A Phase I Report of Paclitaxel Dose Escalation Combined with a Fixed Dose of Carboplatin in the Treatment of Head and Neck Carcinoma

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BACKGROUND. Standard therapy for advanced head and neck carcinoma is surgery and radiation, and the subsequent 5-year survival with this treatment has been less than 50%. New combined modality treatment strategies are being tested to improve survival. New chemotherapy combinations are being developed and administered simultaneously with, or sequenced with, radiation and surgery. This article reports the Phase I results of administering paclitaxel and carboplatin preoperatively. The authors' objective was to develop an outpatient chemotherapy that would downstage tumors and allow organ preservation with equal or improved survival as compared with standard therapy.

METHODS. Thirty-six patients with untreated Stage III/IV head and neck carcinoma were treated and were evaluable for toxicity. All patients had lesions that were measurable in perpendicular planes. A nonrandomized, Phase I design was used, according to which cohorts of patients were treated every 21 days with escalating doses of paclitaxel (150–265 mg/m^2) given as a 3-hour infusion immediately preceding carboplatin. Premedication was used to avoid acute hypersensitivity reactions. Carboplatin was administered intravenously over 1 hour at a constant dose calculated with the Calvert formula (area under the curve, 7.5).

RESULTS. The dose-limiting toxicities were neuropathy and thrombocytopenia at a paclitaxel dose of 265 mg/m^2. Neutropenic fever was observed in 30% of patients at a paclitaxel dose of 250–265 mg/m^2. Other observed adverse effects included pruritus, myalgia, arthralgia, alopecia, nausea, and vomiting.

CONCLUSIONS. Toxicity was acceptable. The maximum tolerated dose of paclitaxel was 230 mg/m^2 without hematopoietic growth factor, or 250 mg/m^2 with hematopoietic growth factor, the carboplatin dose held constant, calculated at area under the curve of 7.5. Phase II studies of this combination are warranted in the treatment of these carcinomas. ***Cancer* 1997;79:2016–23.** © *1997 American Cancer Society.*

KEYWORDS: head and neck carcinoma, paclitaxel, carboplatin, Phase I, maximum tolerated dose, toxicity, medical oncology.

Most patients with head and neck carcinoma (approximately 60%) present with locally advanced, resectable primary tumors (T3, T4) or advanced regional lymph node metastases (N2, N3) (American

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Joint Committee on Cancer Stage III and IV disease). The present ''standard of care'' in the U.S. for these patients is surgery and postoperative radiotherapy, whereas definitive radiotherapy with surgery held in reserve for ''salvage'' is more commonly used elsewhere in the world.[1] The results of these treatments are unacceptably poor, resulting in 5-year survival rates of 0–40%. Less than 30% of these patients will be disease free at 5 years. Furthermore, radical surgery frequently results in poor cosmesis and limited speech and swallowing function. The incidence of locoregional failure is 66%. Systemic metastases develop in 10–30% of patients. The majority of recurrences occur within 2 years of initial treatment. Once locoregional recurrence or distant metastasis manifest, the chances of salvage or long term palliation with chemotherapy are small, with a median duration of survival of 6 months. Approximately 90% of patients die within 2 years. The authors are applying new treatment strategies for untreated patients with advanced disease to increase the 5-year survival. They are attempting to develop new drugs for the more chemosensitive patient with untreated advanced disease to hopefully change the dismal natural history of this disease.[2–7]

In August 1994 the authors initiated a Phase I clinical trial using the novel combination of paclitaxel and carboplatin as preoperative chemotherapy in previously untreated patients (Stage III/IV) with carcinoma of the head and neck. In this article, the authors describe toxicities, response rates, and the maximum tolerated dose (MTD) that can be safely administered preoperatively in this unique patient population.

PATIENTS AND METHODS

Patient Eligibility

Selected patients had histologically proven (Stage III/IV) carcinoma of the head and neck, were previously untreated, had objectively measurable disease, a Karnofsky performance status of ≥60%, acceptable cardiac function as determined by electrocardiogram, adequate renal function with a serum creatinine level < 3.0 mg/dL, adequate hepatic function with a serum bilirubin level ≤ 1.5 mg/dL, adequate bone marrow reserves (polymorphonuclear leukocytes ≥ 1500/mm^3 and platelets ≥ 100,000/mm^3), and a minimum life expectancy of 4 months. Thirty-six patients met entry criteria and agreed to participate. They were entered consecutively after informed consent was obtained in accordance with the Institutional Review Board at Saint Louis University Health Sciences Center.

