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Papers

Temozolomide: A New Oral Cytotoxic Chemotherapeutic Agent with Promising Activity Against Primary Brain Tumours

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Temozolomide, a new oral cytotoxic agent, has been given to 28 patients with primary brain tumours. Treatment was given at a dose of 150 mg/m²/day for 5 days (i.e. total dose 750 mg/m²) escalating, if no significant myelosuppression was noted on day 22, to 200 mg/m²/day for 5 days (i.e. total dose 1000 mg/m²) for subsequent courses at 4 week intervals. A major improvement in computer tomography (CT) scan was noted in 5/10 patients with astrocytomas recurrent after radiotherapy, with a major clinical improvement but minor improvement on CT scan in one further patient. Reduction in the size of the CT lesion was also observed in 4/7 patients with newly diagnosed high grade astrocytomas given 2–3 courses of temozolomide prior to irradiation. 1 patient with recurrent medulloblastoma had a clinical response in bone metastases. Temozolomide was well tolerated with little subjective toxicity and usually predictable myelosuppression and is a promising new drug in the treatment of primary brain tumours.
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INTRODUCTION

THE PROGNOSIS for patients with high grade (i.e. grade 3 or 4) astrocytomas is poor. Prospective randomised studies have confirmed the beneficial effect of adjuvant cranial irradiation but in most series less than 15% of the patients survive for more than 2 years [1, 2]. Because of this dismal prognosis, the role of chemotherapy in the treatment of these patients has been extensively investigated. Studies performed on patients with postradiation recurrence indicate that the nitrosoureas are the most active drugs, with reported response rates to BCNU, CCNU methylCCNU and HECNU of 35–55%, although these responses are usually of short duration [2–4]. However, the definition of response to treatment has varied widely between studies because of the difficulty in interpreting computer tomography (CT) scan changes, so apparent differences between the results of different studies must be interpreted with caution [5, 6]. Reviews of the combined results of randomised studies comparing adjuvant, single agent nitrosoureas after radiotherapy with radiotherapy alone suggest a statistically significant but minor prolongation of survival [2, 7]. There is no convincing evidence that combination chemotherapy produces a superior outcome, and novel approaches such as regional chemotherapy or the use of radiosensitisers have not been shown significantly to improve prognosis [2, 6].

Temozolomide is an imidazotetrazine derivative which has activity against a wide range of experimental tumours and which showed marked schedule dependency in the pre-clinical screen [8]. Phase I testing has confirmed that the drug has excellent oral bioavailability and, using a 5-day schedule repeated every 4 weeks, clinical activity was detected in patients with malignant melanoma, mycosis fungoides and also in 2 patients with high grade astrocytomas which had recurred after radiotherapy [9].

PATIENTS AND METHODS

28 patients (including the 2 patients reported in the phase I study) have been treated and their characteristics and response to treatment are summarised in Table 1. Patients can be divided into three groups: 13 patients with astrocytomas which had recurred after radical radiotherapy who had not received prior chemotherapy; 11 patients with newly diagnosed astrocytomas which had not yet been irradiated; 4 patients with other primary brain tumours. 18 of the 24 patients with astrocytomas (75%) had high grade tumours. The remaining patients had a clinical history compatible with high grade astrocytoma although the original histology was either low grade (3 patients) or not reviewed (3 patients).

Treatment was initially given at a dose of 1000 mg/m² divided over 5 days (i.e. 200 mg/m² orally daily for 5 consecutive days) repeated every 4 weeks. However, following the death from intracerebral haemorrhage while severely thrombocytopenic of a patient with a pineoblastoma who had been pretreated with combination chemotherapy and radiotherapy, the first course of

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Table 1. Patients' characteristics and response to treatment

