A Two-Arm Phase II Study of Temozolomide in Patients with Advanced Gastrointestinal Stromal Tumors and Other Soft Tissue Sarcomas

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BACKGROUND. The authors conducted a two-arm Phase II study of temozolomide to determine its efficacy and toxicity in patients with soft tissue sarcomas (STSs) who had received, had refused, or were not eligible for standard chemotherapy with doxorubicin and ifosfamide (Arm 1) and in patients with gastrointestinal stromal tumors (GISTs; Arm 2). Patients with GIST were eligible regardless of prior therapy before imatinib was available.

METHODS. Sixty patients were enrolled in the current study, 19 of whom had GISTs and 41 of whom had other STSs. The patients received temozolomide at a dose of 85 mg/m^2 orally for 21 days followed by 7 days without treatment. Standard radiographic imaging after every two cycles was used to assess the treatment response.

RESULTS. Of the 39 patients in Arm 1, there was 1 complete response and 1 partial response of 39 evaluable patients, for a total response rate of 5% (95% confidence interval, 0–12%). The responses lasted 7 months and 8 months, respectively. In Arm 2, there was no response in 17 patients. The disease was stable in 22% of the patients with GISTs and 33% of the patients with other STSs. The median overall survival time was 26.4 months in patients with GISTs and 11 months in patients with other STSs. The median time to disease progression was 2.3 months in patients with GISTs and 3.3 months in patients with other STSs. Grade 3 and Grade 4 adverse effects (according to National Cancer Institute Common Toxicity Criteria) were rare and included fatigue (eight patients), anemia (six patients), constipation (four patients), neutropenia (four patients), and thrombocytopenia (four patients).

CONCLUSIONS. The data from the current study suggest that temozolomide is well tolerated but has only minimal efficacy and a limited role in the treatment of patients with STSs. ***Cancer*** **2003;98:2693–9.** © *2003 American Cancer Society.*

KEYWORDS: temozolomide, soft tissue sarcomas (STSs), gastrointestinal stromal tumors (GIST), clinical trial, efficacy.

Soft tissue sarcomas (STSs) are relatively rare tumors with an estimated 8300 new cases expected to be diagnosed in 2003.[1] STSs are a heterogeneous group of diseases comprised of numerous histologic subtypes that display a wide range of natural histories and responses to systemic therapies. For example, gastrointestinal stromal tumors (GISTs), which previously were designated as leiomyosarcomas of the gastrointestinal tract, usually are refractory to the chemotherapeutic agents doxorubicin and ifosfamide whereas leiomyosarcomas of the extremities, uterus, and retroperitoneum are reportedly sensitive to these agents.[2,3] GISTs are mesenchymal neoplasms that appear to arise from mesenchymal stem cells, which also give rise to the inter-

stitial cells of Cajal of the myenteric plexus.[4,5] The drug imatinib mesylate selectively inhibits the constitutive activity of the mutant KIT proteins in GISTs and had a reported response rate of 53% in 1 multicenter trial.[6] However, many patients in whom the disease initially responded to imatinib mesylate eventually develop a disease recurrence. Salvage therapy options after the failure of imatinib mesylate in patients with GISTs and after the failure of frontline chemotherapy in patients with other STSs are to our knowledge very limited; therefore, newer effective agents are needed for these of diseases.

An oral alkylating agent derived from imidazotetrazine, temozolamide exhibits broad-spectrum antitumor activity against murine tumors.[7] Temozolomide was developed as a potential alternative to dacarbazine, which has known antitumor activity against STSs[8]; however, temozolomide was found to offer comparable antitumor activity, good oral bioavailability, and a better toxicity profile in preclinical testing.[9] Both compounds are cytotoxic alkylating agents whose active metabolite is the linear triazine monomethyltriazenoimidazole carboxamide (MTIC).[10] The cytotoxicity of MTIC is believed to be primarily because of alkylation at the O^6 position of guanine,[8] with additional alkylation occurring at the N^7 position. Whereas dacarbazine requires metabolic activation by the liver, temozolomide degrades into MTIC at physiologic pH.[10]

