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M. Bower · E.S. Newlands · N.M. Bleehen · M. Brada
R.J.H. Begent · H. Calvert · I. Colquhoun · P. Lewis
M.H. Brampton

Multicentre CRC phase II trial of temozolomide in recurrent or progressive high-grade glioma

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Abstract *Purpose*: Patients with progressive or recurrent supratentorial high-grade gliomas were entered into a multicentre phase II trial to evaluate the efficacy and toxicity of temozolomide. *Methods*: The treatment schedule was 150–200 mg/m^2 per day orally for 5 days repeated every 28 days. Response evaluation was by a combination of neurological status evaluation (MRC scale) and imaging. *Results*: Of 103 eligible patients enrolled, 11 (11%) achieved an objective response and a further 48 (47%) had stable disease. The median response duration was 4.6 months. Response rates were similar for anaplastic astrocytomas (grade III) and glioblastoma multiforme (grade IV) tumours. Predictable myelosuppression was the major toxicity. *Conclusions*: The observation of objective responses and tolerable side effects in this heterogeneous population of patients supports the further investigation of this agent in high-grade gliomas.

Key words Glioma · Temozolomide

M. Bower (✉) · E.S. Newlands
Department of Medical Oncology, Charing Cross Hospital,
Fulham Palace Road, London W6 8RF, UK
Tel. 0181-846-1418; Fax 0181-846-1443;
E-mail m.bower@cxwms.ac.uk

N.M. Bleehen
Department of Clinical Oncology & Radiotherapy,
Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, UK

M. Brada
Academic Unit of Radiotherapy,
Institute of Cancer Research, Royal Marsden Hospital,
Downs Road, Sutton, Surrey SM2 5PT, UK

R.J.H. Begent
Department of Clinical Oncology, Royal Free Hospital,
Rowland Hill Street, London NW3 2PF, UK

H. Calvert
Division of Oncology, Newcastle General Hospital,
Westgate Road, Newcastle upon Tyne NE4 6BE, UK

I. Colquhoun
Department of Radiology, Charing Cross Hospital,
Fulham Palace Road, London W6 8RF, UK

P. Lewis
Department of Histopathology, Charing Cross Hospital,
Fulham Palace Road, London W6 8RF, UK

M.H. Brampton
32 Howe End, Kirbymoorside, York Y06 6BD, UK

Introduction

Temozolomide is an imidazotetrazine derivative related to mitozolomide but has a methyl group rather than the chloroethyl sidechain. Temozolomide is a prodrug that degrades to form the reactive methylating cytotoxic triazine monomethyl 5-triazeno imidazole carboxamide (MTIC). MTIC resembles DTIC but does not require metabolic activation [1].

A phase I study of temozolomide confirmed oral bioavailability and recommended a total dosage of 750–1000 mg/m^2 divided over 5 days. This trial demonstrated responses in patients with recurrent high-grade glioma [2]. Subsequently, radiological responses in high-grade primary brain tumours were reported for 5/10 patients with recurrent astrocytomas following surgery and irradiation and for 4/7 patients with newly diagnosed astrocytomas [3]. The activity of temozolomide in primary brain tumours and the predictable myelosuppression by this agent led to the establishment of a multicentre phase II study in high-grade gliomas by the Cancer Research Campaign (CRC) phase I/II committee.

Patients and methods

Patients with centrally reviewed (by PL) histologically confirmed supratentorial grade III or IV glioma [4] and measurable or evaluable lesions on computerized tomography (CT) or magnetic resonance imaging (MRI) that had progressed within the past

2 months were eligible for the study. Continuing neurological impairment, a World Health Organisation (WHO) performance status ≤ 3 [5] and a life expectancy of > 3 months were required. Radiotherapy within the preceding 10 weeks or prior chemotherapy within the last 4 weeks (6 weeks for nitrosoureas) excluded patients. If patients were receiving dexamethasone there should have been no alteration in the dosage in the 2 weeks prior to entry. Adequate bone marrow, hepatic and renal function were required.