Treatment

Chemotherapy was administered on Day 1 of each course. Repeat courses were administered every 21 days if there was no evidence of tumor progression and blood counts had returned to normal (absolute neutrophil count [ANC] ≥ 1500/mm^3, and platelets ≥ 100,000/mm^3). A maximum of three preoperative courses were administered. After three courses of preoperative chemotherapy, rebiopsies of the primary tumor site were obtained. If the rebiopsies revealed no pathologic evidence of disease, organ preservation then was attempted by substituting radiation for surgery. Patients who were observed to have residual disease on repeat biopsies underwent surgery followed by postoperative radiation. After the initial 33 patients, the criteria for organ preservation was relaxed so that biopsies were not required to show pathologic absence of residual disease but rather a 50% reduction of primary tumor size. If a patient's tumor did not respond with a 50% reduction in size after 2 courses, chemotherapy then was stopped and the patient proceeded directly to definitive surgery followed by postoperative radiation. Paclitaxel was started at a dose of 150 mg/m^2 and then escalated in cohorts of patients to a maximum dose of 265 mg/m^2 (Table 1). The carboplatin dose was held constant for all patients and calculated using the Calvert formula (area under curve [AUC], 7.5).[8] Treatment was administered in the outpatient clinic. Paclitaxel was administered as a 3-hour intravenous (i.v.) infusion diluted in a concentration of 1 mg/mL of normal saline. Carboplatin was diluted in a concentration of 2 mg/mL of dextrose 5% in water and administered as a 1-hour i.v. infusion immediately after the paclitaxel. All patients were premedicated 30–60 minutes before chemotherapy with granisetron, 1 mg i.v. piggy back (IVPB); dexamethasone, 40 mg IVPB; diphenhydramine, 50 mg i.v. push; and cimetidine, 300 mg IVPB. Weekly complete blood counts, platelet counts, and reticulocyte counts were obtained after each course.

Groups of three patients were entered at each dose level of paclitaxel. Initially, patients did not receive

TABLE 1
Dose Escalation

Paclitaxel mg/m^2	No. of patients	No. of total courses (evaluable)[a]
150	5	14 (13)
175	3	9
200	8	22
230	6	16
250	7	16
265	7	16
		16 (15)

[a] Fully evaluable for all toxicities including hematologic. Two courses were not fully evaluable.

hematopoietic growth factor until >33% experienced neutropenic dose-limiting toxicity during a single course of preoperative chemotherapy. Growth factor then was added to all subsequent patients. Movement to a higher dose level was allowed only after three patients completed two courses at the current dose level without dose-limiting toxicity. A maximum of six patients were entered at a given dose level, and if two or more had dose-limiting toxicity, the MTD then was defined as one lower dose level. If a new patient presented prior to completion of this evaluation, the patient was required to be entered at the current level. No intrapatient dose escalation was allowed during subsequent cycles. The dose-limiting toxicity was defined as the highest dose of paclitaxel at which 33% of patients experienced a Grade 3 nonhematologic toxicity or at which 33% experienced a Grade 4 hematologic toxicity (while receiving hematopoietic growth factor support). Grade 3 nausea or emesis did qualify as a nonhematologic dose-limiting toxicity. Pruritus without rash was scored as a neurosensory toxicity.

Dose-adjustment criteria were based on standard toxicity criteria from the Southwest Oncology Cooperative Group (last revised in February 1991). A 15% dose reduction of paclitaxel in subsequent courses was implemented for a platelet count nadir $< 25{,}000/mm^3$, neurotoxicity (neuromotor/peripheral neuropathy) of nonreversible Grade 2, or pain (myalgia/arthralgia) of nonreversible Grade 2. Hematopoietic growth factor (granulocyte-macrophage–colony stimulating factor [GM-CSF]; sargramostim) was not used with the first course of chemotherapy. It was added only after one of the following observations: ANC at time of nadir $< 500/mm^3$ for $\geq$ 5 days, fever with neutropenia, and persistent neutropenia, defined as ANC $< 1500/mm^3$ on Day 28. The dose of GM-CSF was 250 $\mu g/m^2$/day as a subcutaneous injection on Days 3–19 or until the ANC exceeded $10{,}000/mm^3$.

