A Phase II Trial of Temozolomide in Patients with Unresectable or Metastatic Soft Tissue Sarcoma

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BACKGROUND. The objective of this study was to assess the efficacy and toxicity of the imidazotetrazine derivative temozolomide for patients with unresectable or metastatic soft tissue sarcoma.

METHODS. Twenty-five of 26 patients were eligible and assessable for toxicity and response. Temozolomide was administered twice daily on a 12-hour schedule for 5 days as an oral bolus dose of 200 mg/m^2 followed by 9 doses of 90 mg/m^2 every 4 weeks.

RESULTS. There were 2 partial responses, 2 mixed responses, and 3 patients with stable disease that lasted $>$ 6 months, for an overall objective response rate of 8%. At a median follow-up of 13.2 months, the median progression-free survival and the median overall survival were 2.0 months (95% confidence interval [95% CI], 1.7–2.3) and 13.2 months (95% CI, 4.7–31.1), respectively. All responding patients had leiomyosarcoma of uterine or nonuterine origin; and, in a subset analysis of these patients, the objective response rate was 18% (2 of 11 patients), with disease stabilization occurring in 3 of 11 patients (27%). For this subgroup, at a median follow-up of 24.4 months, the median progression-free survival and the median overall survival were 3.9 months (95% CI, 1.9–21.9) and 30.8 months (lower-bound 95% CI, 7.8), respectively. There were no treatment-related deaths or National Cancer Institute Grade 4 toxicities. Grade 3 toxicities included nausea, anemia, fatigue, elevated alkaline phosphatase levels and nonneutropenic fever (1 patient each).

CONCLUSIONS. Temozolomide at the dose schedule employed in the current study was tolerated well and had modest activity against previously treated unresectable or metastatic leiomyosarcoma of both uterine and nonuterine origin. ***Cancer* 2003; 98:1942–6.** © *2003 American Cancer Society.*

KEYWORDS: chemotherapy, temozolomide, Phase II, soft tissue sarcoma.

Soft tissue sarcomas represent 0.7% of all malignancies diagnosed in the U.S., but the morbidity is great, in that the peak incidence of these tumors is observed in children and young adults.[1,2] A second peak occurs in late middle age, resulting in significant morbidity in productive adults.[2] Treatment of unresectable and metastatic disease remains unsatisfactory, because few systemic chemotherapy agents have significant activity in this disease.[2] Only 3 agents—doxorubicin, ifosfamide, and dacarbazine (DTIC)—have been identified that have useful activity in this population of patients, with reported response rates of approximately 20% in Phase II studies.[2–4] Combination chemotherapy regimens have not demonstrated improved overall survival compared with single agents.[3,4] The median survival remains approximately 12 months. Clearly, new agents with activity in soft tissue sarcomas need to be identified to improve therapy for patients with these tumors.

Temozolomide is a new antineoplastic imidazotetrazinone[5,6] that has been shown to be an oral prodrug exerting its antitumor effects through the formation of 5-3-methyl-1-triazenolimidazole-4 carboxamide (MTIC), the putative, active chemical metabolite of DTIC. Cytotoxicity of the imidazotetrazinones correlates mainly with alkylation by MTIC of the O6 position of guanine in DNA. Temozolomide also may induce programmed cell death.[7]

The form of temozolomide administration usually is cited as a 5-day oral schedule every 4 weeks. Temozolomide antitumor activity is schedule dependent,[8] with a daily 5-day schedule superior to a single dose. In Phase I studies of temozolomide given orally for 5 consecutive days, myelosuppression was the dose-limiting toxicity.

Temozolomide has shown activity against gliomas[9–11] and melanoma[12,13] in both Phase II and Phase III trials, with acceptable toxicity. Because of its structural similarity and a mechanism of action that is partly analogous to DTIC, temozolomide, although it clearly is a distinct agent, warranted evaluation in soft tissue sarcoma patients, resulting in this Phase II study of temozolomide in unresectable or metastatic soft tissue sarcoma.