Previous research concerning temozolomide included Phase I and II studies evaluating its toxicity and efficacy in patients with high-grade glioma, advanced malignant melanoma, and low-grade non-Hodgkin lymphoma. In a Phase II study of 31 patients with STSs (GIST patients were not denoted), 750 mg/m^2 of temozolomide was given orally in divided doses over 5 days on a 28-day cycle to 31 patients; the only response was noted in a patient with leiomyosarcoma.[11–13]

A Phase I study determined the maximum tolerated dose of temozolomide when administered orally daily for a continuous 7-week period to be 75 mg/m^2/day.[14] Twenty-four patients with various tumor types (including 17 gliomas) received temozolomide. The most frequent toxicities observed were myelosuppression and Grades 1 and Grade 2 nausea and emesis (similar to those noted in the dosing schedule of 5 days every 4 weeks). Grade 4 leukopenia and thrombocytopenia were reported to occur in 1 of 4 patients receiving a dose of 100 mg/m^2/day of temozolomide and in 1 of 7 patients receiving a temozolomide dose of 85 mg/m^2/day. Thus, 85 mg/m^2/day is the recommended dose for daily oral temozolamide. Although it was a Phase I study, there were 7 complete responses and 1partial response reported, resulting in an overall response rate of 33%. The disease was reported to be stable in 35% of glioma patients (6 of 17 patients). Based on this Phase I study that demonstrated moderate activity and limited toxicity in patients using a dose of 85 mg/m^2, we planned a 2-arm, Phase II study to investigate the efficacy and toxicity of the same dose of temozolomide administered for 21 days of a 28-day cycle in patients with GISTs and other STSs.

MATERIALS AND METHODS

Eligibility Criteria

Patients with a histologically confirmed diagnosis of advanced or metastatic GIST or any other STS, adequate organ function (defined as an absolute granulocyte count of $\geq$ 1500/μL, a platelet count of $\geq$ 100,000//μL, a total bilirubin level $\leq$ 1.5 mg/dL, a serum glutamate pyruvate transaminase level $\leq$ 1.5 times of normal, and a serum creatinine level $\leq$ 2.0 mg/dL), and an anticipated life expectancy of at least 12 weeks were eligible. Patients with active infections or significant heart disease and pregnant or lactating women were excluded. Prior to the availability of imatinib mesylate, patients with GISTs were eligible to participate regardless of whether they had received prior chemotherapy. Once available, patients with GISTs had to have had documented progressive disease while receiving imatinib mesylate. Patients with other STSs were required to have received, have refused, or not have been eligible for standard chemotherapy with doxorubicin and ifosfamide. The administration of any other concurrent chemotherapy or immunotherapy was not allowed. All patients signed an informed consent form approved by the institutional review board at the University of Texas M. D. Anderson Cancer Center.

Statistical Analysis

Based on the Simon optimal two-stage design, to differentiate between a response rate of $\leq$ 3% and a response rate of $\geq$ 15%, 17 patients were to be enrolled in each of the 2 arms of the study (GIST and other STSs). [15] If 1 response was noted, enrollment would continue until a maximum of 39 patients were evaluable to adequately determine the efficacy of the drug. The false-positive and false-negative rates were established at 10%.

Treatment Plan

Temozolomide (Temodar®, Schering-Plough Corporation, Kenilworth, NJ) was administered orally at a dose of 85 mg/m^2 daily for 21 consecutive days per a 28-day cycle (21 days on treatment followed by 7 days off). Patients who experienced no Grade 3 or Grade 4 non-

hematologic toxicities were treated with an escalated dose of temozolomide (100 mg/m^2 daily; +1 level). The doses were reduced to 75 mg/m^2 daily (-1 level) or 65 mg/m^2 daily (-2 level) in patients experiencing Grade 3 or Grade 4 toxicities.

