynx	5 (14)
Larynx	13 (37)
Unknown origin	2 (6)
Extent of disease	
Locoregional, recurrent	24 (77)
Locoregional, unresectable	11 (23)
Previous therapy	
Surgery alone	9 (26)
Surgery and radiotherapy	10 (29)
Surgery and chemotherapy	1 (3)
Chemotherapy and radiotherapy	1 (3)
Surgery, chemotherapy, and radiotherapy	3 (9)
None	11 (31)

ECOG: Eastern Cooperative Oncology Group.

Treatment Administered

A total of 194 cycles of the study regimen were delivered (median, 6 cycles per patient; range, 2–6 cycles): 28 patients (80%) received the 6 planned cycles, 2 patients (6%) received 5 cycles, 2 patients (6%) received 4 cycles, 2 patients (6%) received 3 cycles, and 1 patient (3%) received 2 cycles. Most chemotherapy cycles (92%) were delivered at the planned doses. Doses were reduced in four patients (after the first cycle in three patients and after the second cycle in one) due to mucositis. Five treatment cycles were delayed by 1 week (due to an episode of Grade 1 neutropenia in 1 case, an episode of Grade 3 thrombocytopenia in 1 case, and an episode of Grade 2 mucositis in 3 cases). Seven patients did not complete the six planned cycles: two patients died of toxicity while on study, three patients were removed from the study (after three, four, and five cycles, respectively) due to the absence of clinical benefit, one patient presented with PD (after five cycles), and one patient developed Grade 4 mucositis (during the third cycle) despite a previous dose reduction.

The median duration of treatment was 12 weeks (range, 4–14 weeks). The median dose intensities were paclitaxel 87.5 mg/m^2 per week (range, 64–87.5 mg/m^2), cisplatin 35 mg/m^2 per week (range, 25.5–35 mg/m^2), 5-FU 1000 mg/m^2 per week (range, 730–1000 mg/m^2), and leucovorin 100 mg/m^2 per week (range, 73–100 mg/m^2). The dose intensity achieved was 97% of the planned dose intensity for all 4 study agents.

Response

Eleven responses were documented in the first stage of the trial (n = 13), and thus accrual continued. The overall response rate was 86% (30 of 35 patients; 95% CI, 74–97%). With regard to best response to therapy, there were 18 CRs (51%), 12 PRs (34%), 3 cases of SD (9%), and 1 case of PD (3%). One patient (3%) died of toxicity after Cycle 1, before the evaluation of responses, and was therefore deemed unassessable. The median time to response was 6 weeks (range, 5–9 weeks). The median duration of response was 12.8 months (range, 2.2–39 months).

No differences were observed when analyzing response according to previous irradiation of the target lesion. Overall response rates were 90% and 79%, respectively, for patients with nonirradiated and radiated lesions (P = 0.32), with CR rates of 62% and 36% (P = 0.13) and PR rates of 29% and 43% (P = 0.45), respectively.

It is noteworthy that only 5 of the 18 CRs were achieved after the third cycle. The other 13 patients had achieved PR by Week 6. In contrast, most patients (11 of 12) who ultimately achieved a PR as their best response to therapy did so after the third cycle, and there was only 1 late response.

Toxicity

Hematologic and nonhematologic toxicities are summarized in Table 2. We recorded only one episode of Grade 1 neutropenia and only one other episode of Grade 4 neutropenia. The latter was accompanied by fever and sepsis and led to the death of the patient, despite aggressive intensive care management. The median nadir ANC count was 6.7 $\times$ 10^9/L (range, 0.34–24.4 $\times$ 10^9/L). We observed thrombocytopenia in 6 patients (17%), with 1 (3%) having Grade 3 thrombocytopenia. Anemia (predominantly Grade 1) was documented in 27 patients (77%). Grade 3 anemia was noted in 2 patients (6%).

