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Phase II Study of Tauromustine in Malignant Glioma

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46 eligible patients with either anaplastic astrocytoma (AA) or glioblastoma (GBM) and clinical and computed-tomography-confirmed relapse following primary surgery and radiotherapy received oral tauromustine 130 mg/m^2 every 5 weeks. A prospective design allowed for concurrent assessment of both clinical and radiological responses and drug toxicity. 41% of patients improved clinically whilst 46% improved radiologically with 3 complete, 7 partial and 7 minimal responses (WHO criteria). Toxicity included grade III or IV gastrointestinal side-effects (15%), grade III or IV leukopenia (24%) and grade III and IV thrombocytopenia (44%). In 9 clinically responding patients, haematological toxicity led to discontinuation of treatment. All patients were followed-up until death and second-line chemotherapy was not used. Median post-treatment survival was 26 weeks for patients with GBM and 57 weeks for patients with AA. Overall 2-year survival rate was 69% for AA and 23% for GBM. Tauromustine given at the time of relapse has demonstrable antitumour activity in patients not previously treated with chemotherapy.
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INTRODUCTION

THE PROGNOSIS of patients with malignant glioma (anaplastic astrocytoma, AA; and glioblastoma, GBM) is poor. Despite optimal surgery and high-dose radiation, 80% of patients relapse within 2 years of diagnosis and most of these die shortly thereafter [1–3]. The effectiveness of chemotherapy is limited by tumour chemoresistance and problems with drug delivery [2]. Nitrosoureas are the most commonly used class of drugs and achieve an objective response rate between 30 and 40% [3–6].

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Tauromustine is a nitrosourea based on the endogenous aminoacid taurine. It has demonstrable activity in a number of experimental models [7]. Its toxicity profile is similar to that of other nitrosoureas, with thrombocytopenia as the dose-limiting factor [8, 9]. Therapeutic levels of tauromustine in the brain and brain tumours can be achieved following administration of a single intraoperative dose in patients with malignant gliomas [9]. Here we report a phase II evaluation of tauromustine in patients with AA and GBM who have relapsed following initial surgery and irradiation.

PATIENTS AND METHODS

Between November 1988 and April 1991 46 patients were entered. The patient characteristics are summarised in Table 1. For entry into the study patients were required to have malignant glioma confirmed by a central review of histopathology using the WHO classification [10]; progressive tumour-related symptoms; computed tomography (CT)-confirmed recurrence; no previous chemotherapy; a minimum of 3 months following completion of high-dose irradiation; WHO performance status 0–2 [11]; and to be clinically stabilised on corticosteroids.

Table 1. Characteristics of 46 eligible patients with relapsed malignant glioma treated in a phase II study of tauromustine

No. of patients	46
Sex (M/F)	31/15
Median age (range)	49 (22–63)
Previous surgery	
Biopsy	11
Subtotal resection	22
Macroscopic resection	13
Tumour histology	
Anaplastic astrocytoma	16
Glioblastoma	30
Performance status (ECOG)*	
0	6
1	27
2	13
Neurophysical score (Bond [13])	
≤1	22
2–4	16
≥5	8
Minimental score (Dick *et al.* [14])	
30	12
29–26	21
≤25	11
Not available	2

*Eastern Cooperative Oncology Group.

The median duration of first remission (survival from initial presentation to relapse) was 41 weeks for patients with GBM and 91 weeks for patients with AA. Seizures were a presenting symptom in 25 patients and in 9 (20%) had been present for more than 3 months. At the time of relapse 27 (59%) of patients had focal deficits, 24 (52%) headaches and in 22 (47%) confusion or personality change was a predominant clinical feature. Dexamethasone requirement on relapse was more than 7 mg in 21 patients and less than 7 mg in 16 patients whilst 9 patients (20%) did not need steroids. Pretreatment assessment included baseline CT obtained after minimum of 2 weeks of stable steroid dosage [12].