Histology (grade)	No. of courses	Clinical symptoms before treatment (MRC grade*)	Clinical response (MRC grade*)	CT response	Duration of response (months)
Gliomas recurrent after surgery and radiotherapy					
4	7	Dysphagia, confusion (2)	Complete recovery (0)	Major improvement	6
4	5	Dysphasia, confusion (3)	Complete recovery (0)	Major improvement	3
4	4	Dysphasia, ataxia (3)	Improvement (1)	Slight improvement	2
4	3	Dysphasia (3)	Progression (3)	Progression	—
2	2	Dysphasia, hemiparesis (3)	Improvement (2)	Not assessible	Died (PE)
4	7	Dysphasia, confusion (3)	Major improvement (1)	Major improvement	6
4	6	Dysphasia, hemiparesis (3)	Major improvement (1)	Major improvement	6
2	8	Dysphasia, immobility (3)	Major improvement (1)	Not assessable	—
1	1	Dysphasia, ataxia (3)	Progression (3)	Progression	—
3	6	Dysphasia, confusion (2)	Improvement (1)	No change	6+
NA†	6	Dysphasia, hemiparesis (2)	Improvement (1)	Slight improvement	6+
NA†	4	Dysphasia (2)	Complete recovery (0)	Major improvement	3+
4	6	Dysphasia (2)	Not assessible	Not assessable	—
Newly diagnosed gliomas					
Histology (grade)	No. of courses	Clinical symptoms before treatment (MRC grade*)	Clinical response (MRC grade*)	CT response	
4	2	None (0)	—	Not assessable	
4	3	Dysphasia, ataxia (2)	Progression (3)	Progression	
4	2	Dysphasia (1)	No change (1)	Progression	
4	2	Dysphasia, ataxia (3)	Progression (3)	Progression	
4	2	Hemianopia (0)	No change (0)	No change	
NA	2	Dysphasia, hemiparesis (3)	Improvement (2)	Slight improvement	
3	2	Dysphasia, hemiparesis (3)	Major improvement (1)	Major improvement	
4	2	Dysphasia (3)	Complete recovery (0)	Major improvement	
4	2	None (0)	—	Not assessable	
4	2	None (0)	—	Slight improvement	
4	2	Dysphasia, hemiparesis (3)	No change	No change	
Other primary brain tumours					
Histology	No. of courses	Clinical symptoms before treatment (MRC grade*)	Clinical response (MRC grade*)	Response	
Medulloblastoma	6	Bone pain	Complete recovery	Improved bone scan	
Pineoblastoma	1	None	Not assessable	Toxic death	
Medulloblastoma	1	Headache, lethargy (2)	Progression (3)	Progression	
Ependymoma	1	Dysphagia	No change	No change	

*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.
†Not assessed.

temozolomide is routinely given at a dose of 750 mg/m^2 divided equally over 5 days (i.e. 150 mg/m^2/day). If no significant myelosuppression was noted on day 22, treatment was escalated to 1000 mg/m^2 on subsequent courses. Treatment was continued until relapse in the majority of patients with post-radiotherapy recurrence. Patients with newly diagnosed astrocytomas received 2–3 courses of temozolomide prior to commencing radical radiotherapy. Clinical response to treatment was measured by assessing the change in the MRC scale of neurological status [6]. CT brain scans were repeated routinely after two courses and 5–6 courses of treatment, and at any sign of progressive disease. In patients with newly diagnosed astrocytomas, response to chemotherapy was assessed by repeating CT scan and neurological examination after two courses of temozolomide, prior to the start of radiotherapy. Given the composite nature of the abnormal image in CT scan of a high grade astrocytoma (a mixture of tumour, necrosis, tumour vasculature and oedema) we do not believe standard response criteria (partial or complete response [5]) are appropriate. We have interpreted the combination of clinical improvement on the MRC neurological scale together with a major reduction in tumour mass effect (i.e. enhancing lesion + surrounding oedema + midline shift, if present) as a major improvement. Clinical improvement together with a smaller but clearly identifiable reduction in tumour mass effect is referred to as a slight improvement (Table 1).

RESULTS

10 of the 13 patients who received temozolomide for postradiotherapy relapse are assessable for response to treatment (Table 1). 5 patients had a major improvement in CT scan findings (Fig. 1) and, in all cases, this improvement was accompanied by

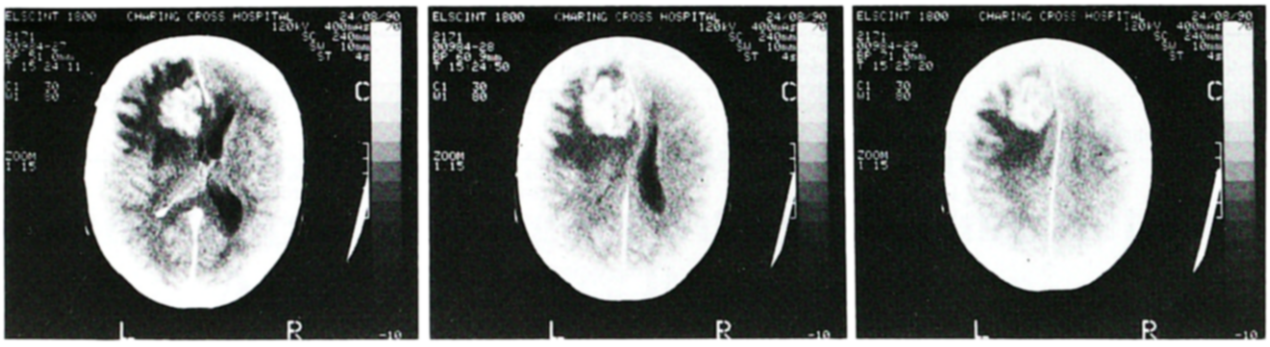

Fig. 1. Pretreatment CT scan (a) and CT scan after six courses of temozolomide (b) of a patient with a grade 4 glioma which had recurred after radiotherapy. The marked improvement in CT scan was accompanied by complete resolution of symptoms.

