Paclitaxel and Tamoxifen

An Active Regimen for Patients with Metastatic Melanoma

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BACKGROUND. In early trials of paclitaxel administered as a 24-hour infusion, an overall response rate of 16% was reported for patients with metastatic melanoma. Paclitaxel is a natural product-based agent and is thus subject to the problem of multidrug resistance (MDR). Tamoxifen is an agent that can abrogate MDR and potentially enhance the effect of paclitaxel. A Phase II trial of the combination was undertaken with previously treated patients.

METHODS. Patients with metastatic cutaneous or mucosal melanoma who were previously treated with the Dartmouth chemotherapy regimen (dacarbazine, carmustine, cisplatin, and tamoxifen) were evaluated. Paclitaxel was administered at a dose of 225 mg/m^2 intravenously over 3 hours every 3 weeks. All patients also took tamoxifen 40 mg orally daily. Treatment continued until disease progression.

RESULTS. Twenty-one patients completed at least two cycles of paclitaxel and were evaluable for response. Five responses were observed, 1 complete response, and 4 partial responses, for an overall response rate of 24%. The combination was well tolerated. The most common nonhematologic side effects were myalgia and paresthesia. Hematologic toxicity was mild. No patients developed neutropenic fever.

CONCLUSIONS. This is the first report of a Phase II trial evaluating paclitaxel as a 3-hour infusion in melanoma patients. The 3-hour infusion is well tolerated and results in little myelosuppression and minimal neurotoxicity. The contribution of tamoxifen is difficult to evaluate because plasma levels were not measured. It is possible that a higher response rate might be observed with larger doses of tamoxifen. Further investigation of paclitaxel in the treatment of patients with metastatic melanoma is warranted. ***Cancer* 2000;88:79–87.**
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The management of patients with metastatic malignant melanoma remains difficult. The most active single-agent, dacarbazine (DTIC), effects responses in 20% of patients. The most widely used combination chemotherapy regimen, the Dartmouth regimen (DTIC, carmustine, cisplatin, and tamoxifen), has a response rate of ≈40%.[1]

The M. D. Anderson biochemotherapy regimen of cisplatin, vinblastine, and DTIC with interleukin-2 (IL-2) and interferon-α produces a seemingly higher response rate of ≈60%,[2,3] but this is at the expense of considerable toxicity. Many patients who initially respond to treatment subsequently relapse. Clearly, there is need for improvement, and evaluation of new agents is warranted.

Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) was isolated from the stem bark of the western yew, *Taxus brevifolia*, in 1971.[4] In early trials with previously untreated metastatic melanoma patients, it produced a reported response rate of 16% when it

was given as a 24-hour infusion.[5] Because paclitaxel is a natural product-based agent, it is subject to the problem of multidrug resistance (MDR), which results from the overexpression of the P-glycoprotein (PGP). A variety of drugs have been evaluated as potential inhibitors of MDR, including tamoxifen.[6–10] For this reason, we elected to explore the efficacy of the combination of paclitaxel and tamoxifen as second-line therapy in patients with metastatic cutaneous melanoma.

In the current study, in which 21 previously treated patients received a 3-hour paclitaxel infusion every 3 weeks and daily tamoxifen, we observed an objective response rate of 24%. This regimen was well tolerated with moderate hematologic toxicity.

MATERIALS AND METHODS

Previously treated patients with metastatic cutaneous or mucosal melanoma were evaluated. Informed consent was obtained from each patient. Chemotherapy was administered in the following fashion: paclitaxel 225 mg/m^2 intravenously over 3 hours every 3 weeks and tamoxifen 40 mg orally daily. All patients had started tamoxifen at least 3 days before receiving their first dose of paclitaxel. Most had been taking tamoxifen as part of the Dartmouth regimen. All patients were pretreated prior to the paclitaxel infusion with intravenous dexamethasone, diphenhydramine, and an H2 blocker, usually cimetidine. Patients had to have completed 6 weeks of therapy (2 cycles) to be considered evaluable for response.