Overall, 23% (8 of 35) of patients experienced Grade 3/4 nonhematologic adverse events. Of these events, the most common and severe were episodes of mucositis (three patients had Grade 3 episodes, and two had Grade 4 episodes), which was unrelated to previous radiotherapy. Mucositis was the only toxicity that required dose adjustments. One patient was removed from the study due to recurrent severe mucosi-

TABLE 2
Summary of Hematologic and Nonhematologic Toxicities (n = 35)

	All grades	Grade 3–4
Toxicity	No. of patients (%)	No. of patients (%)
Hematologic		
Anemia	27 (77)	2 (6)
Thrombocytopenia	6 (17)	1 (3)
Neutropenia	2 (6)	1 (3)
Nonhematologic		
Alopecia	33 (94)	— (—)
Neuropathy	32 (91)	1 (3)
Myalgia	28 (80)	0 (0)
Mucositis	12 (34)	5 (15)
Nausea	12 (34)	0 (0)
Emesis	10 (29)	0 (0)
Diarrhea	8 (23)	0 (0)
Hand–foot syndrome	6 (17)	0 (0)
Asthenia	5 (14)	0 (0)
Thrombosis	2 (6)	2 (6)

tis despite a previous dose reduction. Two episodes of catheter-related thrombosis were observed. One resolved after removal of the catheter (Grade 3), but the other was associated with massive pulmonary embolism (Grade 4) and accounted for the second toxic death in the current study. Neuropathy and myalgia were observed in 91% and 80% of patients, respectively. Only one patient experienced Grade 3 neuropathy.

Table 3 summarizes toxicity data by treatment cycle. Anemia, neuropathy, myalgia, hand–foot syndrome, and alopecia were cumulative. After the third cycle, 20 of 34 (59%) patients presented with neuropathy, whereas this condition was reported by 26 of 28 (93%) patients after the sixth cycle.

Subsequent Therapy

Among patients who completed the 6 planned cycles, 12 were treated with radiotherapy, 5 were treated with surgery, and 6 were treated with surgery plus radiotherapy. No patient underwent reirradiation. Five patients did not receive any further therapy; all had recurrent disease following previous radiotherapy and subsequently achieved CR in the current study. The patient who was withdrawn from the study due to mucositis continued therapy with cisplatin and underwent surgery. Two patients who were withdrawn from the study before completion and the patient who presented with disease progression during therapy received methotrexate with palliative intent. The other patient who was removed from the study due to a lack of clinical benefit chose not to receive further therapy and was treated with supportive care alone.

Outcome: Recurrence and Survival

Twenty-one patients presented with disease progression after therapy. Of these 21 patients, 17 patients had locoregional disease recurrences, 2 had distant metastases, and 2 presented with both locoregional and distant disease. The median PFS was 14 months (95% CI, 11.8–19.3 months), and the median survival after disease progression was 3 months (95% CI, 0.7–5.3 months).

Twenty-six deaths occurred—2 patients died of toxicity during treatment, 21 died of tumor progression, and 3 died of causes unrelated to therapy or HNSCC (1 due to an acute myocardial infarction and 2 due to second tumors [esophageal and small cell lung carcinoma]). The median OS was 18 months (95% CI, 14.3–21.7 months).

Characteristics of Long-Term Survivors

After a median follow-up of 34 months (range, 10–41 months), 9 patients were alive and free of disease. One patient had previously received concurrent chemoradiotherapy, six had received surgical management, and two had received no previous therapy; seven of these patients entered the study with recurrent disease, and two entered with primary malignancies. Two patients had disease that partially responded to the dose-dense regimen and underwent surgery plus radiotherapy. The other 7 patients had complete responses (after 3 cycles in 3 cases and after 6 cycles in 4 cases) and received surgery (n = 1) or radiotherapy (n = 6).

Comparison of Patients with Recurrent Disease and Patients with Unresectable Primary Disease

Response rates were similar for patients with recurrent disease and those with unresectable primary disease (83% vs. 91%, respectively; P = 0.73). The latter group had a nonsignificantly higher CR rate (46% vs. 64%; P = 0.33). Toxicity was equivalent in these two groups. After the completion of treatment, all surviving patients with unresectable disease at diagnosis received further therapy (radiotherapy [n = 5], surgery [n = 1], or surgery plus radiotherapy [n = 4]), whereas 5 patients in the recurrent disease group did not receive any complementary treatment. PFS (13.0 vs. 16.0 months; P = 0.47) and OS (17.0 vs. 19.6 months; P = 0.74) also did not differ between patients with recurrent disease and patients with unresectable primary disease (Fig. 1). Nine patients are alive and free of disease, including seven patients with recurrent disease and two patients with unresectable primary disease. One death due to toxicity and 16 deaths due to disease progression were observed among patients

