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Original Paper

The Charing Cross Hospital Experience with Temozolomide in Patients with Gliomas

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Temozolomide, a new oral cytotoxic agent, was given to 75 patients with malignant gliomas. The schedule used was for the first course 150 mg/m^2 per day for 5 days (i.e. total dose 750 mg/m^2), escalating, if no significant myelosuppression was noted on day 22, to 200 mg/m^2 per day for 5 days (i.e. total dose 1000 mg/m^2) for subsequent courses at 4-week intervals. There were 27 patients with primary disease treated with two courses of temozolomide prior to their radiotherapy and 8 (30%) fulfilled the criteria for an objective response. There were 48 patients whose disease recurred after their initial surgery and radiotherapy and 12 (25%) fulfilled the criteria for an objective response. This gave an overall objective response rate of 20 (27%) out of 75 patients. Temozolomide was generally well tolerated, with little subjective toxicity and predictable myelosuppression. However, the responses induced with this schedule were of short duration and had relatively little impact on overall survival. In conclusion, temozolomide given in this schedule has activity against high grade glioma. However, studies evaluating chemotherapy in primary brain tumours should include a quality-of-life/performance status evaluation in addition to CT or MRI scanning assessment.

Key words: temozolomide, gliomas, astrocytomas, alkylating agents, chemotherapy

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INTRODUCTION

THE PROGNOSIS for patients with gliomas and in particular high grade (grade 3 and 4) tumours is poor. While prospective randomised studies have confirmed the beneficial effect of postoperative cranial irradiation, in most series survival beyond 2 years is 15% or less [1–3]. Attempts to develop effective chemotherapy against gliomas has so far met with limited success. The combination of procarbazine, CCNU and vincristine (PCV) has had limited effect on survival [4, 5]. The most active agents identified so far are the nitrosoureas, BCNU, CCNU, methy-CCNU and HECNU, which have been reported to induce responses in the range of 35–55% although the majority of responses are of short duration [2, 6, 7]. The definition of response to treatment has remained a difficult area when assessing primary brain tumours. The area of abnormality detected on the scan comprises tumour, necrosis, vascularity, oedema and normal neural tissue. MacDonald and associates [8] have argued that traditional response criteria used for tumours at other sites should also be used when assessing responses in gliomas. They have also emphasised the importance of the patient being on a stable dose of corticosteroids for 2 weeks prior to CT or MRI scanning [9]. Unfortunately, in the majority of cases, the end-points of the abnormality on the CT or MRI scan are not sufficiently distinct to make this a truly measurable difference. Since there is a close correlation in the majority of patients between their clinical and neurological performance and their CT or MRI scan appearance, we have used both measures to assess response. Clearly, given the limited improvement in survival outcome in patients receiving surgery and/or radiotherapy and/or nitrosourea-containing chemotherapy, it is important to develop new and better treatments for this disease.

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A range of prognostic factors has been identified in patients with malignant glioma that needs to be considered when assessing trial outcome. Young age, long history of fits, extensive surgical removal and performance status are all predictors of longer survival [10–12]. In addition, there is increasing evidence of an accumulation of genetic defects in gliomas likely to affect prognosis [13] as they evolve from low to high grade tumours.

Temozolomide is an imidazotetrazine derivative that has activity against a wide range of experimental tumours and which has shown clearcut schedule dependency in the preclinical screen [14]. Phase I testing confirmed that the drug has excellent oral bioavailability and, on a 5-day schedule repeated every 4 weeks, clinical activity was detected in patients with malignant melanoma, mycosis fungoides, and in patients with high grade gliomas [15, 16]. The activity of temozolomide against metastatic malignant melanoma has been confirmed in a subsequent phase II trial with a response rate of 12 out of 49 (24%) patients [17]. Temozolomide has also been tested against recurrent low grade non-Hodgkin's lymphoma and only one response was seen in 18 patients [18]. Here, we report our experience of the use of temozolomide in the treatment of malignant glioma.

PATIENTS AND METHODS

The 75 consecutive patients reported here include all the patients treated at the Charing Cross Hospital, including 2 patients reported in the phase I study and 22 patients previously reported [16]. Patients can be divided into two groups: 48 patients with recurrent disease following radiotherapy and 27 patients with newly diagnosed glioma, treated following their initial surgery and prior to their cranial irradiation. Their characteristics are shown in Table 1.