All patients were considered evaluable for adverse reactions after the first dose of therapy. Patients who had received 2 cycles (8 weeks) of chemotherapy were considered evaluable for response unless there was obvious evidence of tumor progression after 1 cycle of therapy. The patients underwent a restaging workup after every two cycles. Patients in whom the disease was stable or responding continued therapy until the disease progressed or until adverse events prevented additional chemotherapy, unless surgical resection of any residual disease was possible. Granulocyte–colony-stimulated factor was used to treat neutropenic fever or infection; however, it was not given concomitantly with the temozolomide.

Patient Evaluation

Prestudy evaluations included a complete history and physical examination; a complete blood count; and measurement of serum blood urea nitrogen, creatinine, alkaline phosphatase, bilirubin, lactate dehydrogenase, alanine aminotransferase, albumin, electrolytes, and glucose. The staging workup included chest radiography, computed tomography, or magnetic resonance imaging of the affected sites according to standard practice. Women of childbearing potential completed a pregnancy test within 7 days of the initiation of treatment.

A history and a physical examination were performed every 4 weeks prior to the initiation of each chemotherapy cycle. Patients were evaluated earlier for adverse reactions if necessary. The complete blood count, differential, and platelet counts were measured every 7 days. Urinalysis and the levels of serum electrolytes, creatinine, bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, and albumin were checked every 4 weeks. A chest radiograph was obtained prior to the beginning of each cycle and treatment response was assessed with computed tomography or magnetic resonance imaging of the affected areas after every 2 cycles (8 weeks) of chemotherapy.

RESULTS

Patient Characteristics

Between July 6, 2000 and October 29, 2002, 60 patients were enrolled in this study: 19 patients with GISTs (2 of whom were inevaluable for response) and 41 patients with other STSs (2 of whom were inevaluable for response). The first GIST patient withdrew from the trial after only one oral dose because the patient did not want to take an oral medication and could not be included in the evaluation of toxicity or response. The second GIST patient was hospitalized during her first cycle of temozolomide for abdominal pain requiring a surgical laparotomy that involved removal of some of the intraabdominal tumor and so this patient could be evaluated for toxicity but not response. A patient with STS was lost to follow-up after the first cycle of temozolomide and could be evaluated for toxicity but not response. An additional patient with STS was lost to follow-up and was not evaluated for toxicity or response. Thus, 17 patients with GIST and 39 patients with other STSs were evaluated for response and 58 patients were evaluated for toxicity. Patient and disease characteristics are summarized in Table1. The median age of the patients was 55 years (range, 21–77 years). Thirty-five patients were women and 23 were

TABLE 1
Patient and Disease Characteristics

Characteristic	Value
Total no. of patients	60
No. evaluable for toxicity	58
No. evaluable for response	56
Age (yrs)	
Median	55
Range	21–77
Zubrod performance status score	
Median	1
Range	0–2
Gender, no. of patients	
Female	35
Male	23
Tumor histology	
Leiomyosarcoma	18
Gastrointestinal stromal tumor	17
Unclassified sarcoma	7
Malignant fibrous histiocytoma	4
Alveolar soft parts sarcoma	3
Liposarcoma[a]	2
Synovial sarcoma	2
Epithelioid sarcoma	1
Extraskeletal chondrosarcoma	1
Extraskeletal Ewing sarcoma	1
Neurofibrosarcoma	1
Sarcomatoid carcinoma	1
No. of metastatic sites	
Median	2
Range	1–6
No. of patients who received prior therapy	
Any prior chemotherapy regimen	52 (90%)
≥ 2 chemotherapy regimens	27 (47%)
Radiotherapy	24 (41%)
Surgical resection	52 (90%)

[a] One was dedifferentiated.

