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Original Paper

Temozolomide in Adult Patients with Advanced Soft Tissue Sarcoma: a Phase II Study of the EORTC Soft Tissue and Bone Sarcoma Group

P.J. Woll,[1] I. Judson,[2] S.M. Lee,[3] S. Rodenhuis,[4] O.S. Nielsen,[5] J.M. Buesa,[6] P.C. Lorigan,[7] S. Leyvraz,[8] C. Hermans,[9] M. van Glabbeke[9] and J. Verweij[10]

[1]City Hospital, Hucknall Road, Nottingham NG5 1PB; [2]Royal Marsden Hospital, Sutton; [3]Christie Hospital, Manchester, U.K.; [4]Netherlands Cancer Institute, Amsterdam, The Netherlands; [5]Kommune Hospital, Aarhus, Denmark; [6]Hospital General de Asturias, Oviedo, Spain; [7]Weston Park Hospital, Sheffield, U.K.; [8]CHUV, Lausanne, Switzerland; [9]EORTC Data Centre, Brussels, Belgium; and [10]Rotterdam Cancer Institute, Rotterdam, The Netherlands

Temozolomide, an oral imidazotetrazine derivative, was given to 31 patients with advanced soft tissue sarcoma. The dose of 750 mg/m^2 was divided over 5 consecutive days, and escalated to 1000 mg/m^2 over 5 days at cycle 2 if myelosuppression no worse than common toxicity criteria grade 2 was noted in the first 28-day cycle. A total of 99 treatment cycles were given to 31 patients. The drug was well tolerated, with nausea and vomiting as the most common side-effects. Only one partial tumour response was documented, giving a response rate of 3.33%, 95% confidence interval, (CI) 0.1–17.2%. The median time to progression was 8 weeks and the median survival was 27 weeks. These results indicate that temozolomide in this schedule is not active as second-line treatment in advanced soft tissue sarcoma.

Key words: chemotherapy, phase II, sarcoma, imidazotetrazine, temozolomide
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INTRODUCTION

FEW DRUGS have significant activity in soft tissue sarcoma. In phase II studies, doxorubicin, ifosfamide and dacarbazine (DTIC) each have reported response rates of around 20%. Unfortunately, combination chemotherapy is only slightly better and the median survival of patients with advanced soft tissue sarcoma remains approximately 12 months [1]. There is, therefore, a continuing need for new treatments for soft tissue sarcoma.

Dacarbazine is an active cytotoxic for soft tissue sarcoma [2, 3]. It requires *N*-demethylation in the liver to the active metabolite, an unstable derivative monomethyltrazeno imidazole carboxamide (MTIC) which circulates to the tumour. Temozolomide is an orally bioavailable MTIC pro-drug which does not require hepatic activation. It has broad-spectrum antitumour activity in experimental models [4, 5]. Myelosuppression is the dose-limiting toxicity. In preclinical studies, its activity was schedule-dependent. In phase II studies it has shown promising activity against metastatic melanoma and primary brain tumours when administered daily for five consecutive days every four weeks [5–7]. We tested temozolomide for activity in advanced soft tissue sarcoma using this schedule.

PATIENTS AND METHODS

Patients with histologically confirmed soft tissue sarcoma and measurable lesions with documented progression in the previous 6 weeks were eligible for the study. Patients with prior malignant disease or other uncontrolled medical conditions were excluded. Patients were required to have normal haematological function at study entry, bilirubin $\leq 25\,\mu M$, transaminases $< 2\times$ upper limit of normal, creatinine $\leq 150\,\mu M$ and to be of WHO performance status 0 or 1. Patients were permitted to have had no more than one previous combination chemotherapy regimen, or two single

Correspondence to P.J. Woll, e-mail penella.woll@nott.ac.uk
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agent regimens for adjuvant therapy or advanced disease. No chemotherapy or radiotherapy was permitted in the four weeks prior to study entry, and patients were required to have a life expectancy of greater than 3 months. The study was performed in accordance with the Declaration of Helsinki and local ethics regulations. Written informed consent was obtained.

Temozolomide was supplied in gelatin capsules by Schering-Plough, Welwyn Garden City, Hertfordshire, U.K. Treatment was given orally to fasting patients at a dose of 750 mg/m^2 divided over 5 consecutive days. If no significant myelosuppression common toxicity criteria (CTC) grade ≥ 2) was noted in the first treatment cycle, subsequent cycles were given at 1000 mg/m^2 divided over 5 days, repeated every 28 days. Patients' blood counts were checked weekly. Drug administration was postponed by one week if there was not full haematological recovery (neutrophils $> 2\times10^9$/l, platelets $\geq 100\times10^9$/l) from the previous cycle. Dose reductions were made for CTC grade 3 thrombocytopenia or CTC grade 4 leucopenia or thrombocytopenia. Anti-emetics were given in accordance with local practice. Response was evaluated after every two treatment cycles using WHO criteria. The study was planned to have less than 5% chance of rejecting a treatment with a response rate of 20%, and to estimate the therapeutic effectiveness with a standard error of 10%.