Responses were defined as follows: complete response (CR), the disappearance of all clinical evidence of tumor for at least 4 weeks; partial response (PR), decrease in the mean greatest dimension of a measurable mass by at least 50% for at least 4 weeks without simultaneous growth of other metastases; progressive disease (PD), an increase $>$ 25% in the area of the measurable lesion(s) or the appearance of new lesions; and stable disease (SD), responses that did not meet the criteria for response or progression.

RESULTS

Patient Characteristics

Twenty-six consecutive patients were treated with paclitaxel and tamoxifen between February 1995 and March 1997. Five patients were excluded from the analysis for the following reasons: 24-hour administration of paclitaxel (1 patient), paclitaxel dose of only 175 mg/m^2 (1 patient), and completion of only 1 cycle of paclitaxel (3 patients). Of the patients who received only 1 cycle, 1 patient had rapidly progressing disease and expired at another hospital 2 weeks after receiving the first cycle, 1 patient developed intractable hemorrhage from an adrenal metastasis, and 1 patient developed a prolonged cutaneous allergic reaction after the first dose. Therefore, 21 patients completed at least 2 cycles of a 3-hour paclitaxel infusion at a dose of 225 mg/m^2 and were evaluable for response. Patient characteristics are shown on Table 1. Three of the patients had mucosal primary lesions (2 anorectal, 1 oral). Five patients had liver metastases. All patients had been treated previously with the Dartmouth regimen. Six patients had received additional therapy, including continuous infusion carmustine and cisplatin (1 patient); radiation to a bony lesion (1 patient); interferon-α (1 patient); IL-2 (1 patient); 5-fluorouracil, doxorubicin, and cyclophosphamide for a simultaneous breast carcinoma (1 patient); and adjuvant DNP-conjugated melanoma vaccine (1 patient). Ninety-two total cycles of chemotherapy were administered. The maximum number of cycles received was 10 by 2 patients. Three patients received 8 cycles, 1 patient received 6 cycles, 4 patients received 4 cycles, and 9 patients received only 2 cycles. The median age was 56 years (range, 28–85 years), and 66% of the patients were men.

TABLE 1
Patient Characteristics

Characteristic	No. of patients
Evaluable patients	21
Gender	
Male	14
Female	7
Age (yrs)	
Median	56
Range	28–85
Site of primary tumor	
Skin	18
Mucous membrane	3
Site of metastases	
Lymph nodes	13
Skin	4
Lung	12
Liver	5
Other[a]	13

[a] Includes adrenal (n = 3 patients), peritoneum (n = 1 patient), muscle (n = 1 patient), bone (n = 3 patients), soft tissue (n = 1 patient), brain (n = 4 patients).

Response

Five responses were observed: 1 CR and 4 PRs, for an overall response rate of 24%. Two patients had stable disease: 1 for 8 cycles, and another for 4 cycles. The median overall survival for all patients was 38.3 weeks. For the 5 responders, the median overall survival was

