Phase II Study of Paclitaxel in Patients with Previously Treated Osteosarcoma and Its Variants

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BACKGROUND. Patients with osteosarcoma and its variants who did not respond to standard chemotherapy including doxorubicin, ifosfamide, cisplatin, and high dose methotrexate were treated with paclitaxel so that its therapeutic activity in these patients could be determined.

METHODS. We conducted a Phase II study of paclitaxel in patients with conventional osteosarcoma (10), malignant fibrous histiocytoma of the bone (3) and dedifferentiated chondrosarcoma (2) whose disease had progressed after prior standard chemotherapy including doxorubicin, cisplatin, ifosfamide, and high dose methotrexate. Paclitaxel was administered at a starting dose of 175 mg/m^2 as a 24-hour infusion with standard premedication every 21 days or upon hematologic recovery (absolute granulocyte count [AGC] $>$ 1500/μl, platelets $>$ 100,000/μl). Neupogen was not used routinely. The study was conducted based on a two-stage design. A total of 17 patients were entered into the protocol. Two were ineligible since they had Ewing's sarcoma. Responses were assessed radiographically and pathologically when feasible, using standard criteria.

RESULTS. Fifteen eligible patients were treated in the first stage of the study. Median age of the patients was 31 years (range, 19–61 yrs). There were 8 females and 7 males with a Zubrod performance status of 0 or 1. One patient achieved a mixed response and 14 developed progressive disease. Median AGC nadir was 0.3, on Day 13, lasting 5 days. Median platelet nadir was 134, on Day 8. There were no Grade III or IV nonhematologic toxicities and no deaths related to treatment.

CONCLUSIONS. Paclitaxel, at this dose and schedule, is well tolerated but inactive in this patient population. ***Cancer* 1996; 78:741–4.** © *1996 American Cancer Society.*

KEYWORDS: bone sarcomas, osteosarcoma, chemotherapy, paclitaxel (Taxol®).

Paclitaxel (Bristol-Meyers Squibb Co., Princeton, NJ) is a novel antimicrotubule agent with a unique mechanism of action. It has been studied in a wide variety of malignancies with varying levels of efficacy.[1] Given its "broad spectrum" activity, we performed a Phase II study of paclitaxel in patients with osteosarcoma and its variants, i.e., malignant fibrous histiocytoma (MFH) of bone and dedifferentiated chondrosarcoma, who had failed standard chemotherapy. The major objectives of the study were to evaluate the efficacy and the toxicity profile of paclitaxel in patients with these malignant bone tumors.

PATIENTS AND METHODS

Eligibility

Patients older than 16 years with histologic proof of osteosarcoma, MFH of bone, or dedifferentiated chondrosarcoma, resistant to one prior alternating or combination regimen of standard chemotherapy drugs including adriamycin, cisplatin, dacarbazine, ifosfamide, and high dose methotrexate were eligible. Patients were required to have

TABLE 1
Dose Modification Scheme

Dose levels		Criteria for hematologic toxicity				Criteria for nonhematologic toxicity	
Dose (mg/m^2)		Granulocyte nadir/μL		Platelet nadir/μL	Modification	Grade	Dose modification
−2	135	> 2000	and	> 100,000	Increase 2 levels	0–1	Increase 1 level
−1	150	1000–2000	and	75000–100,000	Increase 1 level	2	No change
		< 500 & significant		< 50,000 & significant			
0	175	morbidity[a]	or	morbidity[b]	Decrease 1 level	3	Decrease 1 level
+1	200					4	Decrease 2 levels or stop
+2	225						

[a] Organ infection, sepsis syndrome, failure to recover to ≥ 1500/μL by Day 28.
[b] Bleeding, platelet transfusions for ≥ 7 days, failure to recover to ≥ 100,000/μL by Day 28.

a Zubrod performance status of 0 to 2, a life expectancy of at least 12 weeks, measurable or evaluable disease, and relatively normal organ function defined as absolute granulocyte count of ≥ 1500/μL, platelet count of ≥ 100,000/μL, total bilirubin < 1.5 mg/dl, serum creatinine < 1.6 mg/dl, and cardiac ejection fraction of > 50% without evidence of congestive heart failure. No other concurrent therapy was allowed and all patients signed an informed consent. Exclusion criteria included pregnancy, serious nonmalignant intercurrent illnesses, serious conduction abnormalities or cardiac arrythmias requiring antiarrythmic medications.