RESULTS

Patients

From August 1, 1994 through February 1, 1996, 36 patients were enrolled. A total of 94 courses of preoperative paclitaxel and carboplatin were administered through 6 dose escalations (Table 1). One patient (3%) received 1 course, 13 patients (36%) received 2 courses, and 22 patients (61%) received 3 courses. Two courses were not fully evaluable. Major events occurred in both courses. One septic death occurred 10 days after Course 1; the patient had neutropenic and thrombocytopenic toxicities. One death occurred 4 days after Course 3 due to tumor progression into the brain.

Patient characteristics included a median age of 57 years (range, 17–78 years); 28 patients (78%) were men. None of the patients had received prior therapy (Table 2). At the time of diagnosis 86% of patients were Stage IV. Breakdown by TNM staging is illustrated in Table 3.

TABLE 2
Patient Characteristics

Characteristic	No.
Patients entered	36
No. of courses (evaluable)	94 (93)[a]
Patients evaluable for toxicity	36 (35)[a]
Age (yrs)	
Median (range)	57 (17–78)
Karnofsky performance status	
Median (range)	80 (60–100)
Histology	
Squamous	34
Nonsquamous	2
Stage[b]	
III	4
IV	32

[a] Fully evaluable for all toxicities including hematologic. One not fully evaluable.
[b] TNM staging system.

Toxicity

Myelosuppression

Once a threshold dose of paclitaxel of $\geq$ 230 mg/m^2 was reached, granulocytopenia was observed to be cumulatively more severe during Courses 2 and 3 (Fig. 1). At paclitaxel doses of 265 mg/m^2, 30% of patients were observed to have Grade 4 neutropenic fever requiring i.v. antibiotics and hospitalization. One patient died of small bowel infarction with associated neutropenia and sepsis 10 days after receiving Course 1. The dose was reduced to 250 mg/m^2, resulting in 30% of patients developing Grade 4 neutropenia. After adding hematopoietic growth factor (GM-CSF, 250 $\mu g/m^2$/day on Days 3–19), neutropenia became nondose-limiting at a paclitaxel dose of 265 mg/m^2 (Table 4).

Thrombocytopenia was cumulative in Courses 2 and 3 at paclitaxel doses of $\geq$ 250 mg/m^2 (Fig. 2). At a dose of $\geq$ 200 mg/m^2, Grade 4 thrombocytopenia was observed in 5 of 31 patients (16%), and at a dose of 250 mg/m^2, 29% of patients experienced Grade 4 thrombocytopenia, indicating a direct dose-toxicity relationship. At a paclitaxel dose of 265 mg/m^2, 1 patient died of small bowel infarction and sepsis with a platelet count $< 20{,}000/\mu L$. A second patient required platelet transfusions during each of 3 courses of preoperative chemotherapy due to a platelet count $< 20{,}000/\mu L$ (Table 4).

TABLE 3
T and N Status

Stage		N0	N1	N2	N3	Total
	TX				2	2
	T1					
I						
II	T2		1		1	2
III	T3	5	1	3	4	13
IV	T4	5	2	9	3	19
Total		10	4	12	10	36