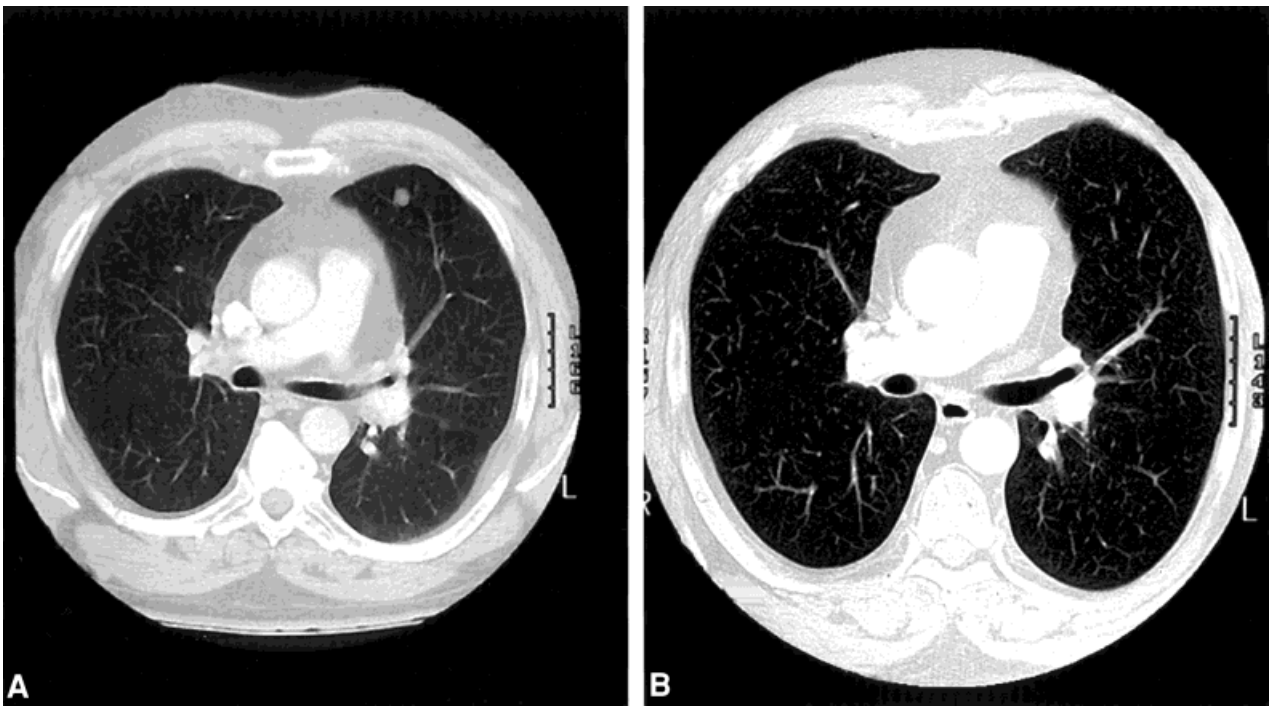

FIGURE 1. A complete response for Patient 1 is represented. (A) Before: Computed tomography (CT) shows pulmonary nodules prior to the start of chemotherapy. (B) After: This CT followed six cycles of of paclitaxel and tamoxifen.

50.8 weeks. Responses were observed in the lung (2 patients), lymph nodes (3 patients), subcutaneous tissues (1 patient), and liver (1 patient). The CR was observed in a man age 55 years (Patient 1) with pulmonary nodules. He had presented with axillary and liver metastases 3 years previously. His initial treatment, 4 cycles (8 months) of the Dartmouth regimen, resulted in complete resolution of the liver metastases and almost complete resolution of the axillary lymph node metastases. Axillary lymph node dissection showed necrotic melanoma in 1 of 27 lymph nodes. Seven months later, he was found to have multiple pulmonary nodules, and biopsy confirmed recurrent metastatic melanoma. Reevaluation after 4 cycles of paclitaxel and tamoxifen showed that all of the lung nodules had disappeared or decreased in size. Reevaluation after 6 cycles demonstrated a CR (Fig. 1). He received 2 more cycles for consolidation, then chemotherapy was discontinued. His CR lasted for 10.9 months before disease recurred in retroperitoneal lymph nodes. He is alive 36+ months after initiating the regimen.

A PR was observed in a white female age 33 years (Patient 2) who developed widespread adenopathy after adjuvant immunotherapy with an autologous melanoma vaccine. She progressed while on the Dartmouth regimen and experienced neurotoxicity from IL-2. After 2 cycles of paclitaxel and tamoxifen, she was found to have a significant decrease in the size of her palpable adenopathy (Table 2). Evaluation after 4 cycles showed complete regression of the lymph node masses in her left neck, right axilla, and chest wall; continued decrease in her intraabdominal adenopathy (Fig. 2); and the disappearance of a lung lesion. She ultimately received 10 cycles of therapy before developing progressive disease. She survived for 12 months after initiating treatment.