Temozolomide was administered orally as capsules at an initial dose of 750 mg/m^2 divided as equally as possible over 5 days (i.e. 150 mg/m^2 on days 1–5) given every 4 weeks. The capsules contained 20, 50 or 100 mg and daily doses were rounded up or down so that the planned total 5-day dosage was achieved as closely as possible. If no grade 2 or greater myelosuppression [6] was observed on day 22 of the first cycle then subsequent courses were administered at 1000 mg/m^2 split as equally as possible over 5 days. In patients with midline shift or where the tumour/oedema occupied more than half of one cerebral hemisphere, the dose was reduced to 500 mg/m^2 in divided doses over 5 days. If no deterioration was observed, this was repeated on days 15–20 and subsequent cycles were at full dosage. Antiemetics (usually ondansetron) were prescribed prophylactically with each course of temozolomide.

Nadir blood counts were measured on day 22 of each course. Dose modification for myelosuppression was specified and drug administration was delayed by 1 week if there was not full haematological recovery following the previous course of treatment (i.e. WBC count $> 3000/\mu l$, platelet count $> 100\,000/\mu l$). Dose reduction after a 1-week delay was 75% for a WBC $< 2000/\mu l$ or platelet count $< 75\,000/\mu l$ and 50% for a WBC $< 1000/\mu l$ or platelet count $< 25\,000/\mu l$.

The measurement of tumour size using CT or MRI is frequently difficult, since areas of vascularity, necrosis and oedema may be indistinguishable from the tumour. As a consequence, tumour shrinkage, as demonstrated by these techniques, was not acceptable alone as a measurement of response. An objective response (OR) required the improvement in one or more neurological symptoms sufficient to improve the neurological status by one grade on the MRC scale [7] documented by two observations not less than 4 weeks apart. In addition, there was required to be no deterioration of any other neurological symptoms or signs and no new neurological deficits. A reduction of 50% or more in the tumour size (measured by serial CT or MRI scans, as the product of the two largest perpendicular diameters of the lesion) may have been measurable in some patients, but in the majority it was only possible to establish a definite reduction in mass effect. Imaging criteria were accepted only if associated with clinical improvement.

Radiological evaluation was performed prior to the first and third cycles of temozolomide and after alternate cycles thereafter. All scans were reviewed by a panel of two oncologists and a neuroradiologist at the completion of the study and responses evaluated in conjunction with the CRC trial monitor. Stable disease (SD) was defined as neither improvement nor deterioration in neurological status over a minimum of 8 weeks, irrespective of a radiological change in tumour size but without an increase in the corticosteroid dose except on days of temozolomide administration when the dose could be increased for prophylactic cover of cerebral oedema. Progressive disease (PD) was defined as a deterioration of the neurological status and/or an escalation in the corticosteroid dose. Early death and progression were defined as death or disease progression within 4 weeks of commencing temozolomide.

The CTC criteria for toxicity were applied [6]. All patients gave informed consent in this multicentre study and the trial protocols received local ethics committee approval. Survival was calculated from the first day of temozolomide treatment until death or the date of last follow-up. The duration of response was measured from the commencement of temozolomide until the documentation of progression.

Table 1 Characteristics of the patients (*NK* not known)

Total number of patients entered	116
Number of eligible patients	103
Gender (male/female)	64/39
Median age (range)	44 years (24–78 years)
WHO performance status at entry (0/1/2/3/NK)	9/44/22/27/1
MRC neurological status at entry[a] (1/2/3/4/NK)	42/42/14/1/4
Histology at entry	
Glioblastoma multiforme (grade IV)	73
Anaplastic astrocytoma (grade III)	20
Unclassified high grade astrocytoma (grade III-IV)	9
Anaplastic oligoastrocytoma (grade III)	1
Prior therapy	
Surgery alone	5
Surgery and radiotherapy	67
Surgery, radiotherapy and chemotherapy	31

[a]MRC scale of neurological status: 0 no neurological deficit, 1 function adequate for useful work, 2 moderate functional impairment, 3 major functional impairment, 4 no useful function

Results

Of 116 patients entered into the study, only 103 were eligible including 14 with biopsy-confirmed transformation of previously low-grade glioma. The remaining patients were ineligible because tumours were not supratentorial high-grade gliomas (5), there was no persisting neurological deficit (1) or evaluable disease (1) at entry, patients were not on a stable dosage of corticosteroids (3), patients had received recent chemotherapy (2) or their WHO performance status was 4 (1). The patient characteristics are listed in Table 1.