complete or near complete resolution of clinical signs and symptoms (response duration 3, 3+, 6, 6 and 6+ months). There were a further 3 patients who had a slight reduction or no change in mass effect on CT scan. Of these patients 1 had a clinical improvement of two grades on the MRC scale and the other 2 patients had an improvement of one grade on the MRC scale. In all cases, responses were maintained in the presence of a stable or reducing dose of steroids. 2 patients had progressive disease when assessed after two courses of treatment. Response to temozolomide could not be assessed in 3 patients: 1 patient had no baseline CT scan repeated between surgery and starting temozolomide but remains alive 8 months after starting treatment; 1 patient died following a pulmonary embolus after two courses of treatment with evidence of clinical response; 1 patient completed radiotherapy 1 month before starting temozolomide and, although he had a major clinical improvement with a slight improvement on CT scan remained for 10+ months, the relative contributions of radiotherapy and chemotherapy could not be separated.

11 patients have received two or three courses of temozolomide prior to starting cranial irradiation for newly diagnosed high grade astrocytoma (Table 1). 2 patients had a major improvement in CT scan after two courses of temozolomide accompanied by marked clinical improvement. As in the case of patients with relapsed astrocytoma, these improvements were maintained in the presence of a decreasing dose of steroids. 2 further patients have had a slight reduction in tumour size and 2 patients had no change in clinical or CT findings. 3 patients had evidence of tumour progression and 2 patients were not assessable for response.

4 patients with other primary brain tumours have received temozolomide (Table 1). 1 patient with medulloblastoma which had recurred following radiotherapy and chemotherapy experienced complete resolution of bone pain from metastatic disease and an improvement in isotope bone scan which was maintained for 6 months.

Treatment was generally well tolerated. At a dose of 1000 mg/m^2 significant (> WHO grade 2) leukopenia was noted during 3/57 (5%) courses and significant (> WHO grade 2) thrombocytopenia was observed in 4/57 (7%) of courses. No significant leukopenia or thrombocytopenia was observed following treatment at 750 mg/m^2. All patients had prophylactic oral ondansetron during treatment and no significant (>WHO grade 1) gastrointestinal toxicity was noted. Clinical deterioration was observed in 2 patients with very large tumours (tumour + oedema occupying > 50% of one cerebral hemisphere with marked midline shift) towards the end of the first 5 day treatment at a dose level of 1000 mg/m^2 and our approach to the management of this problem will be reported elsewhere. No other significant toxicities have been noted.

DISCUSSION

This extended phase I study demonstrates that temozolomide is an active agent in the treatment of primary brain tumours. Major clinical improvement was noted in 6/10 evaluable patients with high grade astrocytomas which had relapsed after radiotherapy, and this was accompanied by a marked improvement in CT scans in 5/10 patients. Improvement in CT scan findings tended to lag behind clinical improvement, which was often noticeable after the first course of treatment. Reduction in the size of tumour on CT scan was also noted in 4/7 patients with unirradiated astrocytomas and one patient with recurrent medulloblastoma had a symptomatic response in bone metastases. Further randomised studies are needed to assess whether these responses are translated into improved survival. However, the combination of a high response rate with ease of administration makes this an exciting new drug in the treatment of tumours for which, at present, we have little effective therapy.

1. Walker ME, Alexander E, Hunt WE, *et al.* Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. *J Neurosurg* 1978; **49**: 333–343.
2. Stewart DJ. The role of chemotherapy in the treatment of gliomas in adults. *Cancer Treat Rev* 1989, **16**, 129–160.
3. Rodriguez LA, Levin VA. Does chemotherapy benefit the patient with a central nervous system glioma? *Oncology* 1987, **1**, 29–36.
4. Georges P, Przedborski S, Brotchi J, Chatel M, Gedouin D, Hildebrand J. Effect of HECNU in malignant supratentorial gliomas: a phase II study. *J Neuro-oncol* 1988; **6**, 211–219.
5. MacDonald DR, Cascino TL, Schold SC, Cairncross G. Response criteria for Phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990, **8**, 1277–1280.
6. Bleehen NM, Freedman LS, Stenning SP. A randomised study of CCNU with and without benznidazole in the treatment of recurrent grades 3 and 4 astrocytoma. *Int J Radiat Oncol Biol Phys* 1989, **16**, 1077–1081.
7. Bleehen NM. Studies on high grade cerebral gliomas. *Int J Radiat Oncol Biol Phys* 1990, **18**, 811–813.
8. Stevens MFG, Hickman JA, Langdon SP, *et al.* Antitumour activity and pharmacokinetics in mice of 8-carbomyl-3-methyl-imidazo [5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M&B 39831), a novel drug with potential as an alternative to dacarbazine. *Cancer Res* 1987, **47**, 5846–5852.
9. Newlands ES, Blackledge GRP, Slack JA, *et al.* Phase I trial of Temozolomide (CCRG 81045: M&B 39831: NSC 362856). *Br J Cancer* 1992, **65**, 287–291.

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