TABLE 2
Tumor Measurements for Patient 2

Site	Pretreatment measurements (cm)	After 2 cycles (cm)	After 4 cycles (cm)
Angle of left jaw	3.5	<1	Nonpalpable
Right axilla	3	Nonpalpable	Nonpalpable
Right lateral chest wall	3.5	1.5	Nonpalpable
Lateral right breast	2.0 × 1.5	No change	1 × 1
Right supraclavicular mass	4.5 × 3.5	No change	3.5 ×3.0
Left paraaortic lymph node	Encasing blood vessels	2.8 × 3.0	No change
Aortocaval lymph node	Encasing blood vessels	3.2 × 2.0	2.5 × 2.0
Retrocaval lymph node	Encasing blood vessels	3 × 3	2 × 2
Mesenteric lymph node	Encasing blood vessels	3.1 × 3.1	3 × 3

A second PR was observed in a woman age 47

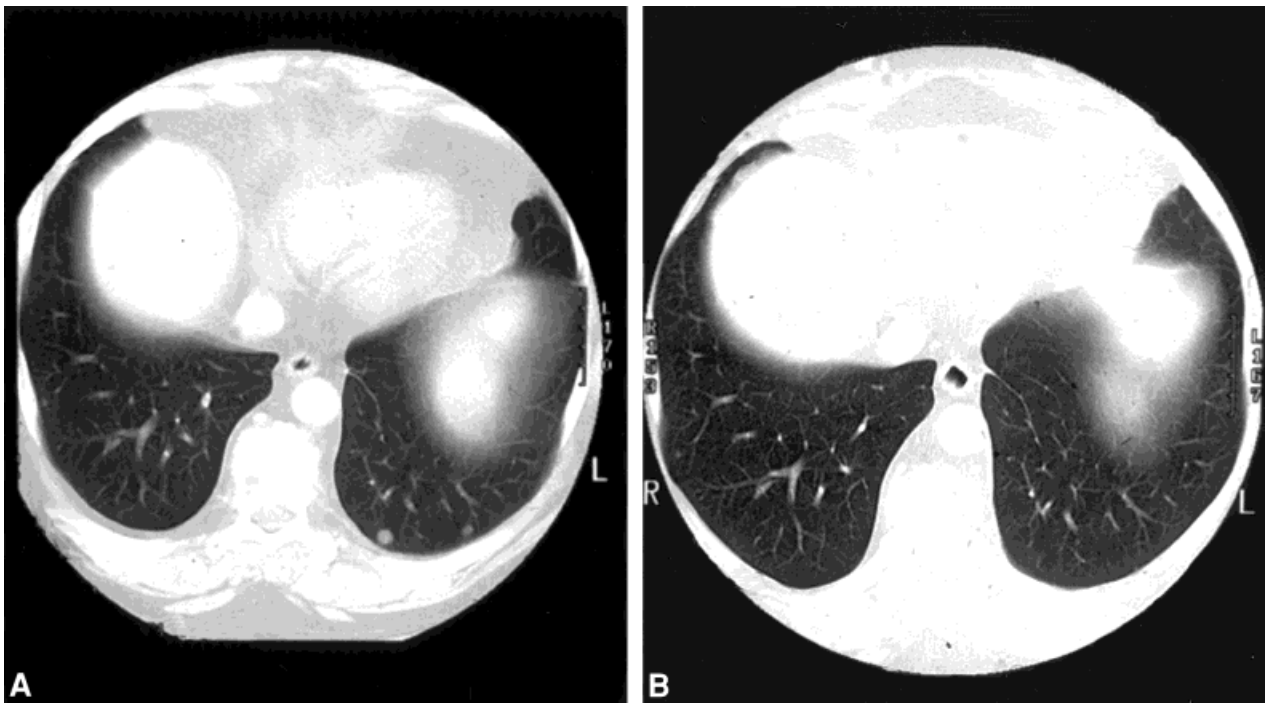

FIGURE 2. A complete response for Patient 1 is represented. (A) Before: Computed tomography (CT) shows pulmonary nodules prior to the start of chemotherapy. (B) After: This CT followed six cycles of of paclitaxel and tamoxifen.

TABLE 3
Palpable Tumor Measurements for Patient 3

Site	Pretreatment measurements (cm)	After 2 cycles (cm)	After 4 cycles
Right temple	1.5 × 1.0	1.0 × 0.8	Nonpalpable
Right posterior lateral chest	2.0 × 1.0	1.2 × 0.8	Nonpalpable
Left parotid	2 × 2	1 × 1	Nonpalpable

years (Patient 3) who developed metastases in her lungs, liver, and subcutaneous tissue. Her disease progressed on the Dartmouth regimen. Evaluation after 2 cycles of paclitaxel and tamoxifen showed that 3 subcutaneous lesions had decreased significantly in size (Table 3). After 4 cycles, they had all disappeared, and a decrease in the size of the liver metastases was noted (Fig. 3). Unfortunately, evaluation after Cycle 8 showed disease progression. She survived for 12 months after initiating treatment.