Treatment was initially given at a dose of 150 mg/m^2 per day for 5 days (i.e. total dose 750 mg/m^2), escalating, if no significant myelosuppression was noted, on day 22 to 200 mg/m^2 per day for 5 days (i.e. total dose 1000 mg/m^2) for subsequent courses at 4-week intervals. Approximately 1 in 20 patients receiving temozolomide in this schedule experience myelosuppression of grade 2 or more at the initial dose of 750 mg/m^2, and their dose is not escalated further. In this series of 75 patients, 6 (8%) continued their treatment at 750 mg/m^2 in subsequent courses. Patients received ondansetron 8 mg orally twice daily on the days they received temozolomide. Treatment was continued until disease progression in patients who showed evidence of response. In patients with newly diagnosed gliomas, two to three courses of temozolomide were given prior to commencing radical radiotherapy. Clinical response was assessed using the Medical Research Council's (MRC) scale of neurological status [20]. Baseline CT or MRI scans were made after stabilisation of the dexamethasone dose for a minimum of 2 weeks prior to starting temozolomide [9], and were repeated routinely after two courses and then after five to six courses of treatment, and at any clinical indication of disease progression. In patients with newly diagnosed gliomas, response was assessed after two courses of temozolomide by CT or MRI scanning and clinical examination prior to the start of radiotherapy. We interpreted a combination of clinical improvement on the MRC neurological scale of one or more for a minimum of 4 weeks with a clearcut reduction in tumour mass effect on CT or MRI scanning as an objective response. All scans were reviewed by a neuroradiologist (I.C.) who was blinded to the treatment the patient had received. In our experience, the clinical correlation between the neurological assessment of a patient and the CT scan is close. There was only one patient in the series who showed a reduction in tumour mass effect on CT scan who did not experience clinical benefit. Even in relatively silent areas of the brain such as the frontal or temporal lobes, tumour progression is usually detected by clinical assessment as well as CT or MRI scanning.

Table 1. Patients' characteristics

Disease status	
Primary glioma	27 (36%)
Recurrent glioma	48 (64%)
Male	48 (64%)
Female	27 (36%)
Mean age (range)	46.6 (20–72) years
Tumour grade*	
2	1 (1%)
3	14 (19%)
4	58 (77%)
Mixed (3/4)	2 (3%)
Previous treatment	
Biopsy	43 (57%)
Resection	32 (43%)
Subsequent therapy before temozolomide†	
Radiotherapy	42 (56%)
Radiochemotherapy‡	5 (7%)
None§	28 (37%)

* According to [19]. † All patients who received dexamethasone had stable disease for 2 weeks prior to trial entry, then rescanned before starting temozolomide. ‡ The chemotherapy included nitrosoureas, but there were no responses. § All 27 primary glioma patients received temozolomide after surgery, but before cranial radiation.

RESULTS

There were 27 patients with newly diagnosed disease and their response was assessed after two courses of temozolomide (i.e. after 8 weeks and prior to their irradiation). Their responses on the MRC scale correlated with their radiological assessment by CT or MRI scanning (Table 2). Of these, 8 (30%) showed evidence of objective response. CT scan of a patient showed a rapid response during the initial 8-week assessment (Figure 1). No increase in clinical (neurological or skin) toxicity was seen in patients receiving temozolomide prior to radiotherapy. 17 patients received two courses of temozolomide prior to their radiotherapy. Since this was well-tolerated, a further 10 patients received two courses of temozolomide prior to radiotherapy and two further courses during their radiotherapy, which was also well-tolerated.

There were 48 patients with recurrent disease. The response assessment is shown in Table 1. Here, 12 (25%) were assessed as having an objective response. The response duration from the start of therapy ranged from 3.4 to 16.9 months with a median of 6.1 months. An example of major reduction in tumour size as assessed by contrast-enhanced CT scanning is shown in Figure 2. The overall response using temozolomide in this schedule was 20 (27%) out of

*Table 2. Assessment of response by both CT/MRI scanning and MRC grade**

	Patients treated prior to radiotherapy ($n = 27$)	Patients with recurrent disease† ($n = 48$)
Progressive disease	2 (7%)	14 (29%)
No change	13 (48%)	18 (38%)
Objective response	8 (30%)	12 (25%)
Not assessable	4 (15%)	3 (6%)
Early deaths	—	1 (2%)

*MRC scale of neurological status: 0 = no neurological deficit; 1 = function adequate for useful work; 2 = moderate functional impairment; 3 = neurological deficit causing major functional impairment; 4 = no useful function. †Assessed at maximum neurological and CT/MRI scan improvement, i.e. usually 2 or 5 months after starting temozolomide.