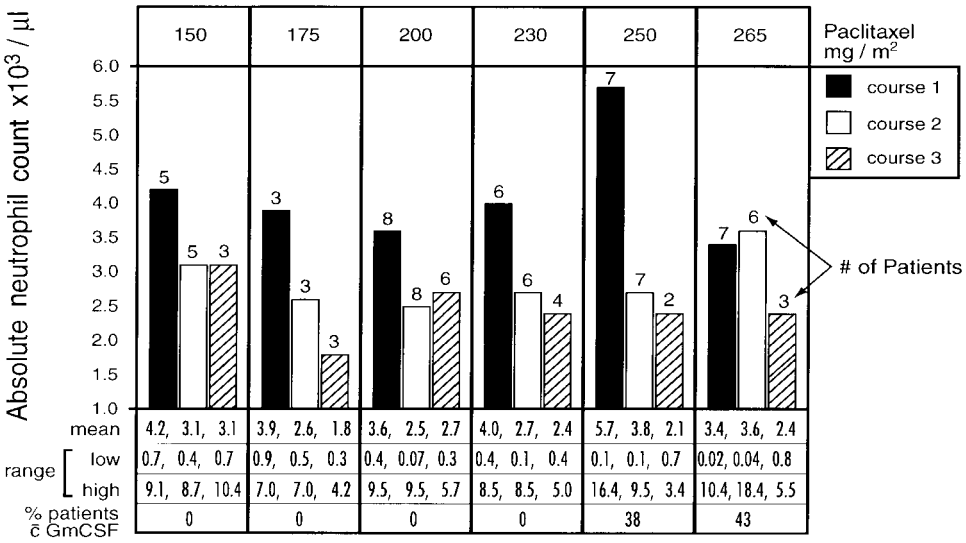

FIGURE 1. Profile of mean absolute neutrophil count in Courses 1, 2, and 3. c̄: with, GM-CSF granulocyte-macrophage–colony stimulating factor.

No anemia was observed in 5 of 36 patients (14%), moderate (Grade 1–2) anemia in 28 of 36 patients (78%), and severe anemia (Grade 3–4) was observed in 3 of 36 patients (8%) (Table 4). It was observed to be cumulative in Courses 2 and 3 at all dose levels of paclitaxel (Fig. 3). Four patients required red blood cell transfusions during preoperative chemotherapy.

Nonhematologic toxicity

Neuropathy was observed at doses of paclitaxel ≥ to 200 mg/m^2. In all patients it manifested as a stocking glove sensory loss of the feet and/or hands. In some patients, painful paresthesias, hyperalgesia, or pruritus blended with the sensory loss. At paclitaxel doses of 200–250 mg/m^2, 10 patients experienced neuropathy (5 with Grade 1, 3 with Grade 2, and 2 with Grade 3). One developed motor loss at a dose of 250 mg/m^2 that was observed as disabling footdrop and 50% loss of extensor-flexor motor function in the hands (Grade 3), which partially reversed 6 months after chemotherapy. This patient was an alcoholic with continued excessive alcohol intake before and during chemotherapy. The other patient who experienced Grade 3 sensory loss had noninsulin-dependent diabetes. He developed Grade 3 sensory loss in both feet that reversed over the ensuing 6 months to Grade 1 nondisabling neuropathy (Table 3).

A dose-toxicity relationship was observed for neuropathy. Grade 2 sensory neuropathy occurred in 12.5%, 28.5%, and 83.3% of patients at paclitaxel doses of 200, 250, and 265 mg/m^2, respectively. At a paclitaxel dose of 265 mg/m^2, neuropathy was cumulatively worse with each subsequent course in 4 of 6 patients. Two of the six patients treated at this level developed Grade 2 sensory neuropathy after their second course that did not improve to Grade 1 within 3 weeks. This necessitated a 15% paclitaxel dose reduction during their third course. One patient receiving dose of 265 mg/m^2 developed nondisabling weakness in the dorsiflexors of the feet (Grade 2), which improved after chemotherapy. One patient receiving a paclitaxel dose of 265 mg/m^2 developed temporary blurred vision of 2 days' duration 3 weeks after Course 2. Ophthalmologic evaluation revealed mild hypertensive retinopathy. No

TABLE 4
Hematologic Toxicity

Pac mg/m^2	No. of courses	Neutropenia Grade					Thrombocytopenia Grade					Anemia Grade				
		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
150	13	5	0	4	3	1	6	3	2	2	0	1	7	3	2	0
175	9	1	2	0	5	1	2	7	0	0	0	2	7	0	0	0
200	22	6	3	4	2	7	10	8	3	0	1	5	13	4	0	0
230	16	5	2	1	5	3	4	4	4	0	4	8	8	0	0	0
250	11	2	3	1	3	2	3	4	2	1	1	3	6	2	0	0
250	5 + GM	2	0	0	0	3	1	2	0	1	1	1	3	1	0	0
265	8	0	0	1	4	3	2	3	2	0	1	5	2	0	0	1
265	8 + GM	3	1	1	3	0	2	1	2	0	3	3	2	3	0	1

Pac: paclitaxel; GM: granulocyte-macrophage colony–stimulating factor.