TABLE 3
Toxicity by Treatment Cycle

	C1				C2				C3				C4				C5				C6			
Toxicity	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**	**G1**	**G2**	**G3**	**G4**
Anemia	3	0	0	0	4	2	1	0	11	1	0	0	16	2	0	0	13	4	0	0	11	4	1	0
Neutropenia	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Thrombopenia	0	0	0	0	0	1	1	0	0	0	0	0	1	1	0	0	2	0	0	0	0	1	0	0
Nausea	5	1	0	0	3	0	0	0	3	0	0	0	2	0	0	0	1	1	0	0	1	0	0	0
Emesis	4	1	0	0	2	0	0	0	2	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0
Diarrhea	2	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0	3	1	0	0	1	0	0	0
Mucositis	2	1	2	0	0	4	1	1	4	0	0	1	3	2	0	0	4	1	0	0	4	3	0	0
Hand–foot syndrome	0	0	0	0	1	0	0	0	1	1	0	0	3	2	0	0	1	4	0	0	1	4	0	0
Neuropathy	9	1	0	0	8	2	0	0	16	4	0	0	14	8	0	0	12	15	0	0	10	15	1	0
Myalgia	6	0	0	0	7	2	0	0	9	1	0	0	14	2	0	0	13	7	0	0	13	9	0	0
Asthenia	0	0	0	0	1	2	0	0	3	0	0	0	3	2	0	0	2	3	0	0	1	2	0	0
Thrombosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1	0
Alopecia	0	0	—	—	11	8	—	—	14	15	—	—	8	23	—	—	4	24	—	—	3	24	—	—

G: grade; C: cycle.

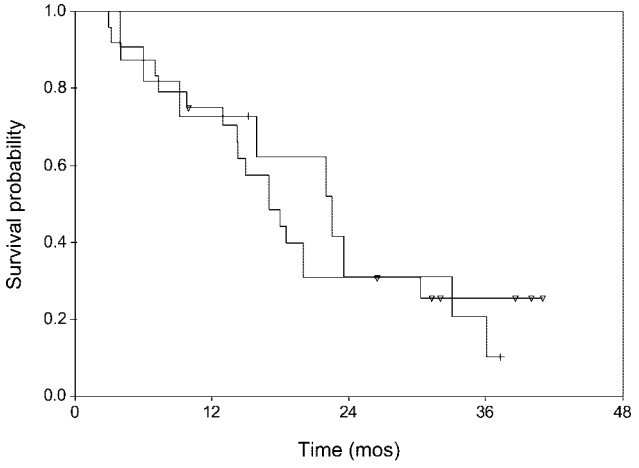

FIGURE 1. Overall survival for patients with recurrent disease (triangles) and patients with unresectable disease (crosses).

with recurrent disease, and 1 death due to toxicity, 5 deaths due to disease progression, 2 deaths due to a second malignancy, and 1 death due to an acute myocardial infarction were observed among patients with primary disease.

DISCUSSION

It is of paramount importance to note that, given the inherent biases in patient selection in dose-dense chemotherapy studies, caution must be exercised before applying the following results to the general population of patients with HNSCC. To our knowledge, the current trial is the first to explore the use of a dose-dense, four-agent, taxane-containing biweekly schedule in patients with recurrent or unresectable HNSCC. The observed response rate and median OS, both of which were somewhat higher than those consistently reported in association with the standard cisplatin/5-FU regimen in this setting, are noteworthy.[5,6] Compared with other paclitaxel-containing combinations, the current regimen was equally active in the induction setting[15–17] but had a higher level of activity in patients with recurrent disease.[11–14] This finding also holds true for the comparison of the study regimen with docetaxel-containing regimens.[24,25] Due to the differences between patients with recurrent disease and those who had never before received treatment (primarily patients with unresectable disease), both groups were analyzed separately. Similar response rates, as well as PFS and OS rates, were observed in patients with recurrent disease and those with unresectable primary disease, but the limited number of patients examined prevents any solid conclusion from being drawn. The response rate for patients with irradiated lesions was greater than the reported response rates (20–40%) for patients whose lesions were treated with other chemotherapy combinations.[2,7] Most patients in the current study had responses after three cycles. However, for the majority of patients (13 of 18), 6 cycles were needed to induce a CR. This observation casts some uncertainty on the optimal number of cycles to be administered in the induction setting. The median number of cycles administered and the dose intensity achieved for all four study agents highlight the feasibility of this regimen (the primary objective of the current trial). For both cisplatin and paclitaxel, median dose intensities and median total doses were equivalent to those reported previously,[11–17,26] but the