TABLE 2
Response and Survival Data for Patients with GIST and other STSs

	No. (%)	
Outcome	**GIST**	**Other STS**
Overall response	0 (0%)	2 (5%)
–Complete responses	0 (0%)	1 (2.5%)
–Partial partial responses	0 (0%)	1 (2.5%)
Stable disease	4 (22%)	13 (33%)
Progressive disease	12 (67%)	25 (62%)
Inevaluable	2 (11%)	0 (0%)
Median overall survival (mos)	26.4	11.0
Median time to progression (mos)	2.3	3.3

GIST: gastrointestinal stromal tumor; STS: soft tissue sarcoma.

men. The median Zubrod performance status was 1 (range, 0–2). Approximately 90% of the patients had received systemic chemotherapy (47% had been treated with ≥ 2 regimens) and surgery prior to entering the study; 41% had received radiotherapy. The majority of patients had a leiomyosarcoma (18 patients) or a GIST (17 patients); unclassified STSs (7 patients) and malignant fibrous histiocytomas (4 patients) also were common.

Efficacy

Responses were assessed by standard World Health Organization criteria[16] and reviewed by two investigators in addition to a radiologist. One partial response (which was defined as a $> 50\%$ reduction in the sum of the product of perpendicular dimensions of the indicator lesions) and 1 complete response were noted in 39 patients with various STS histologies for an overall response rate of 5% (95% confidence interval, 0–12%) (Table 2). The patient in whom a partial response was achieved had a metastatic leiomyosarcoma of the pelvis with lung metastases; the response lasted 7 months. The patient in whom a complete response was achieved had a malignant fibrous histiocytoma, also with lung metastases; the response lasted 8 months (Fig. 1) No objective responses were observed in the 17 patients in the GIST arm who were evaluable for response. The disease was determined to be stable in 22% of the patients with GISTs and 33% of the patients with other STSs.

The median time to disease progression was 2.3 months in patients with GISTs (Fig. 2) and 3.3 months in patients with other STSs (Fig. 3). The median overall survival time was 26.4 months in patients with GISTs (Fig. 4) and 11 months in patients with other STSs (Fig. 5).

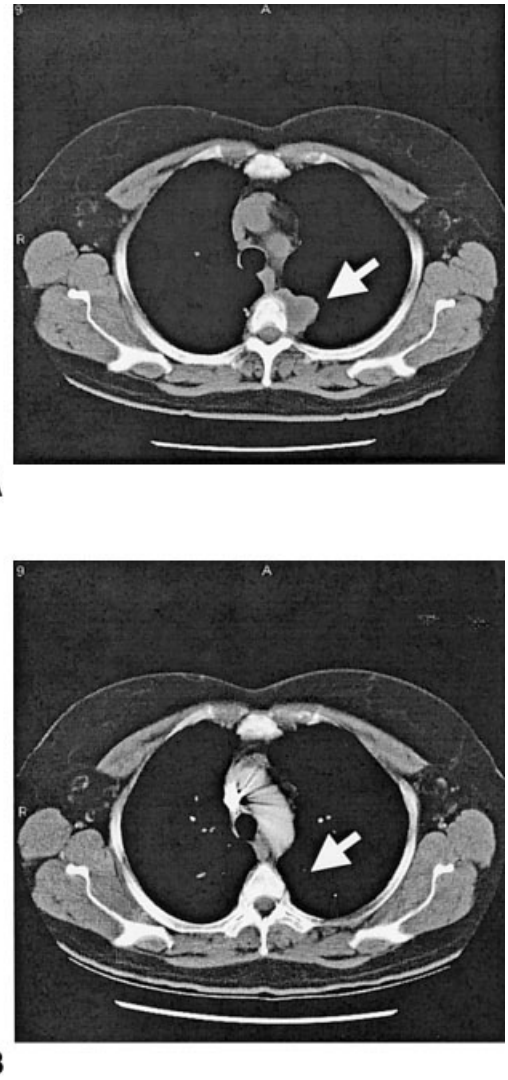

FIGURE 1. Complete response in a patient with malignant fibrous histiocytoma. (A) Baseline magnetic resonance image. (B) Magnetic resonance image obtained 2 months after therapy with temozolomide was initiated.