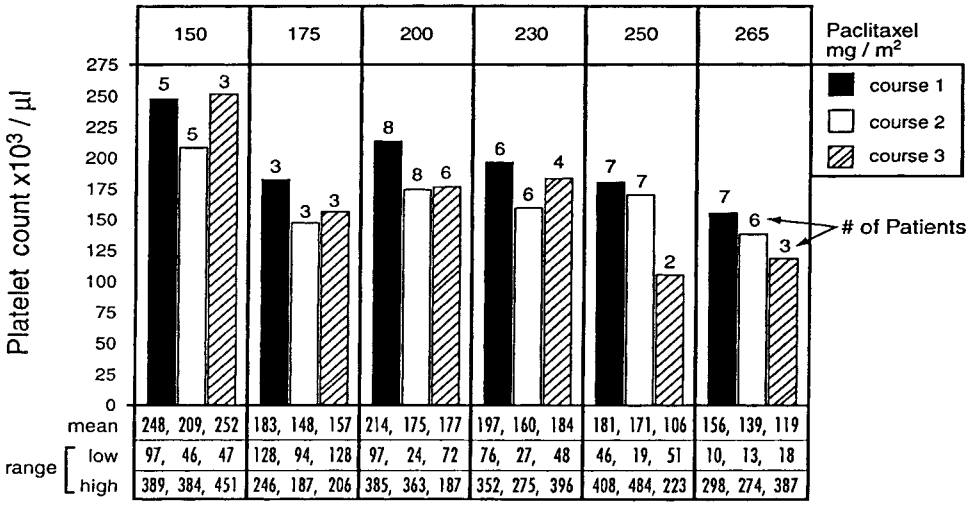

FIGURE 2. Profile of mean platelet count in Courses 1, 2, and 3.

visual problems occurred with Course 3 administered at a 15% dose reduction. One patient receiving a paclitaxel dose of 200 mg/m^2 had a grand mal seizure during a bronchoscopy after lidocaine premedication was administered. This seizure occurred on Day 2 of Course 3. Workup, including computed tomography of the brain, showed an old scar in left temporal lobe that may have contributed to a seizure focus. This patient had no further seizures throughout the remainder of his follow-up.

Five patients experienced pruritus at paclitaxel doses of 250–265 mg/m^2. It was distributed over the extremities but was generalized in two patients. Onset was observed within 48–72 hours after administering chemotherapy. The duration was of 1 to 3 weeks, after which time it would partially or totally improve before the next course. One patient developed disabling pruritus (Grade 3) during Course 2, necessitating a 15% dose reduction of paclitaxel in Course 3. This patient's pruritus was observed to totally reverse 2 months after the third dose. The other patients who experienced pruritus had total resolution after chemotherapy was stopped. Pruritus was observed to have either no or minimal improvement after treatment with either prednisone, diphenhydramine, or phenytoin.

Pain (myalgia/arthralgia) was mild to moderate and not observed to be greater than Grade 2. It was often described by patients as being flu-like in nature, distributed to the lower extremities and pelvis. Onset was generally within 24–48 hours after chemotherapy administration and persisted for 3–5 days. As the dose of paclitaxel escalated, the pain was observed to become more severe in intensity and of longer duration with subsequent courses. This adverse effect occurred at the highest frequency (83%) at a dose of 230 mg/m^2. At this dose level, the authors added prednisone, 40 mg/day for 5 days, on onset of myalgia/arthralgia. A fall in the intensity of pain was observed as dose