A third PR was observed in a white male age 78 years (Patient 4), who had an anal melanoma metastatic to left inguinal lymph nodes, right pelvic lymph nodes, and right internal obturator lymph nodes. Evaluation after 1 cycle of the Dartmouth regimen revealed the development of a liver metastasis and growth of the obturator lymph node, although there was a decrease in the size of the pelvic lymph nodes and rectal mass. Paclitaxel and tamoxifen were initiated, and reevaluation after 4 cycles showed that the right pelvic lymph nodes, the left inguinal lymph nodes, and the right internal obturator lymph nodes all had decreased in size; the liver lesion remained stable. He ultimately received 10 cycles of paclitaxel and tamoxifen before developing brain metastases. He survived for 9.6 months after initiating treatment.

The fourth PR was observed in a white female age 67 years who presented with inguinal lymph node metastases that progressed on the Dartmouth regimen. Paclitaxel and tamoxifen were initiated, and evaluation after 3 cycles showed that the size of the inguinal mass had decreased from 5 × 5 cm to 3 × 3 cm. At the start of Cycle 4, the mass measured 1.5 × 1.5 cm. At the start of Cycle 5, the mass was barely palpable. She ultimately received 8 cycles before developing progressive disease. She survived for 10.9 months after initiating treatment.

Toxicity

Treatment-related toxicity is summarized in Table 4. The combination of paclitaxel and tamoxifen was well tolerated. The most common nonhematologic side ef-