MATERIALS AND METHODS

Patients with a pathologically verified diagnosis of soft tissue sarcoma who had histologic, cytologic, or clinical evidence of distant metastatic, unresectable locally advanced, or recurrent disease and bidimensionally measurable lesions by X-ray, scans (computed tomography or magnetic resonance images), or physical examination within 4 weeks of registration were eligible for the study. Patients with central nervous system metastases were not eligible. Patients who had a prior malignant disease or other uncontrolled medical conditions were excluded. Patients had to have a Southwest Oncology Group performance status of 0–2, and a life expectancy > 12 weeks. Patients were required to have adequate bone marrow reserve (platelet count $\geq 100{,}000/mm^3$, hemoglobin > 10.0 g/dL, and leukocyte $\geq 3500/mm^3$ or an absolute neutrophil count $\geq 1500/mm^3$), hepatic function (bilirubin and liver enzymes $\leq 1.5 \times$ the institutional upper limit of normal), and renal function (serum creatinine or blood urea nitrogen $< 1.5 \times$ the institutional upper limit of normal or 24-hour creatinine clearance > 60 mL per minute). Patients must have received no more than two prior chemotherapy regimens for advanced, recurrent, or metastatic disease. At least 4 weeks were required to have elapsed since the previous administration of chemotherapy, immunotherapy, or biologic therapy. Prior radiation therapy was allowed, but at least 3 weeks were required to have elapsed prior to study entry. Patients may have received prior surgery within 4 weeks of study entry. Written informed consent was obtained.

Temozolomide was supplied in gelatin capsules by Schering Plough (Kenilworth, NJ). Treatment was administered in a fasting state on a twice-daily, 12-hour schedule for 5 days as an oral bolus dose of 200 mg/m^2 followed by 9 doses of 90 mg/m^2. Treatment cycles were repeated every 28 days. Doses were rounded up to meet the limitations of available capsule forms. Patients' blood counts were checked weekly. A maximum delay of temozolomide for 3 weeks was allowed. If the patient had not recovered from toxicity by that time, then he or she was withdrawn from the study. Dose reductions were made for National Cancer Institute Common Toxicity Criteria (CTC) Grade 3 or 4 neutropenia or thrombocytopenia and for CTC Grade 3 or 4 nonhematologic toxicity (total temozolomide doses, 740 mg/m^2 and 500 mg/m^2, respectively). If a CTC Grade 3 or 4 nonhematologic toxicity recurred, then the patient was withdrawn from the study. Patients who required dose reductions to a total dose < 500 mg/m^2 were removed from the study. Antiemetics were prescribed as clinically indicated by the treating physician. Response was evaluated after every two treatment cycles using World Health Organization criteria. Responding patients or patients with stable disease continued on the study until tumor progression or for up to 1 year (drug administration over 1 year required reconsent).

This was a pilot Phase II, nonrandomized, single-arm study. A response probability of 25% was of interest, whereas further testing would not be pursued if the response probability was $\leq 5\%$. A 2-stage design was adopted: 15 patients were entered initially, and a further 10 patients were entered if at least 1 response was observed. Four or more responses of 25 were considered evidence that warranted further study. This design had a significance level of 5% and a power of 90% to correctly declare an agent with a 25% response probability to warrant further study. The time to disease progression and overall survival also were estimated using he Kaplan–Meier method.

RESULTS

Patient Characteristics

Twenty-six patients were enrolled in the study at Herbert Irving Comprehensive Cancer Center, Columbia University between November 1998 and September 2000. Twenty-five patients were eligible. Their characteristics at study entry are shown in Table 1. All 25 eligible patients were assessable for toxicity and response. All but one patient received two or more cy-