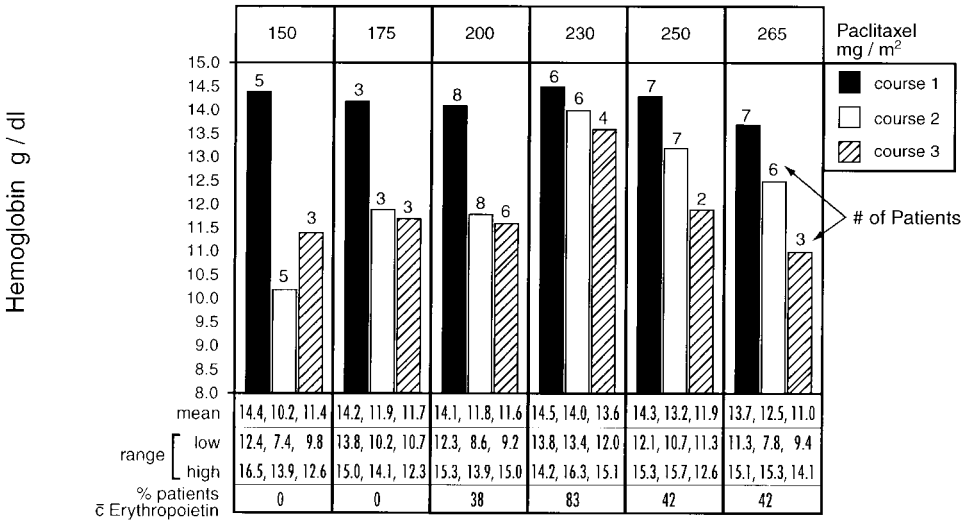

FIGURE 3. Profile of mean hemoglobin in Courses 1, 2, and 3. c̄: with.

escalation was continued. The lowest frequency of pain (28%)-occurred at a paclitaxel dose of 250 mg/m^2 (Table 5). Serositis (reactive arthritis) of the left ankle was observed in one patient.

Gastrointestinal toxicity was mostly Grade 1–2 emesis. It was observed in 9 of 36 patients (25%) and occurred 15 times after 93 courses of chemotherapy. Diarrhea was observed infrequently, occurring as Grade 2 and 3 in 2 of 36 patients treated (0.05%). It occurred twice in 93 courses. Grade 1–3 mucositis was observed in 5 of 36 patients (14%). It occurred 6 times in 93 courses. Complete alopecia was observed in all patients.

One patient who received paclitaxel, 150 mg/m^2, experienced atrial fibrillation during Course 1. Further history revealed this condition preceded his chemotherapy. After digoxin therapy the atrial fibrillation converted to normal rhythm. During the second and third courses of chemotherapy, cardiac monitoring revealed no further atrial fibrillation.

Two patients treated at a dose of 265 mg/m^2 were observed to have ankle swelling (Grade 1 and 2) during each administered course of preoperative chemotherapy. One had preexisting ankle swelling before starting chemotherapy that became worse during and after each of the two chemotherapy treatments.

The second patient developed ankle swelling during each of three courses of preoperative chemotherapy. This second patient did not have a preexisting history of ankle swelling but did have preexisting hypertension requiring treatment.

DISCUSSION

The authors have presented toxicity, MTD, and preliminary response data on 36 previously untreated patients with head and neck carcinoma. In this specific head and neck carcinoma population, a paclitaxel dose of 265 mg/m^2 and carboplatin (AUC 7.5) was dose limiting with unacceptable thrombocytopenia and neuropathy. The MTD of paclitaxel was 230 mg/m^2 without hematopoietic growth factor or 250 mg/m^2 with the use of hematopoietic growth factor and carboplatin held at a constant dose of AUC 7.5 calculated using the Calvert formula.[8] The 29% complete response rate and 32% partial response rate were observed in a group of advanced stage patients with poor prognosis (23% Stage III and 77% Stage IV). This was a study to administer an outpatient regimen with acceptable toxicity.

Two trials administering single agent paclitaxel as 24-hour infusions have reported a similar frequency of neutropenia, less thrombocytopenia, and less neuropathy than in the current study. Holmes et al. treated patients with metastatic breast carcinoma with doses of paclitaxel ranging from 200–250 mg/m^2 for a median of 11 courses. The authors reported Grade 3–4 neutropenia and thrombocytopenia in 100% and 0% of patients, respectively, and neutropenic fever in 36%. Grades 2 and 3 neuropathy was observed in 52% and 8% of patients respectively.[9] Seidman et al. treated patients with metastatic breast carcinoma with paclitaxel doses of 200–250 mg/m^2. The authors reported febrile neutropenia in 21%, severe Grade 4 thrombocytopenia in 16%, mild Grade 1–2 sensory/motor neuropathy 67%, and Grade 3 sensory/motor neuropathy in 4% of patients.[10]

Studies administering single agent paclitaxel as 3-hour infusions have generally shown more severe neuropathy and similar degrees of bone marrow suppression compared with 24-hour schedules. Speilmann