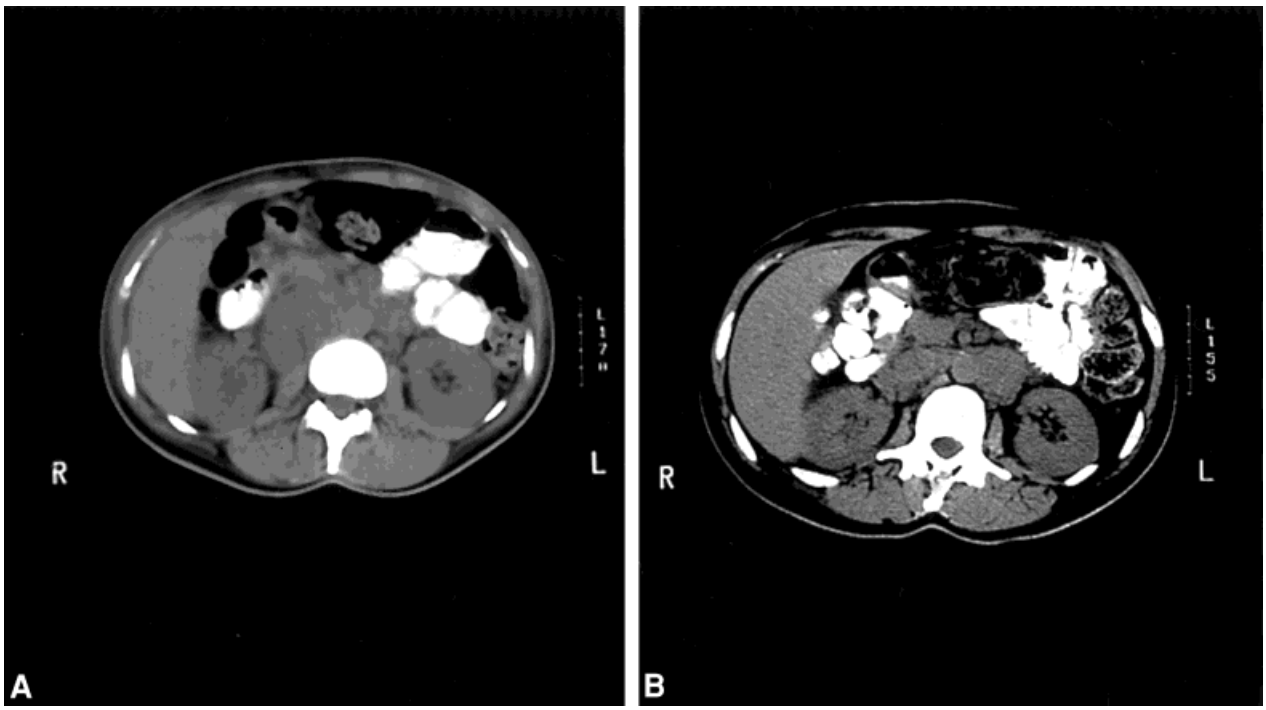

FIGURE 3. A partial response for Patient 2 is represented. (A) Before: Computed tomography (CT) shows intraabdominal adenopathy prior to the start of chemotherapy. (B) After: CT following four cycles of paclitaxel and tamoxifen shows a decrease in the patient's adenopathy.

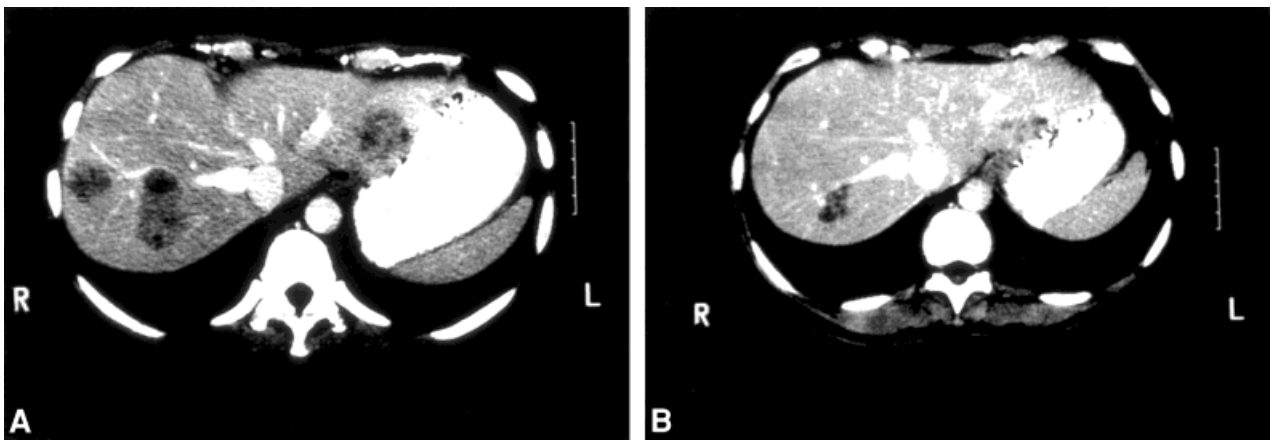

FIGURE 4. A partial response for Patient 3 is represented. (A) Before: Computed tomography (CT) shows liver metastases prior to the start of chemotherapy. (B) After: CT following four cycles of paclitaxel and tamoxifen shows a decrease in the size of the liver metastases.

fects were myalgia and paresthesia, although none exceeded Grade 2 in intensity. The myalgias generally occurred 2–3 days after paclitaxel administration. One patient experienced Grade 2 myalgia, and 6 patients reported Grade 1 myalgia. Four patients experienced Grade 2 paresthesia, and 7 patients reported Grade 1 paresthesia. All patients developed total alopecia. Hematologic toxicity was mild. There were 25 episodes of Grade 3 or 4 granulocytopenia among 10 patients in the 92 cycles. No patients developed neutropenic fever. There were 6 episodes of Grade 3 or 4 anemia among 4 patients, including 2 patients with known bowel metastases that could have bled. There were no episodes of Grade 3 or 4 thrombocytopenia. Two patients had dose reductions because of absolute granulocyte nadir < 500. A 20% dose increase was instituted in Patient 2 for Cycles 3 and 4, but the dose was decreased to the original dose when she developed