Treatment Plan

To minimize the risk of anaphylactoid reactions all patients were premedicated with 20 mg of dexamethasone given orally, 12 and 6 hours prior to paclitaxel, and 50 mg of diphenhydramine and 300 mg of cimetidine given intravenously (i.v.) 1 hour prior to paclitaxel. The starting dose of paclitaxel was 175 mg/m^2 administered as a 24-hour continuous i.v. infusion via a central venous catheter. Cycles were repeated every 21 days or upon complete recovery. Granulocyte colony stimulating factor was not used prohylactically, but was allowed for therapeutic indications. Dose modification was performed based on hematologic and nonhematologic toxicities as outlined in Table 1.

Pretreatment Evaluation and Follow-Up Studies

Prior to enrollment in the protocol, all of the patients underwent a complete history and physical examination. Laboratory studies included a complete blood count (CBC) with differential and platelets, chemistry profile (SMA 12), electrolytes and magnesium, repeated prior to each cycle. Appropriate radiographic studies were performed to define the extent of tumor. A cardiac scan or 2-D echocardiogram was performed to document the cardiac ejection fraction prior to initiation of treatment. Following paclitaxel, patients were followed with at least once weekly CBC with differential and platelet counts. Radiographic imaging to assess response was performed every 2 cycles.

Response Criteria

Complete response (CR) was defined as the disappearance of all clinical evidence of tumor. Partial response (PR) was defined as a ≥ 50% reduction in the sum of the products of the biperpendicular diameters of measurable lesions without the appearance of new lesions for at least 3 weeks. Minor response was defined as a decrease in tumor size between 25 and 49%. Stable disease was defined as a < 25% change in the dimensions of the tumor, and progressive disease was defined as a ≥ 25% increase in the sum of the perpendicular diameters and/or appearance of new lesions. In patients with resectable disease, response was defined based on the percentage of tumor necrosis. CR was defined as ≥ 90% necrosis, PR as 60 to 89% necrosis, and < 60% necrosis was defined as no response.

Statistical Considerations

The trial was conducted in two stages using the optimal two-stage design proposed by Simon.[2] Based on the hypothesis that a response rate of ≤ 5% would be of no interest and a response rate of ≥ 20% would be significant, 15 patients were entered in the first stage of the study. If no responses were seen in these first 15 patients the study would have to be terminated, otherwise a total of 35 patients needed to be accrued. This design afforded a power of 92% to detect a response rate of at least 20% with a rejection error of 10%.

RESULTS

Patient Characteristics

Seventeen patients were entered into the study. Two were considered ineligible because they had Ewing's

TABLE 2
Patient Characteristics

Characteristic	Number
Evaluable patients	15
Age (yrs)	
Median	31
Range	19-61
Zubrod performance status	
0	3
1	12
Sex	
Male	7
Female	8
Race	
Asian	1
Hispanic	1
White	13
Histology	
Dedifferentiated chondrosarcoma	2
MFH	3
Osteosarcoma	10
Axial skelton	6
Appendicular skelton	4
Disease status	
Metastases	10
Uncontrolled primary or local recurrence	5
Prior therapy	
Surgery	15
Radiation	5
Chemotherapy	15

MFH: malignant fibrous histiocytoma.

sarcoma (Table 2). The median age was 31 years (range: 19–61 yrs). There were 8 females and 7 males with a Zubrod performance status of 0 or 1. Ten patients had conventional osteosarcoma, three had MFH, and two had a dedifferentiated chondrosarcoma. Ten patients had metastatic disease and five had persistent or locally recurrent disease. All of the patients had prior surgery and chemotherapy and five had prior radiation therapy. The median number of cycles of paclitaxel chemotherapy administered was 2 (range: 1–4).

Response

No objective CR or PR was seen. One patient with metastatic lung disease from a dedifferentiated chondrosarcoma had a mixed response. A 1.5 × 1.3 cm left upper lobe nodule disappeared while the remainder of the disease in both the hila and the right lung progressed in size and number. The two patients with Ewing's sarcoma considered ineligible for this study also did not respond to paclitaxel.