Table 2 Worst adverse events observed in 101 evaluable patients (irrespective of causality). All adverse events were recorded although these were not necessarily related to temozolomide administration (*ALT* alanine transaminase, *ALP* alkaline phosphatase)

	CTC Grade				
	0	1	2	3	4
Lymphocytes	12	10	20	43	16
Platelets	53	29	6	6	7
Neutrophils	82	6	8	1	4
Leucopenia	72	13	8	2	4
Anaemia	64	32	4	0	1
Nausea	40	18	21	22	0
Vomiting	41	8	27	24	1
Lethargy[a]	49	5	14	33	0
Anorexia[a]	64	17	10	10	0
Constipation	59	13	17	12	0
Infection	77	6	13	4	1
Raised ALT	53	36	9	3	0
Raised ALP	75	26	0	0	0
Raised bilirubin	95	0	5	0	1
Hypocalcaemia	96	5	0	0	0
Hypercalcaemia	99	2	0	0	0
Mucositis	76	14	8	3	0

[a]No CTC grading available, so classified as 1 = mild, 2 = moderate, 3 = severe

Table 3 Overall neurological response according to prior therapy

Response	Surgery	Surgery and radiotherapy	Surgery and radiotherapy and chemotherapy	Total
Objective response	0 (0%)	10 (15%)	1 (3%)	11 (11%)
No change	1 (20%)	32 (48%)	15 (48%)	48 (47%)
Progressive disease	3 (60%)	2 (3%)	3 (10%)	8 (8%)
Early progression	0 (0%)	11 (16%)	7 (23%)	18 (17%)
Not evaluable	1 (20%)	12 (18%)	5 (16%)	18 (17%)
Total	5	67	31	103

Table 4 Characteristics of patients achieving objective responses (*M* male, *F* female, *5FU* 5-fluorouracil, *GBM* gliobastoma multiforme, *AA* anaplastic astrocytoma, *HG* high-grade unclassified)

	Sex	Age (years)	WHO status at start	MRC status at start	Prior surgery	Prior Radiotherapy	Prior Chemotherapy	Histology	Number of courses of temozolomide
1	M	42	1	2	Craniotomy	Yes	No	GBM	17
2	F	63	3	3	Craniotomy	Yes	No	GBM	3
3	M	65	3	3	Biopsy	Yes	No	AA	5
4	M	24	2	1	Craniotomy	Yes	No	GBM	4
5	M	43	1	2	Biopsy	Yes	No	GBM	5
6	M	40	1	2	Craniotomy	Yes	No	GBM	6
7	M	54	2	2	Craniotomy	Yes	No	HG	9
8	M	37	2	2	Biopsy	Yes	No	AA	11
9	M	48	1	1	Craniotomy	Yes	5FU	GBM	19
10	F	45	3	2	Craniotomy	Yes	No	GBM	6
11	F	51	3	3	Biopsy	Yes	No	GBM	6

Of the 103 eligible patients, 101 were evaluable for toxicity and received a total of 475 courses of temozolomide. One patient received a single dosage of temozolomide and then refused further therapy and a second patient was lost to follow-up during the first cycle of treatment. The most frequent adverse events are listed in Table 2. Myelosuppression was the major toxicity including 16 episodes of grade 4 lymphopenia which were generally asymptomatic and 7 episodes of grade 4 thrombocytopenia.

The median number of courses received per patient was 4 (range 1–19), 84 patients received two or more courses and the dose was escalated in all but 8 (6 because of cytopenia, 2 in error). The OR rate for the 103 eligible patients (including 18 not evaluable for response) was 11% (including five radiological ORs) with a further 47% having SD (Table 3). The clinicopathological details of the patients achieving OR are shown in Table 4. Only 57 patients were evaluable by radiological criteria: 5 (9%) had partial responses, 50 (87%) SD and 2 (4%) PD. The median number of courses received for the 11 patients achieving OR was 6 (range 3–19) and the median duration of response was 4.6 months (range 2–18 months). The 48 patients with SD received a median of 4.5 cycles of temozolomide (range 2–14) and the median time to progression was 4.2 months (range 1.8–29.5 months). The OR rate was 3% (95% confidence interval 0–9%) in the 31 patients who had received prior chemotherapy (after surgery and irradiation) and 15% (95% confidence interval 6–24%) in the 65 patients who had received surgery and radiotherapy only.