Study design

Tauromustine was given orally at a dose of 130 mg/m^2 for a minimum of two courses every 5 weeks. Patients continued with chemotherapy for a maximum of six courses unless progression or toxicity prohibited further treatment.

Dose modifications

If the white cell count was less than 3.0×10^{-9}/l and/or platelets less than 100×10^{-9}/l at the scheduled time of treatment, chemotherapy was delayed for 1 week or until recovery. If full haematological recovery did not occur within 3 weeks of scheduled time of treatment the patient was taken off the study. Dose modifications were performed according to nadir counts at 4 weeks. Patients with a nadir leucocyte count of less than 1×10^{-9}/l and/or platelets less than 25×10^{-9}/l received tauromustine at 50% doses subsequently. Patients with nadir leucocyte counts greater than 2×10^{-9}/l and platelets greater than 50×10^{-9}/l continued at full dosage. Phenothiazine antiemetics were given prophylactically with chemotherapy. Additional antiemetics were recorded and patients requiring these classified as having grade 3 nausea and vomiting.

All eligible patients who received at least two cycles of tauromustine were evaluated for response and all patients receiving at least 1 dose of tauromustine were evaluated for toxicity. Survival analyses included all eligible patients.

The study design was approved by local ethical committees and informed consent was obtained from all patients.

Patients were seen on weeks 3, 4 and 5 of each chemotherapy course for clinical review and assessment of toxicity including full blood count. Prior to each chemotherapy course the toxicity assessment was supplemented by assessment of clinical response. The latter was determined by alterations in neurological status, performance status [11], a neurofunctional scale [13] and cognitive function assessed by the minimental state examination [14]. Toxicity was assessed using WHO criteria [11]. Radiological assessment was performed before the 3rd and between the 5th and 6th courses of chemotherapy on a GECT/T8800 (or equivalent) scanner using conventional 1 cm slices with contrast enhancement.

Definitions of response

Clinical response was defined as improving or stable neurofunctional status which was sustained for a minimum of 10 weeks with reducing or discontinued dexamethasone therapy. Radiological response was assessed from a review of CT by a panel comprising a neuroradiologist (R.S.) and trial coordinators. Coplanar measurements of areas of enhancement and low density in marker CT slices were made. In addition a 3-point scale grading of mass effect was used and features of ventricular dilatation, cortical atrophy or calcifications were noted. Radiological response was defined using standard WHO criteria of >50% reduction in area of enhancement [11] and by the neuroradiologist, who was unaware of the patients' clinical status; grading the overall radiological appearances as better, unchanged or worse.

RESULTS

19 out of 46 eligible patients (41.3%) have showed clinical improvement. Their scores of performance status, neurophysical assessment (13) and minimental scores [14] and dexamethasone dosage are summarised in Table 2.

Patients received median of four treatment courses; five for responders and three in non-responders. In 6 patients CT was not available for review: 5 died of tumour before the 2nd chemotherapy course (not evaluable for response), and in 1 patient receiving four courses CT scans were lost. In 40 patients available for radiological review 21 (52.5%) were classified (45.6% of total population) as showing overall improvement.

Table 2. Performance status, neurophysical and minimental scores and dexamethasone dosage in 19/46 (41.3%) patients clinically responding to tauromustine

	Better	Stable	Fluctuating	Worse	Not done
Performance status	6 (37.5%)	8 (50%)	1	1	3
Neurophysical score	5 (27.7%)	8 (44%)	5	—	1
Minimental score	3 (16.7%)	5 (27.7%)	8	2	1
Dexamethasone	14 reducing	(73.7%)			
	3 zero	(15.8%)			
	2 fluctuating	(10.5%)			

Table 3. Summary of neuroradiological (CT) data in 21 patients with either complete (CR) or partial (PR) response to tauromustine

	Radiological response (WHO)			
	CR	PR (>50% reduction)	Minimal response (25–50% reduction)	No change (<25% reduction)
High density	3	7	7	4
Low density	1	8	3	9

The relationship of contrast enhancement and low-density measurement using WHO response criteria [11] is shown in Table 3. In 38 patients synchronous radiological and clinical assessments could be compared. In 23 (60%) there was agreement, in 5 (13%) CT improvement was not reflected in the patients' clinical status and in 10 (26%) the converse was seen.