TABLE 4
National Cancer Institute Common Toxicity Criteria

	Cycle no. (patients)										
Toxicity	**1 (n = 21)**	**2 (n = 21)**	**3 (n = 12)**	**4 (n = 12)**	**5 (n = 6)**	**6 (n = 6)**	**7 (n = 5)**	**8 (n = 5)**	**9 (n = 2)**	**10 (n = 2)**	**Total**
AGC											
Grade 3	4	2	6	4	1	1	2	1	0	0	21
Grade 4	1	1	0	2	0	0	0	0	0	0	4
HCT											
Grade 3	1	3	0	1	0	0	0	0	0	0	5
Grade 4	1	0	0	0	0	0	0	0	0	0	1
PLT											
Grade 3	0	0	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0	0	0
Myalgia											
Grade 1	5	5	3	2	1	1	1	1	0	0	19
Grade 2	0	1	0	0	0	0	0	0	0	0	1
Paresthesia											
Grade 1	5	6	6	4	1	1	1	1	0	0	25
Grade 2	0	1	0	2	2	2	2	2	1	1	13

AGC: absolute granulocyte count; HCT: hematocrit; PLT: platelet count.

TABLE 5
Previous Trials of Paclitaxel for Metastatic Melanoma

Phase/schedule	Paclitaxel dose (mg/m^2)	No. Patients	No. previous chemotherapy	No. responses (%)	Reference
Phase I, 24 hrs	125–275	12	4	4 (33)	11
Phase I, 6 hrs	175–275	12	NA	0 (0)	12
Phase I, 24 hrs	250–400	10	0	2 (20)	13
Phase II, 24 hrs	250	25	0	3 (12)	14
Phase II, 24 hrs	250	28	0	4 (14)	15
Total		87		13 (15)	—

paresthesia. There were no treatment delays for toxicity issues. Five patients had treatment delays for reasons that included problems with intravenous access (2 patients), weather (1 patient), and development of brain metastases (2 patients).

DISCUSSION

We observed a 24% overall response rate, including 1 CR, in previously treated patients with metastatic melanoma who received the combination of paclitaxel and tamoxifen. This is the first report of a Phase II trial evaluating paclitaxel as a 3-hour infusion in melanoma patients. All of the previous reports of paclitaxel in melanoma patients have been either Phase I studies or studies evaluating prolonged (6-hour or 24-hour) infusions (Table 5).[11–15] Tamoxifen was included in our study because of its ability to modulate MDR.[6–10]

In one of the first Phase I trials of 24-hour infusional paclitaxel, Wiernik et al. observed 4 partial responses among 12 patients (33%) with metastatic melanoma.[11] Only 1 of the 4 patients had been treated previously with chemotherapy. In another Phase I trial of 6-hour paclitaxel evaluating the necessity of premedication, no responses were observed among 12 patients with metastatic melanoma.[12] Einzig et al. observed 2 partial responses among 10 patients in a Phase I trial evaluating escalating doses of 24-hour infusional paclitaxel and granulocyte colony-stimulating factor. None of these patients had received prior chemotherapy.[13] In a Phase II trial of 24-hour infusional paclitaxel in previously untreated patients, Legha et al. reported a 12% response rate (3 responses among 25 patients).[14] Four responses were observed among 28 evaluable patients (14%) in another Phase II trial of 24-hour paclitaxel. None of these patients had been treated previously with chemotherapy.[15] Paclitaxel was administered as a prolonged infusion in these studies because of early reports of acute ana-

phylactic reactions in many patients receiving short (1-hour) infusions.[16,17] It has been demonstrated subsequently that there is no difference in the incidence of hypersensitivity reactions between 3-hour and 24-hour infusions when patients are premedicated.[18] We elected to evaluate the 3-hour regimen, which is more suitable for the outpatient setting. Also, the shorter regimen results in less myelosuppression that the 24-hour regimen.[18]

In the current study, side effects were mild to moderate, and no patient discontinued treatment due to toxicity. A range of doses of paclitaxel has been used in the treatment of a variety of malignancies. The dose we used is higher than what is recommended for the every 3 week, 3-hour infusions in the treatment of breast carcinoma (175 mg/m^2) and ovarian carcinoma (135 mg/m^2 or 175 mg/m^2), and it is somewhat lower than what was used in the 24-hour infusional studies for metastatic melanoma (250 mg/m^2).[11,14]