TABLE 5
Nonhematologic Toxicity

Paclitaxel mg/m^2	No. of courses	Neurosensory Grade					Myalgia and arthralgia Grade				
		0	1	2	3	4	0	1	2	3	4
150	13	13	0	0	0	0	10	1	2	0	0
175	9	9	0	0	0	0	4	4	1	0	0
200	22	18	2	1	1	0	9	11	2	0	0
230	16	12	4	0	0	0	4	4	8	0	0
250	16	6	5	4	1	0	10	4	2	0	0
265	15	0	4	10	1	0	10	4	1	0	0

treated patients with metastatic breast carcinoma using a dose range of 135–175 mg/m^2. The author observed Grade 3–4 neutropenia in 62%, Grade 3–4 thrombocytopenia in $<$ 5% and Grade 3 neuropathy in 4% of patients.[11] Seidman et al. treated 49 metastatic breast carcinoma patients with doses of 175–250 mg/m^2. Grade 3–4 toxicities were reported in 2 groups (Group 1 had no prior chemotherapy whereas Group 2 had 2 prior chemotherapy regimens): neutropenia (36% and 33%, respectively), thrombocytopenia (0% and 8%, respectively), and neuropathy (8% and 0%, respectively).[12] Schiller et al. reported a Phase I trial of escalating doses. Neutropenia was dose-limiting at 250 mg/m^2 of paclitaxel without hematopoietic growth factor and peripheral neuropathy was dose-limiting at 300 mg/m^2 with the use of hematopoietic growth factor (16% of patients developed Grade 3 neuropathy).[13] Younes et al. used 200 mg/m^2 of paclitaxel to treat refractory and relapsed non-Hodgkin's lymphoma. The neutropenic fever rate was 11%, the rate of sensory neuropathy Grade 1–2 was 28%, and the rate of Grade 3 neuropathy was 9%.[14] Gianni et al. treated anthracycline-resistant recurrent breast carcinoma. The doses used were 175–225 mg/m^2 for a median of 5 courses. Grade 4 neutropenia occurred in 14% of patients at higher doses but was not associated with fever or infection. Peripheral neuropathy occurred in 92% of patients (11% with Grade 3). Generalized pruritus was also observed at higher doses. To the authors' knowledge, this is the only other report in the literature that describes pruritus as a toxicity of paclitaxel treatment.[15]

One combined paclitaxel and carboplatin trial reported similar toxicities to those observed in the current study. Langer et al. reported cumulative thrombocytopenia and neuropathy when using six courses to treat advanced nonsmall cell lung carcinoma. Paclitaxel was administered as a 24-hour infusion to a maximum dose of 215 mg/m^2 and carboplatin was administered over 1 hour using the Calvert formula with AUC of 7.5. The authors reported cumulative Grade 3–4 thrombocytopenia in 30% of patients and mild neuropathy affecting 38% of patients by the last course. With the use of a hematopoietic growth factor, Grade 3–4 neutropenia was not cumulative and was observed at a constant rate of 22%.[16]

In 1993, Rowinsky et al. reviewed the toxicities encountered with single agent paclitaxel in Phase I studies. They noted the dose of paclitaxel appeared to be the most important risk factor for the development of significant neurotoxicity. They observed that other factors may predispose patients to developing neurotoxicity, such as prior exposure to known neurotoxic agents and antecedent medical disorders such as diabetes mellitus or chronic alcoholism.[17] Similarly, as mentioned earlier, neurotoxicity (neurosensory/neuromotor) was the dose-limiting nonhematologic toxicity. The two patients in the current study with Grade 3 extremity neurotoxicity had comorbid medical conditions that could have contributed to their neuropathy. One patient had noninsulin-dependent diabetes and the other was an alcoholic. The third patient in the current study with Grade 3 neurotoxicity developed generalized pruritus that prohibited school attendance. The pruritus was initially believed to be allergic. However, after observing no rash and its crescendo-decrescendo temporal relationship to each paclitaxel treatment, it was believed to represent paresthesia.

The combination of paclitaxel and carboplatin was able to be safely administered as a simple outpatient regimen for three courses prior to definitive surgery or radiation. The observed overall response rates in the current study approach that of standard induction trials using 5-fluorouracil and cisplatin that enrolled patients with smaller tumors and used vague endpoint response criteria. The authors are currently performing a Phase II trial of this program using preoperative paclitaxel, 250 mg/m^2, and carboplatin (AUC 7.5) with hematopoietic growth factor support using GM-CSF.

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