Clinical response was significantly influenced by histological tumour grade. 11 of 16 (69%) with AA and 8 of 27 (29.6%) re-evaluable patients with GBM improved ($p=0.015, \chi^2$). The differences in CT response between patients with AA (10/15) and 44% for patients with GBM (11/25) did not reach statistical significance.

Toxicity, which is summarised in Table 4, was mild apart from haematological problems. 14 (30.4%) patients required tauromustine dose reductions and in 31 (67.4%) patients therapy was delayed due to haematological toxicity. 9 patients, all of them clinically improving, had to discontinue treatment because of persistent grade III or IV thrombocytopenia.

Overall median survival time after starting tauromustine was 31.4 (range 5.1–82.3) weeks. For patients with GBM median survival time was 26 (5–73) weeks and for patients with AA median survival was 57 (7–82) weeks. 18 patients (39%) had survived 2 years from initial diagnosis. 7 (23%) had GBM and 11 (69%) AA. 3 patients with AA survived more than 4 years and at the time of writing 2 other patients with AA are alive more than 3 years following initial presentation. The prognostic value of histological classification on overall survival and post-tauromustine survival is demonstrated in Figs 1 and 2.

DISCUSSION

This study has confirmed that tauromustine has antitumour activity against malignant glioma (AA and GBM) in patients who relapsed after initial surgery and radiotherapy. The clinical and radiological response achieved compares favourably to response rates with other nitrosoureas [2–6].

Assessment of 'response' in primary brain tumours is difficult.

Table 4. Tauromustine toxicity

	WHO grade				
	0	1	2	3	4
Nausea/vomiting	12/(26)	6/(13)	21/(46)	7/(15)	0/(0)
Leukopenia	10/(22)	9/(20)	16/(35)	10/(22)	1/(2)
Thrombocytopenia	10/(22)	8/(17)	8/(17)	16/(35)	4/(9)

Figures show no. of patients (%).

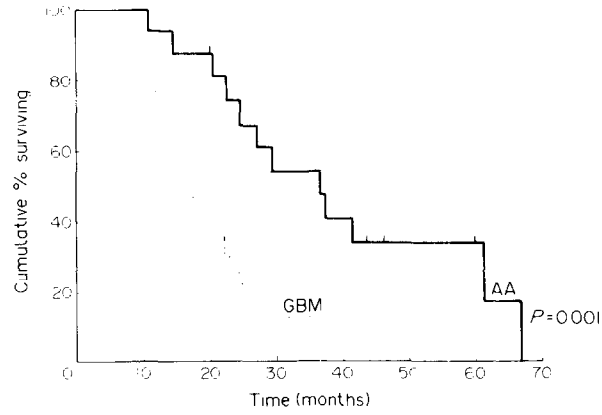

Fig. 1. Overall survival of 46 patients with malignant glioma (AA = 16, GBM = 30) treated in phase II study of tauromustine demonstrating influence of histology.

The conventionally used WHO criteria [11] of reduction in tumour size cannot be applied because of difficulties relating radiological 'tumour' size to true tumour margins. Radiological assessment of tumour size uses indirect measurements of blood–brain barrier function and mass effect. Both contrast-enhancing and hypodense cerebral lesions are profoundly influenced by factors that may be independent of tumour size [12, 16].

Clinical evaluation is also difficult since for any individual clinical deficits may be related to tumour, surgical intervention, and supportive treatment and may fluctuate with intercurrent events and clinical progress.

The parallel clinical and radiological assessment and controlled, carefully documented steroid dosage in this study allow separate assessments of clinical course and neuroradiological tumour appearance.