TABLE 1
Patient Characteristics

Characteristic	Value
Total no.	26
Treated	25
Gender	
Male	12
Female	13
Age (yrs)	
Median	57
Range	29–77
SWOG performance status	
0	2
1	20
2	3
Histology	
Leiomyosarcoma	11
Synovial sarcoma	2
Malignant fibrous histiocytoma	2
Chondrosarcoma	1
Gastrointestinal stromal tumor	7
Angiosarcoma	2
Prior therapies	
Surgery	23
Radiotherapy	5
Chemotherapy	14
Doxorubicin-containing chemotherapy	9
Dacarbazine-containing chemotherapy	3
One regimen	11
Two regimens	3

SWOG: Southwest Oncology Group.

cles of temozolomide. Fourteen patients had received treatment with ≤ 2 prior regimens, including doxorubicin-containing regimens in 9 patients, and DTIC either as a single agent or in combination in 3 patients. Twenty-three patients underwent prior surgery for their tumor. Only five patients received prior radiotherapy.

Temozolomide Treatment

One hundred twenty-five cycles of temozolomide treatment were given to 25 patients. Patients received a median of 2 cycles (range, 1–27 cycles). There were no treatment delays.

Temozolomide Toxicity

There were no treatment-related deaths or National Cancer Institute (NCI) Grade 4 toxicities. Hematologic toxicity and nonhematologic toxicity are shown in Table 2. NCI Grade 3 anemia occurred in 1 patient. There were no treatment delays or dose reductions for NCI Grade 3 or 4 neutropenia or thrombocytopenia. There were no episodes of neutropenic sepsis. The most common nonhematologic toxicities seen were elevated alkaline phosphatase levels, fatigue, and nausea. NCI Grade 3 toxicities were nausea, fatigue, elevated alkaline phosphatase levels, and infection (nonneutropenic fever), each of which occurred in 1 patient.

TABLE 2
National Cancer Institute Hematologic and Nonhematologic Toxicity for 25 Eligible Patients

	NCI grade				
Toxicity	0	1	2	3	4
Neutrophils	25	0	0	0	0
Platelets	20	3	2	0	0
Hemoglobin	9	11	4	1	0
Nausea	14	9	2	1	0
Emesis	22	2	2	0	0
Diarrhea	24	1	0	0	0
Constipation	22	2	1	0	0
Headache	24	0	1	0	0
Fatigue	18	3	3	1	0
Infection	24	0	0	1	0
Alkaline phosphatase	16	3	5	1	0
Edema	23	0	2	0	0
Dyspnea	24	0	1	0	0
Hemoptysis	24	1	0	0	0
Anorexia	22	1	2	0	0

NCI: National Cancer Institute.

Response

Among the 25 evaluable patients, there were 2 objective responses (partial responses), 2 mixed responses, and 3 patients with stable disease that lasted > 6 months, for an overall objective response rate of 8%. All of these patients had leiomyosarcoma (of uterine and nonuterine origin). In addition, 2 patients with gastrointestinal stromal tumors had stable disease that lasted 8 weeks. One patient continued to receive temozolomide off study as a result of distance from the treatment center (18 cycles), with an objective response prior to subsequent progression after 19 months on therapy. Of the two patients with leiomyosarcoma who responded, one patient had pulmonary nodules, and the other patient had a large pelvic/abdominal mass. One responding patient had received prior single-agent doxorubicin, and the other patient had received no prior chemotherapy. Neither patient had received prior radiation therapy.

At a median follow-up of 13.2 months, the median progression-free survival and the median overall survival were 2.0 months (95% confidence interval [95% CI], 1.7–2.3) and 13.2 months (95% CI, 4.7–31.1), respectively. In a subgroup analysis of patients with leiomyosarcoma histology, there was an objective response rate of 18% (2 of 11 patients), with disease

stabilization occurring in 27% (3 of 11 patients) and a mixed response in 2 patients. At a median follow-up of 24.4 months, the median progression-free survival was 3.9 months (95% CI, 1.9–21.9). The median overall survival was 30.8 months (lower-bound 95% CI, 7.8).

DISCUSSION

In this study, temozolomide also was tolerated well, with no major myelosuppression seen with this dose schedule. There were no documented NCI Grade 4 hematologic or nonhematologic toxicities, and there were no treatment-related deaths.