RESULTS

Patient characteristics

32 patients were enrolled in the study from 16 treatment centres between July and October 1996. Their characteristics at study entry are shown in Table 1. One patient refused treatment. All 31 treated patients were included in the treatment and toxicity analysis. Two were ineligible (late registration) and were excluded from the efficacy analysis. Three patients had received prior chemotherapy as adjuvant to primary treatment and 27 for advanced disease. None had received prior dacarbazine. Eight patients had responded to prior therapy for advanced disease (2 complete responses (CR) and 6 partial responses (PR).

Table 1. *Patient characteristics*

Number	32
Treated	31
Gender	
Male	16
Female	16
Age, median (range)	50 (27–73) years
WHO performance status	
Grade 0	11
Grade 1	21
Histology	
Leiomyosarcoma	10
Miscellaneous sarcoma	5
Neurogenic sarcoma	4
Unclassified sarcoma	4
Liposarcoma	3
Malignant fibrous histiocytoma	3
Synovial sarcoma	3
Site of primary	
Head & neck	3
Trunk	5
Intra-abdominal	13
Upper limb	3
Lower limb	8
Prior therapies	
Surgery	26
Radiotherapy	18
Adjuvant chemotherapy	3
Advanced chemotherapy	27

WHO, World Health Organisation.

Table 2. *Haematological toxicity of temozolomide treatment, shown as worst CTC grade per patient in* 31 *patients*

	CTC grade				
	0	1	2	3	4
Leucocytes	24	4	3	0	0
Neutrophils	26	4	0	0	0
Platelets	24	3	3	1	0
Haemoglobin	13	13	5	0	0

CTC, common toxicity criteria.

Temozolomide treatment and toxicity

Ninety-nine cycles of temozolomide treatment were given to the 31 treated patients (median 2 cycles, range 0–10). Six patients were not dose-escalated at cycle 2, in violation of the protocol. 15 cycles were dose reduced or delayed because of thrombocytopenia, leucopenia and vomiting. Haematological toxicity is shown in Table 2. The most commonly reported side-effects of temozolomide treatment were nausea and vomiting, which were usually controlled with anti-emetics, although one patient had grade 4 vomiting and four had grade 3 nausea and vomiting (Table 3). 23 patients withdrew from the study with progressive disease, 1 with toxicity (vomiting). There were no episodes of neutropenic sepsis.

Response

Among the 30 eligible patients, one partial response was documented, 9 patients had stable disease for more than 8 weeks, and 19 had progressive disease. One patient did not start treatment. The responding patient had metastatic retroperitoneal leiomyosarcoma in breast, liver and skin. An objective tumour response was seen at all these disease sites. The patient received eight treatment cycles but was finally withdrawn with progressive disease. The duration of this

Table 3. *Non-haematological toxicity of temozolomide treatment, shown as worst CTC grade per patient attributable to temozolomide in* 31 *patients*

	CTC grade				
	0	1	2	3	4
Nausea	5	14	8	4	0
Vomiting	14	9	3	4	1
Stomatitis	24	4	1	1	0
Diarrhoea	25	2	0	1	0
Headache	24	3	2	1	0
Lethargy	20	6	2	0	0
Infection	25	3	1	0	0
Skin rash	27	0	2	0	0

Not every row adds up to 31. Some patients had symptoms attributable to their disease (not the treatment). CTC, common toxicity criteria.

response was 36 weeks. Thus, the overall response rate was 3.33% (95% confidence interval (CI) [0.1–17.2]). The median time to progression was 8 weeks and the median survival was 27 weeks.

DISCUSSION

Temozolomide was well tolerated in this study. In previous studies, myelosuppression caused concern. Here, dose escalation was safely achieved, with no patient experiencing grade 4 haematological toxicity or neutropenic sepsis. Nausea was usually controlled with simple anti-emetics. The low reported toxicity in this study suggests that higher doses could be used in this patient group.

Although dacarbazine has documented activity in advanced soft tissue sarcoma, this phase II study indicates that temozolomide is inactive in previously treated patients (96% certainty that the response rate is < 20%). Patients were ineligible for study if they had received more than two prior cytotoxic drugs, so they were not heavily pretreated. However, only 8/26 had achieved a response to prior chemotherapy for advanced disease. Importantly, none had received prior dacarbazine. The time to progression and overall survival were comparable with other phase II studies in this patient population.

A previous study of the EORTC Soft Tissue and Sarcoma Group evaluated another imidazotetrazine, mitozolomide. No responses were seen among 25 evaluable patients [8]. This drug had severe and unpredictable myelotoxicity which precluded further development [5].

One of the main effects of temozolomide is depletion of the DNA repair protein O^6-methylguanine-DNA methyltransferase [9, 10]. If response to treatment is a consequence of cumulative O^6-methylguanine-DNA methyltransferase depletion, alternative schedules of temozolomide administration, such as 4-hourly dosing, might be more effective [11]. In conclusion, temozolomide cannot be recommended for further study in advanced soft tissue sarcoma at this dose and schedule.

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