75 patients. Responding patients continued on regular courses of temozolomide until there was evidence of disease progression. The number of courses given ranged from 1 to 29 (median = 7).

The survival of the two cohorts of patients is shown in Figure 3. The performance status in patients with newly diagnosed disease was better than in patients with recurrent disease. In addition, those patients in the newly diagnosed group received cranial irradiation following temozolomide treatment. These two factors probably account for the slightly better survival in this group of patients (1 year overall survival = 43%, 95% confidence interval 26–62%) compared with the patients with recurrent disease (1 year overall survival = 22%, 95% confidence interval 12–36%). Overall, these results in terms of survival are disappointing and, although, when responses occurred, they were of clinical benefit to the patient, their duration was not sufficiently long to alter overall survival when compared with historical series [3–5, 10–12].

In general, temozolomide was well-tolerated when given with ondansetron. The haematological toxicity of the 5-day schedule is predictable and has already been reported extensively ([15–17]; Table 3).

DISCUSSION

These results extend and confirm our previous reports [15, 16] that temozolomide, when given in this 5-day schedule, has activity against high grade gliomas. It is generally a well-tolerated agent, with myelosuppression being the only dose-limiting toxicity normally encountered. The improvement in quality of life of those patients who responded was clearly useful. Where there was clearcut improvement on the MRC scale, the dose of dexamethasone could be reduced progressively and in some cases stopped completely. The MRC scale of neurological impairment that was used here is simple, but observers are likely to interpret the scale differently. In this study, four observers working clo-

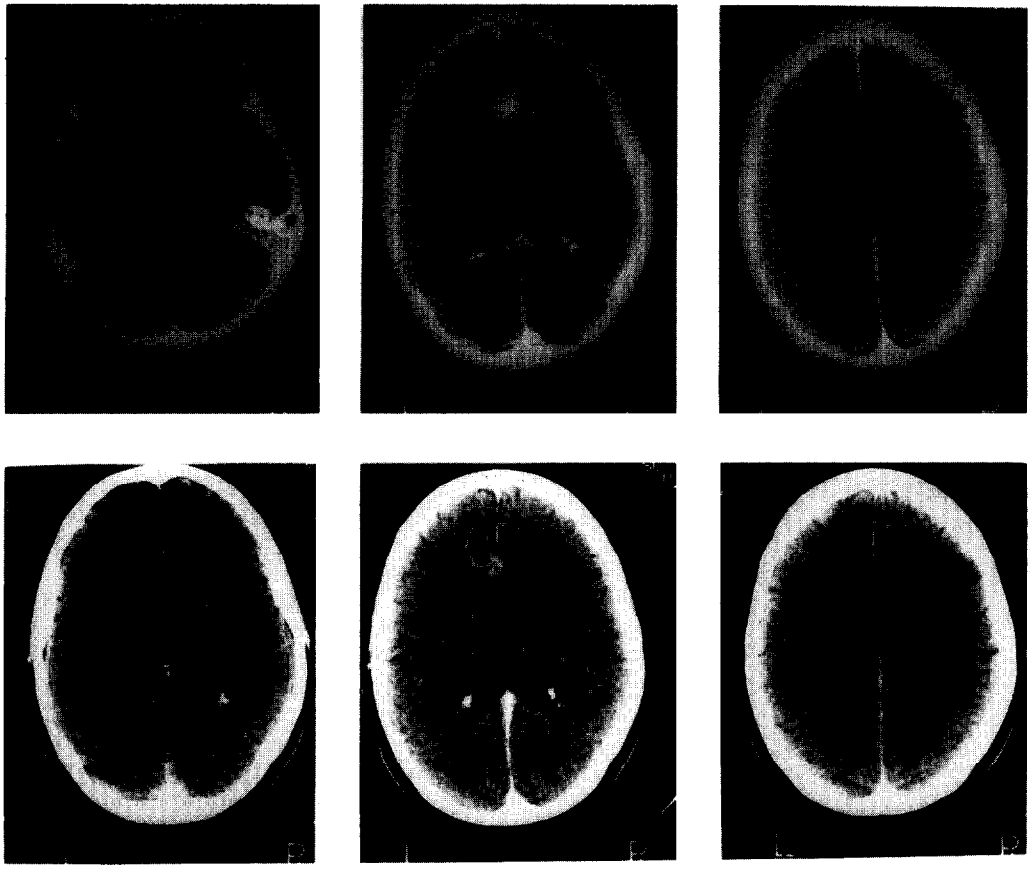

Figure 1. A 48-year-old female patient presenting with a psychotic episode. Biopsy confirmed grade 4 glioma. The upper three panels show bilateral, partly cystic tumour after her biopsy. The lower three panels show the reduction in mass and enhancement after two courses of temozolomide (i.e. after 8 weeks).