Toxicity

Fifteen patients received 36 courses at dose level 0, and 2 of these also received 2 cycles at dose level 1. The National Cancer Institute common toxicity criteria were used to assess toxicities. The median absolute granulocyte count nadir was 300/μL on Day 13 of the cycle, lasting a median of 5 days (range: I–II) and the median platelet count nadir was 134,000/μL on Day 8 of the cycle. Only one cycle was complicated with febrile neutropenia. There were no Grade 3 or 4 nonhematologic toxicities and no deaths related to treatment.

DISCUSSION

According to the American Cancer Society estimates, approximately 2070 new bone malignancies were diagnosed in 1995.[3] The most common malignant bone tumor is osteosarcoma. It is characterized by the formation of osteoid by malignant cells. Since it arises from multipotential mesenchymal tissue, fibrosarcomatous and chondrosarcomatous tissues are also components of the tumor, and therefore, the conventional osteosarcoma is subclassified into three basic types namely osteoblastic, chondroblastic, and fibroblastic osteosarcoma. Malignant fibrous histiocytoma is a pleomorphic, spindle cell malignancy in which the cells look similar to fibroblastic osteosarcoma but do not produce detectable osteoid. This tumor is treated similarly to osteosarcoma although the outcome is significantly poorer than with a conventional extremity osteosarcoma.[4] Dedifferentiated chondrosarcoma is a tumor in which a low grade chondrosarcoma dedifferentiates into most commonly an osteosarcoma or an MFH and is therefore treated for the high grade component.[5] All these tumors however, have a pronounced tendency to early hematogenous dissemination and are for practical purposes considered variants of osteosarcoma.

Patients with newly diagnosed osteosarcoma of the extremity without overt metastatic disease have an expected cure rate of more than 60% after treatment with preoperative chemotherapy followed by surgical ablation of the primary tumor and continued adjuvant i.v. therapy. Four chemotherapeutic agents including adriamycin, cisplatin, ifosfamide, and high dose methotrexate have significant activity in this disease.[6] Patients failing such an intensive front line therapy have a guarded prognosis, and trials of new and interesting drugs are warranted. We chose to evaluate the activity of paclitaxel at a dose of 175 mg/m^2 administered as a 24-hour infusion every 3 weeks in patients failing prior treatment with standard chemotherapy. No objective responses were noted in our trial suggesting a low

level of activity of this drug in this patient population. A recently reported trial of paclitaxel in patients with previously untreated advanced soft-tissue sarcomas revealed a response rate of 12.5%.[7] The patient population selected for our trial was refractory to standard chemotherapy, and therefore less likely to respond to paclitaxel. Additionally, a third of the patients had high-risk histology (MFH and dedifferentiated chondrosarcoma) and 60% of osteosarcomas were of axial skeletal in origin, which are known to have a poor prognosis and also have lower response rates compared with extremity osteosarcoma.

In conclusion, paclitaxel at a dose of 175 mg/m^2 over 24 hours every 3 weeks in patients with osteosarcoma and its variants refractory to standard chemotherapy is well tolerated but not active. Phase II trials of new agents are warranted.

REFERENCES

1. Rowinsky EK, Donehower RC. Drug therapy: Paclitaxel (Taxol). *N Engl J Med* 1995;332(15):1004–14.
2. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
3. Wingo PA, Tong T, Bolden S. Cancer statistics 1995. *CA Cancer J Clin* 1995;45:12.
4. Patel SR, Armen T, Carrasco CH, Raymond AK, Ayala AG, Murray JA, et al. Primary chemotherapy in malignant fibrous histiocytoma of bone—updated U.T.M.D./Anderson Cancer Center Experience. Cancer Treatment—An Update (Banzet P, Holland J, Khayat D, Weil M, Editors.) 1994;577–80.
5. Benjamin RS, Chu P, Patel SR, Raymond AK, Murray JA, Romsdahl MM, et al. Dedifferentiated Chondrosarcoma—A treatable disease. *Proc Am Assoc Cancer Res* 1995;36:243.
6. Jaffe N, Patel SR, Benjamin RS. Chemotherapy in Osteosarcoma—Basis for application and antagonism to implementation. Early controversies surrounding its implementation. *Hematol Oncol Clin North Am* 1995;9:825–40.
7. Balcerzak SP, Benedetti J, Weiss GR, Natale RB. A Phase II trial of Paclitaxel in patients with advanced soft-tissue sarcomas—A Southwest Oncology Group Study. *Cancer* 1995;76:2248–52.