The issues of high dose versus low dose and long infusion versus short infusion were addressed in one randomized study of ovarian carcinoma patients.[18] In that study, patients were randomized to receive either 175 mg/m^2 or 135 mg/m^2 of paclitaxel over 24 hours or over 3 hours. There was a no statistically significant improvement in the response rate of patients who received a dose of 175 mg/m^2 compared with patients who received a dose of 135 mg/m^2. The 3-hour infusion was found to be safe when given with premedications, and it resulted in less neutropenia than the 24-hour infusion. In a more recent study of patients treated for breast carcinoma, a higher response rate was observed in those who received a 3-hour infusion of paclitaxel compared with those who received a 24-hour infusion.[19] There was no difference in survival, however. There are now several reports evaluating the feasibility and toxicity of a 1-hour infusion.[20–24] This shorter infusion appears to be well tolerated, with little myelosuppression and minimal neurotoxicity. Further investigation of different infusion schedules in patients with melanoma seems warranted.

Did the inclusion of tamoxifen improve the response rate? Tamoxifen is most used commonly in the treatment of patients breast carcinoma for its hormonal antiestrogenic properties; however, this is not its role in the Dartmouth combination, although it is an essential part of the regimen. In the initial reports of the Dartmouth regimen, there was an overall response rate of 50%,[25,26] which dropped to 10% when the tamoxifen was eliminated to reduce the incidence of thrombosis.[27] The precise role of tamoxifen in this combination remains unexplained. Tamoxifen at concentrations > 2 μM in vitro enhances the cytotoxicity of other chemotherapeutic agent at concentrations;[6,28] however, this concentration, using a dose of 40 mg/day, is not reached in the Dartmouth regimen.[29] To evaluate a possible dose response effect in this setting, our group initiated a trial in which patients received a 7-day loading dose of 160 mg/day of tamoxifen prior to receiving the intravenous chemotherapy. Although there was a greater proportion of CRs in the high dose group (27% vs. 9%), the overall response rate was similar at 47%.[30]

Tamoxifen also is an agent that can modulate MDR.[6–10] It has been demonstrated that increased MDR activity is an important factor in the development of resistance to the taxanes,[31] including paclitaxel.[32] Tamoxifen has been shown to circumvent MDR in cell lines when combined with doxorubicin,[6,7,33] daunorubicin,[8,34] mitoxantrone,[35] vinblastine,[9] and etoposide[36] as well as docetaxel (Taxotere; Rhône-Poulenc Rorer Pharmaceuticals, Inc., Collegeville, PA).[37] This effect has been observed in estrogen receptor negative cell lines[6,8,34,37] as well as in vivo in patients with malignancies other than breast carcinoma,[38,39] suggesting that it is independent of its hormonal effects. The usual oral dose of paclitaxel, 10–20 mg per day, results in steady-state plasma levels of 0.4–1.0 μM. Studies have shown that levels ranging from 2 μM to 6 μM may reverse MDR in vitro,[35,40] and levels from 4 μM to 6 μM have been effective in vivo[38] and have been achieved safely.[34,38,39] The doses of tamoxifen administered in these studies were fairly high (150 mg/m^2/day,[38] 200–700 mg/day,[34] and 320 mg/day[39]). We did not measure tamoxifen levels, and the dose we used was much lower; therefore, it is possible that, using larger doses, a higher response rate may result. Of course, it is possible that the inclusion of tamoxifen did not affect the response rate at all. Certainly, our observed response rate of 24% is within the range of response rates reported previously in earlier trials. Nevertheless, a 24% response rate in previously treated patients, associated with minimal toxicity, is a cause for cautious optimism. Certainly, the observation of a prolonged (10-month) CR in one of our patients indicates activity for this combination. In addition, this was a CR in a visceral site in a patient who had received previous systemic therapy. The observation of a PR in three previously treated patients further substantiates the activity of the regimen. Further investigation of paclitaxel in the treatment of metastatic melanoma is warranted. One approach may be to integrate it into other regimens, such as the Dartmouth regimen or other combination regimens. A second approach would be further evaluate different schedules of administration of paclitaxel. Certainly,

paclitaxel is another agent to be used in the treatment of patients with melanoma.

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