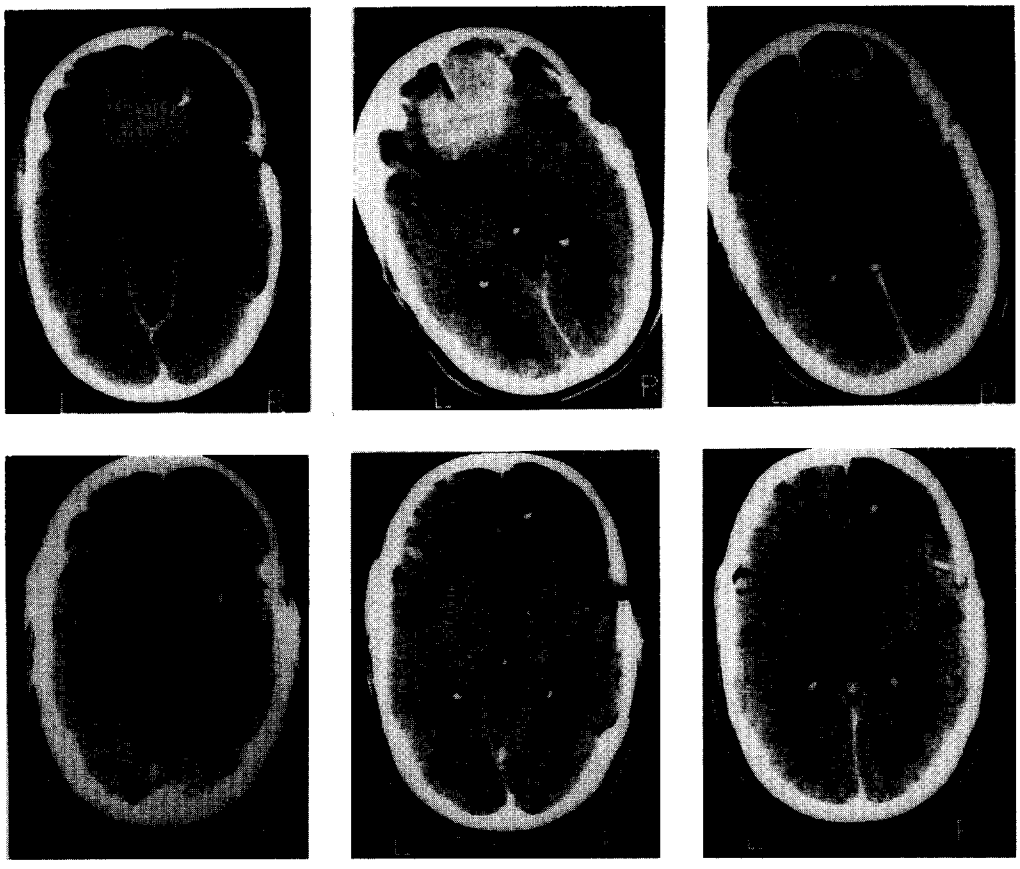

Figure 2. A 42-year-old male patient who originally presented in 1989 and had a grade 2 glioma resected and was treated with radiotherapy. Recurrence in 1993 and further craniotomy confirmed grade 3 glioma. Upper three panels show subsequent relapse and in the lower three panels the major improvement in the mass and enhancing lesion after 12 months on temozolomide (i.e. after 11 courses).

sely together (ESN, SMO'R, HE, CB) had a high degree of concordance in using this scale. However, its application in multicentre trials is probably unsatisfactory.

The Phase I/II subcommittee of the Cancer Research Campaign has also completed a multicentre phase II trial of temozolomide also administered in the same schedule as reported here [21]. In this group of 103 eligible patients, 31 (30%) had received prior chemotherapy as well as surgery and/or radiotherapy, and 11 (11%) achieved an objective response, with 48 (47%) having stable disease. This study emphasises the subjective nature of interpretation of the MRC neurological scale when the trial is multicentre. The need for more reproducible and objective methods for evaluating patients' neurological status and serial scans in trials of chemotherapy in patients with gliomas is clearly required.