The overall response rate was 8% (2 objective responses), with a median progression-free survival and a median overall survival of 2.0 months (95% CI, 1.7–2.3) and 13.2 months (95% CI, 4.7–31.1), respectively. However, prolonged benefit was observed for responding patients and for patients with disease stabilization, all of whom had leiomyosarcoma of either uterine or nonuterine origin. There were no appreciable differences in response for different numbers of prior treatments.

In a subset analysis of the 11 patients with leiomyosarcoma histology, there was an objective response rate of 18%, with disease stabilization occurring in 27%. For this subgroup, at a median follow-up of 24.4 months, the median progression-free survival and the median overall survival were 3.9 months (95% CI, 1.9–21.9) and 30.8 months (lower bound 95% CI, 7.8), respectively. The differences in survival for this subgroup compared with the group with nonleiomyosarcomas did not reach statistical significance when the Kaplan–Meier curves were compared. DTIC had been administered previously to only one patient within this subgroup, with subsequent disease stabilization occurring on temozolomide.

The European Organization for Research and Treatment of Cancer (EORTC) also reported on a Phase II study of 31 patients with advanced soft tissue sarcoma.[14] Ten of their 31 patients had leiomyosarcoma. Only 1 partial response was documented, for an overall response rate of 3.33%; however, 9 patients had documented stable disease for $>$ 8 weeks. The one partial responder had metastatic leiomyosarcoma. This patient received 8 cycles of treatment and had a response that lasted 36 weeks. The histology of the patients with stable disease was not specified. Temozolomide was tolerated well in that study.

All patients entering the study were told of the availability of other regimens, including conventional treatment with combinations using intravenous doxorubicin/ifosfamide. Thus, patients chose the temozolomide because it was an outpatient oral regimen, with the knowledge that doxorubicin/ifosfamide always could be given at a later time if they progressed on temozolomide.

The EORTC reported an 18% objective response rate (1 complete response and 7 partial responses) for previously treated patients who had advanced soft tissue sarcoma using 1.2 g/m^2 of DTIC every 3 weeks.[15] Although the overall response rate may appear higher, the median duration of response was 8 weeks, and the outcome for patients with the histologic subtype of leiomyosarcoma was not commented on specifically.

The treatment of soft tissue sarcoma remains unsatisfactory, as discussed earlier, because few systemic chemotherapy agents have significant activity in this disease.[2–4] It is becoming increasingly evident that all soft tissue sarcoma subtypes do not behave similarly and that different treatment approaches may be required. The treatment of gastrointestinal stromal tumors, which previously were considered chemoresistant, has changed remarkably in the recent past with impressive response rates to STI 571.[16,17] In addition, there is evidence of activity of specific chemotherapeutic agents for different tumor subtypes: for example, paclitaxel for angiosarcoma[18,19] and high-dose ifosfamide for synovial sarcoma.[20] Our data from this Phase II study suggest that there may be a specific therapeutic benefit from temozolomide for patients with leiomyosarcoma of both uterine and nonuterine origin.

New guidelines have been developed to evaluate the response to treatment in solid tumors.[21] For solid tumors such as soft tissue sarcoma, stable disease may be a significant response, and time to disease progression may be a more appropriate endpoint than response rates for Phase II trials of chemotherapeutic agents. A study from the EORTC attempted to look at this premise by attempting to provide an appropriate baseline reference for progression-free rates in patients with this disease.[22] It was found that the usefulness of progression-free rates as a target for Phase II designs depended largely on prior therapy and histology. Such an endpoint may become an increasingly important part of future Phase II studies in this disease.

Temozolomide at this dose schedule was tolerated well and had modest activity against unresectable or metastatic leiomyosarcoma of both uterine and nonuterine origin. A further study of this drug alone or in combination with other agents, such as thalidomide, would appear warranted in this subtype of soft tissue sarcoma to further confirm the responses seen in this study.

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