The OR rates according to histology were: 2/20 (10%) for anaplastic astrocytoma (grade III), 8/73 (11%) for gliobastoma multiforme (grade IV) and 1/9 (11%) for unclassified high-grade astrocytoma (grade III–IV). The median survival of all eligible patients was 5.8 months (95% confidence interval 4.6–7.0) and the progression-free survival at six months was 22% (95% confidence interval 14–31).

Discussion

The standard therapy for high-grade gliomas remains surgical debulking where anatomically possible with postoperative external beam radiotherapy. However, a meta-analysis of randomized studies of nitrosourea-containing adjuvant chemotherapy has demonstrated a survival advantage of 9% at 1 year for patients randomized to receive chemotherapy [8]. This survival benefit has been confirmed in a second meta-analysis of 16 randomized trials [9]. Nevertheless, the prognosis for high-grade gliomas remains very poor with a median survival of 10–12 months. The recognition that high-grade glioma may be a chemosensitive tumour has led to the search for more efficacious drugs for the management

of this disease as well as the development of other more novel approaches [10].

Numerous single-agent and combination chemotherapy phase I and II trials have been undertaken for progressive and recurrent supratentorial gliomas. Most have shown disease stabilization or responses in 20–70% of patients but the benefit is short lived (typically 10–40 weeks) [11]. This phase II trial of temozolomide in patients with PD showed an overall OR rate, as determined by improvement in the neurological status, of 11% with SD recorded for 47%. This response rate is less than that previously published for a small series of newly diagnosed and recurrent high-grade gliomas using the same response evaluation criteria based upon the MRC neurological performance scale [3]. These values can also be compared with the single institution experience from Charing Cross Hospital where the same schedule and assessment criteria were employed. For 48 patients (including 19 in the current study) with recurrent disease following surgery the OR rate was 25% and a further 38% had SD [12]. The reduced response rates observed in this larger multicentre trial may reflect interpersonal differences in the interpretation of the MRC five-point neurological scale which is a subjective evaluation. These variations in subjective assessments are inevitable in studies recruiting patients from many centres and more objective and reproducible measurements of neurological performance are required. Evaluation scales of quality of life with particular reference to primary brain tumours have been developed that could be valuable tools for assessment of interventions [13, 14].

Similarly, the evaluation of gliomas by imaging remains controversial. It has been proposed that tumour dimensions on enhanced CT or MRI scans can be interpreted for response evaluation so long as patients are receiving stable doses of corticosteroids [15, 16]. However, gliomas are infiltrative tumours and the borders between tumour and adjacent tissues are frequently indistinct radiologically. Furthermore, associated oedema, necrosis, haemorrhage and abnormal vascularity may obscure changes in the tumour size. The development of ^{18}FDG-PET scanning to evaluate the metabolic activity of tumours may provide a more accurate and objective indicator of tumour behaviour [17, 18].

The difficulties in evaluation of response to therapeutic interventions in primary brain tumours are highlighted by this study. Therefore, it has been proposed that the progression-free survival of patients with high-grade gliomas at 6 months may be employed as an endpoint in phase II evaluations of new treatments (V. Levin, personal communication). In this trial 22% of the patients had no neurological or radiological evidence of disease progression at 6 months.

Advances in survival are unlikely to be documented in phase II studies even for effective agents as a result of the patient selection for these trials. The observation of ORs and tolerable side effects in the setting of a phase II study supports the further investigation of this agent in high-grade gliomas. A phase I study is being completed giving temozolomide on a continuous 6- or 7-week schedule [19]. This regimen may be combined with fractionated irradiation in the primary management of high-grade gliomas and will be investigated in a new study shortly. Improvements in survival for these tumours are most likely to come from more effective adjuvant treatment and the future trial will address the role of temozolomide in this context.

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