In recognition of the limitations of the MRC scale of neurological impairment, a prospective assessment of a quality-of-life questionnaire has been developed for patients with primary brain tumours, to be used in combination with

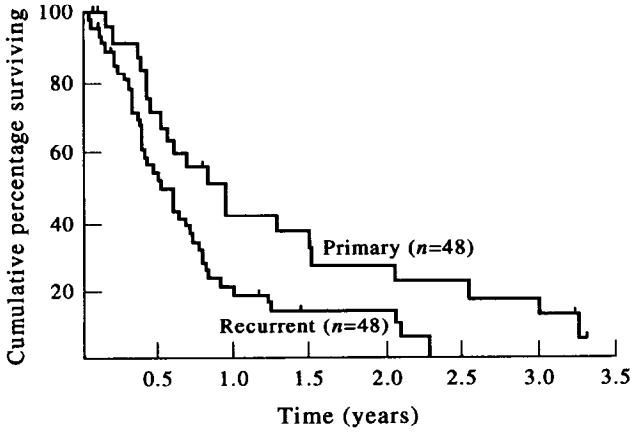

Figure 3. Survival of patients from the start of treatment with temozolomide. Primary group was the patients treated after their initial surgery and before their radiotherapy. Recurrent group was treated on relapse after their initial treatment.

Table 3. Worst adverse events observed in 75 patients (irrespective of causality). All adverse events were recorded although these were not necessarily related to temozolomide administration

	CTC Grade			
	1	2	3	4
Lymphocytes	9	24	31	10
Platelets	14	10	6	1
Leucopenia	7	2	3	2
Anaemia	56	4	3	0
Raised ALT	18	6	1	0
Raised AST	5	2	1	0
Raised bilirubin	8	6	0	0
Hypercalcaemia	1	1	0	0

ALT, alanine transaminase; AST, aspartate transaminase.

general cancer-specific questionnaires such as the EORTC QOL-C30 [22–24]. It is likely that by using both the general and brain-specific modules of these quality-of-life questionnaires, a more objective and more reproducible assessment of clinical improvement can be made and used in future trials in patients with primary brain tumours.

As emphasised above, we felt that the end-points of the abnormality as assessed by CT and MRI scanning are unsatisfactory for straightforward linear or volumetric estimations of disease extent since these are composite images. While Figures 1 and 2 show clearcut biological response to temozolomide, it is very questionable where one would choose the end-points in the post-treatment scans for comparison with the initial area of abnormality. Alternative methods of assessing tumour response to new therapeutic measures have recently become available and include positron emission tomography (PET). A small cohort of the patients included in this report also had PET scanning with ^{18}F-fluorodeoxyglucose (FDG) [25]. Although these results are preliminary, they show that within 7–14 days of initiating therapy with temozolomide, changes in FDG metabolism could be detected in those who went on to respond. The reduction in FDG uptake in the responders was −30%, −30% and −29%. This contrasted with little change in FDG metabolism (−2%, −11%) in patients with stable disease. In contrast, patients with progressive disease had an increase in FDG uptake of +25%, +25%, +25%, +20%. In addition to PET scanning, registration MRI scanning provides a method of superimposing sequential scans for subtracting areas of abnormality to increase sensitivity [26]. Ideally, these new techniques should be assessed in parallel including quality-of-life inventories, PET scanning and registration MRI, at the same time points and in the same patients, to identify the most relevant and sensitive means of assessing tumour response and clinical benefit.

While temozolomide given on the 5-day schedule once every 4 weeks, as described here, has activity in patients with both primary and recurrent gliomas, the duration of response is relatively short and the overall survival is probably not extended in either of these two groups when compared with the natural history of the disease. Temozolomide is a very schedule-dependent drug and there are alternative ways of administering it other than the 5-day schedule described here. We are currently completing a phase I trial, giving temozolomide orally for 6 and 7 weeks continuously. This is well tolerated, with myelosuppression again being dose limiting. Clearcut clinical activity has been seen both in patients with metastatic melanoma and high grade gliomas. The plan for this schedule is to combine the daily administration of temozolomide with concurrent radiotherapy. In the phase I trial [15], there were clinical hints that temozolomide enhanced the effectiveness of radiotherapy.

Over the last decade, an increasingly large body of evidence suggests that DNA repair within tumour cells is an important aspect of resistance both to radiotherapy and to chemotherapy in common human cancers [27–32]. There is considerable interest in developing inhibitors of DNA repair such as the alkyltransferase inhibitor, O^6-benzylguanine [33–37]. We and others have shown that O^6-benzylguanine can enhance the antitumour activity of both BCNU and temozolomide [38–40]. Provided the toxicity profile of the combination of agents is satisfactory, there is considerable potential for developing combinations of radiotherapy, temozolomide and DNA inhibitors such as O^6-benzylguanine.

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