Toxicity Data

One hundred sixty-one cycles were given at the starting dose level, 2 cycles were administered at the -1 dose level, and 13 cycles were administered at the -2 dose level. The treatments generally were well tolerated in the 58 patients evaluated. The number of patients who experienced various toxicities are detailed in Table 3. Toxicities were graded using the standard National Cancer Institute Common Toxicity Criteria.

Hematologic toxicities were relatively infrequent. The median absolute neutrophil count nadir was 2.8 cells/μL (range, 0.2–9.0 cells/μL), and was reported to occur on Day 13. Grade 3 or Grade 4 neutropenia was observed in four patients. The median platelet count nadir was 211 cells /μL (range, 6–843 cells/μL) and

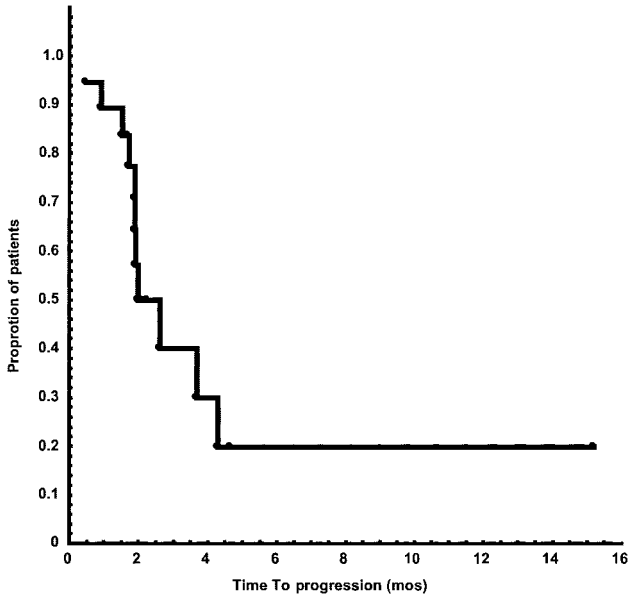

FIGURE 2. The median time to disease progression (in months) for patients with gastrointestinal stromal tumors ($n = 17$).

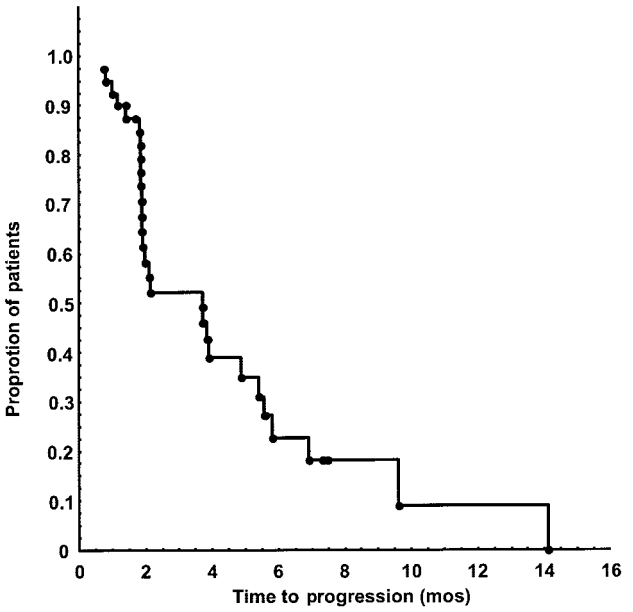

FIGURE 3. The median time to disease progression (in months) for patients with other soft tissue sarcomas ($n = 39$).