duration of treatment was significantly shorter in the current study.

The findings of the current study are consistent with the mathematic prediction that more frequent administration of chemotherapy would disable cellular regrowth between treatment cycles, with the resulting possibility of improved therapeutic outcomes. Tumor regrowth between treatment cycles in patients with bulky or locally advanced disease who have initial responses to chemotherapy is a common occurrence. Thus, optimization of the interval between treatment cycles has potential value. Recent studies involving patients with adjuvant breast carcinoma suggest that a dose-dense approach may be more effective than conventionally scheduled therapy in terms of survival results.[19,20]

The observed toxicity in the current cohort was moderate. Anemia (predominantly Grade 1) was the most common hematologic toxicity, and filgrastim support proved to be efficacious in the treatment of this toxicity. The median nadir ANC count was well above normal limits, and only two episodes of neutropenia were documented; however, the lone patient who developed Grade 4 neutropenia died of related infectious complications. The most common nonhematologic toxicities were mucositis, neuropathy, myalgia, and alopecia. Mucositis was severe in five patients and was the primary reason for dose reductions and treatment delays. A previous study of docetaxel in combination with cisplatin, 5-FU, and leucovorin as induction chemotherapy documented a 46% incidence of severe mucositis (i.e., mucositis requiring inpatient supportive measures),[24] and estomatitis was the dose-limiting toxicity associated with a cisplatin + 5-FU + leucovorin schedule for untreated locally advanced HNSCC.[26] Both regimens included a 120-hour 5-FU infusion. The use of a 48-hour, leucovorin-modulated 5-FU infusion did not appear to compromise the efficacy of the study regimen and yielded a more favorable toxicity profile in comparison with more lengthy 5-FU infusions. Peripheral neuropathy occurred in the majority of the patients in a cumulative fashion, but this toxicity was severe in only one patient (after six cycles). The observed incidence of neuropathy is in accordance with previous reports of the toxicity associated with taxane-cisplatin combinations.[11–14,17] Eight of nine long-term survivors had not previously received radiotherapy or chemotherapy, a nonsignificantly higher proportion compared with the corresponding proportion of patients who died; however, there were no other differences in terms of baseline clinical profile, response, or toxicity. Therefore, we are unable to identify a subgroup that might benefit most from the current regimen.

The single-center nature of the current study and the highly selected study population (all patients had a PS of 0–1, one-third had not previously received treatment, and the majority had not previously received chemotherapy) make it necessary to interpret these results with caution. This is especially true for the separate analysis of patients with recurrent disease, 10 of whom had not received radiotherapy as a part of their initial therapy and therefore could not be classified as having previously incurable disease; 7 of these patients are currently classified as long-term survivors.

Standard combinations containing cisplatin and 5-FU are associated with increased response rates when compared with single-agent regimens in patients with HNSCC, but they do not induce a significant improvement in median survival.[5–8] However, a combination containing paclitaxel, cisplatin, and 5-FU has recently been shown to increase rates of response and PFS in comparison with cisplatin and 5-FU administered as induction therapy for patients with HNSCC.[27]

In summary, the current dose-dense, four-agent, taxane-containing biweekly regimen for patients with recurrent or incurable HNSCC is feasible and effective in terms of tumor response. On the basis of the current study, multicenter confirmatory and/or comparative trials in patients with good performance status are warranted.

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