It is interesting to compare radiological changes with clinical progress, particularly in a group of patients where simple and effective palliation is often the only realistic goal. Disparity between clinical and radiological assessment occurred in 39% of patients. In 10 out of 38 (26%) neurological improvement and reducing dexamethasone was not reflected in radiological evidence of tumour response. In 5 patients clear CT improvement was accompanied by clinical deterioration. The cause of

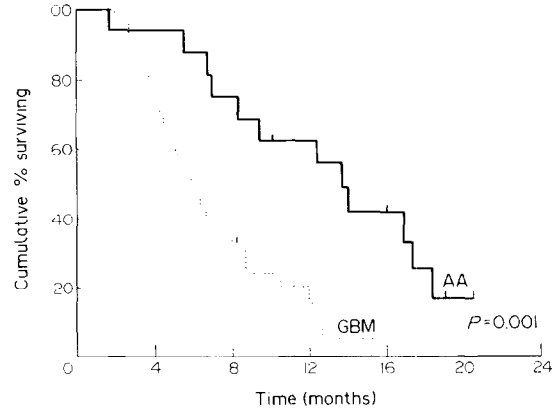

Fig. 2. Post-tauromustine survival of patients with malignant glioma.

such dichotomy is multi factorial and ill-understood, but shows the limitations of using either response independently [16].

In our study clinical response was assessed using validated measures of neurological and cognitive deficit. Neurophysical score [13] was easy to use and reproducible. It gives an ascending numerical score to increasing focal neurological deficits. At entry into the study most patients had minor focal abnormalities but only 8 reached scores of 5 or over. Amongst the 19 patients clinically improved with tauromustine, 5 had a neurophysical score which fluctuated by up to 2 points in either direction. This reflected the varying degree of 'fixed' deficits and did not demand increase in dexamethasone dosage. In 8 patients neurophysical scores remained normal or stable and in 5 clear improvement was seen.

Performance status [11] is a global measurement influenced by toxicity and other intercurrent events. 1 patient with improved neurological deficit had his performance status change from 1 to 2 due to deep-vein thrombosis (Table 2).

Assessment of cognitive function is an important part of overall functional evaluation. We have chosen the minimental score [14] for its ease of administration and low demand on patients' and assessors' time. In our experience it is, however, too crude a measure for this patient population. At the start of study 72% of patients had scores between 30 and 25, i.e. the top 17% of the scale. This reflects the poor sensitivity of this test. Furthermore frequent longitudinal fluctuations in the score were seen. Patients with relatively normal cognitive functions had been able to memorise the test questions, reducing validity of repeated assessments. Our experience would indicate that a different instrument and probably more time-consuming method of cognitive assessment needs to be found if reliable, sensitive and reproducible data is to be obtained.

The statistically significant difference in post-tauromustine survival between AA and GBM subgroups (Fig. 2) confirms the well-known prognostic value of tumour histology on survival [1–5, 17]. As well as increase in survival time, there was also a significantly higher response rate in patients with AA. The overall survival of this study group receiving tauromustine at the time of first relapse compares favourably with patients receiving adjuvant chemotherapy from the time of diagnosis [3, 4, 15]. This may partly be due to patient selection but suggests that randomised comparison of adjuvant chemotherapy with chemotherapy on relapse is needed. The survival advantage of the adjuvant approach is small and limited to AA [4, 15] and may have an impact on quality of life of these patients.

The dose-limiting toxicity of tauromustine in common with other nitrosoureas was thrombocytopenia [7, 8]. In no patient was it life-threatening, but it led to premature discontinuation of chemotherapy in 9 patients who were otherwise clinically responding at the time. Other toxicity was mild and for most patients tauromustine was an easily tolerated outpatient treatment regimen. This is particularly important when considering palliation and quality of life issues in this group of patients.

Tauromustine is an active drug and deserves further study in patients with malignant glioma.

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