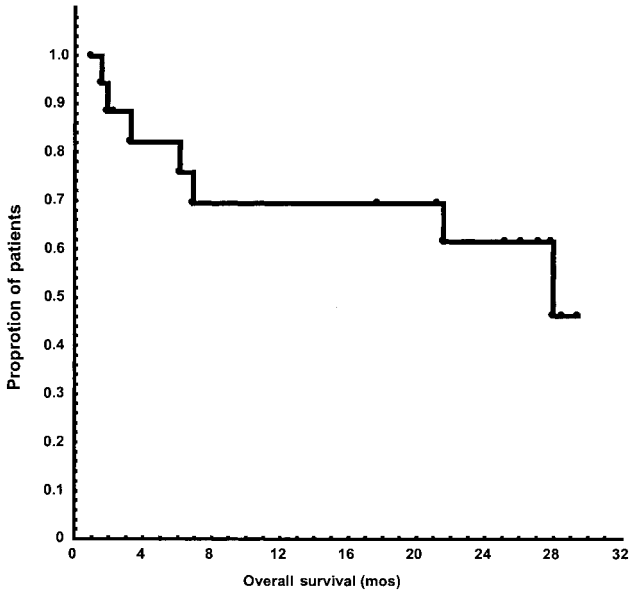

FIGURE 4. The median overall survival time (in months) for patients with gastrointestinal stromal tumors ($n = 17$).

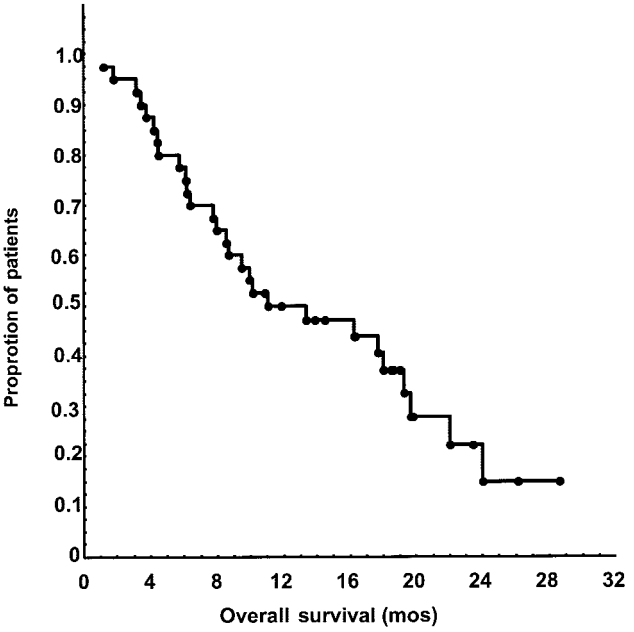

FIGURE 5. The median overall survival time (in months) for patients with other soft tissue sarcomas ($n = 39$).

was reported to occur on Day 15. Grade 3 thrombocytopenia was noted in three patients. Grade 4 thrombocytopenia was observed in only one patient. Although no bleeding complications were encountered, one patient developed prolonged thrombocytopenia that prevented additional therapy with temozolomide. Five patients had Grade 3 anemia and one patient experienced Grade 4 anemia.

DISCUSSION

Temozolomide was found to be well tolerated in the current study. Given orally for 21 days on a 28-day cycle, temozolomide resulted in few Grade 3 or Grade 4 toxicities. Fatigue, which affected 8 patients (14%), was the most common Grade 3 or Grade 4 toxicity,

TABLE 3
Grades 3 and 4 Toxicities (n = 58)

Toxicity[a]	No. of patients (%)
Hematologic	
Anemia	6 (10)
Neutropenia	4 (7)
Thrombocytopenia	4 (7)
Nonhematologic	
Fatigue	8 (14)
Constipation	4 (7)
Nausea	3 (5)
Headache	2 (3)
Stomatitis	2 (3)
Emesis	1 (2)
Melena	1 (2)
Anorexia	1 (2)

[a] Toxicities were graded according to the Common Toxicity Criteria of the National Cancer Institute.

followed by anemia (6 patients [10%]), neutropenia (4 patients [7%]), constipation (4 patients [7%]), and thrombocytopenia (4 patients [7%]).

Although to our knowledge the activity of oral temozolomide given at this dose on this schedule is limited, there may be a role for this agent in the treatment of selected patients, particularly those with leiomyosarcomas. It is interesting to note that in the current study, one of the responding tumors was a pelvic leiomyosarcoma that had metastasized to the lung and paraspinal soft tissue. The response lasted 7 months. In a previous study in which a dose of 750 mg/m^2 of temozolomide was given orally in divided doses over 5 days on a 28-day cycle to 31 patients,[13] the only response was noted in a patient with leiomyosarcoma. Although the authors did not identify the one responding tumor as a GIST, the tumor appeared to arise from a retroperitoneal structure, metastasized to three sites (breast, skin, and liver), and responded well to the temozolomide. These features suggest that the responding tumor was not a GIST but more likely a leiomyosarcoma.

In another study, one of three responses was achieved in a uterine leiomyosarcoma. In the study, temozolomide (taken orally at a dose of 75 mg/m^2/day for 6 weeks followed by a 3-week break) was administered to 28 patients with metastatic STSs who had received prior chemotherapy.[17] Three of the patients achieved a partial response, including a patient in whom the uterine leiomyosarcoma responded to the temozolomide for 10 months, for an overall response rate of 13%.

In 3 studies examining temozolomide therapy for STSs, a combined total of 31 patients with leiomyosarcoma were treated, 3 of whom achieved either a complete or partial response for an objective response rate of 10%. Because 10 of the patients from the European Organization for Research and Treatment of Cancer (EORTC) study had histologic diagnoses of leiomyosarcoma that could not be distinguished from a GIST, it is possible that some of the leoimyosarcoma cases actually were GISTs; therefore, the pooled response rate of the leiomyosarcomas to the temozolomide could have been $>$ 10% (perhaps as high as 14%).

Because of the known resistance of GISTs to chemotherapeutic agents, patients with GISTs were enrolled in the current study regardless of whether they had received prior therapy. In our study, no objective responses were noted among the GIST cases, thus confirming that GISTs are resistant to chemotherapy and should be studied separately from other STSs.

It is interesting to note that, in the current study, the median overall survival time for patients with GISTs was longer than expected (Fig. 3).[18] Although the median overall survival time in the current study was 26.5 months, another study reported a median overall survival time of 15 months in patients with leiomyosarcomas of the gastrointestinal tract.[18] The longer-than-expected median overall survival time for patients with GISTs was likely influenced by the introduction of a new advance in the treatment of GISTs, namely imatinib mesylate. When the current trial began, imatinib mesylate was not yet available for patients with GISTs. After the tumors progressed in those patients receiving temozolomide therapy, the majority of GIST patients were treated with imatinib mesylate. That the unexpectedly long median overall survival time for patients with GISTs is because of the imatinib mesylate rather than the temozolomide is apparent when one considers that the median time to disease progression for GIST patients who were being treated with temozolomide was only 3.3 months (Fig. 2), which is similar to that noted with other chemotherapy regimens.[3,19] Conversely, the median time to disease progression for patients receiving imatinib mesylate in 1 study was reported to be 19.5 months.[20] These findings underscore the importance of including data concerning time to disease progression when determining the efficacy of a therapeutic intervention because the overall median survival reflects the effects of the study intervention as well as subsequent interventions.

Although responses have been described in patients with STSs, particularly leiomyosarcomas, the results of the current study confirmed that temozolomide has little activity in STSs, including GISTs. The 21-day oral dose schedule was well tolerated, with Grade 3 and Grade 4 fatigue reported in 14% of pa-

tients. Thus, temozolomide appear to have only a limited role in the treatment of STSs.

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