Temozolomide chemotherapy for progressive low-grade glioma: clinical benefits and radiological response

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Background: The optimal treatment for low-grade glioma (LGG) is still controversial. Recent data indicate a potential influence of chemotherapy on the natural evolution of these tumors, allowing for the deferral of more aggressive therapies.

Patients and methods: Forty-three patients affected with LGG (29 astrocytoma, four oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with temozolomide (TMZ) at the time of documented clinical and radiological progression. McDonald’s response criteria were utilized to evaluate TMZ activity. Thirty patients (69.7%) had previously received radiotherapy; 16 (37.2%) had received prior chemotherapy. Clinical benefit was evaluated measuring seizure control, reduction in steroid dose and modification of Karnofsky performance status and Barthel index. Quality of life was assessed with the QLQ-C30 questionnaire.

Results: We observed a complete response in four patients, 16 partial responses, 17 stable disease (with four minor response) and six progressive disease. Median duration of response was 10 months [95% confidence interval (CI) 8–12], with a 76% rate of progression free survival (PFS) at 6 months, and a 39% rate of PFS at 12 months. A relevant clinical benefit was observed particularly in patients presenting epilepsy.

Conclusions: The high response rate of 47% (95% CI 31% to 61%) confirms that TMZ chemotherapy is a valid option in the treatment of progressive LGG. The present preliminary results seem interesting and warrant further evaluation of TMZ clinical activity in a larger series of progressive LGG.

Key words: chemotherapy, epilepsy, low-grade glioma

Introduction

The optimal treatment for low-grade glioma (LGG) is still controversial. A substantial incidence of radiation-induced cognitive deficits has been described in patients with LGG who received whole-brain or focal radiotherapy, and emerging data in the literature suggest that potential late neurotoxic effects should be considered in the timing of radiotherapy [1–4]. Moreover, recent studies indicate that early radiotherapy has no survival advantage over delaying the treatment until disease progression [5]. Treatment selection in young patients with small asymptomatic, unresectable or partially resected LGG is not easy. Thus, consensus is growing for careful observation and considering delay of radiotherapy until recurrence and/or clinical-radiological progression [6].

In this context, there is increasing attention on the potential influence of chemotherapy on the natural evolution of these tumors, allowing for the deferral of more aggressive therapies. In recent years, there have been many reports on the efficacy of chemotherapy in children with newly diagnosed or recurrent LGG treated with a variety of drugs [7–9]. The results of these studies have demonstrated that objective responses can be achieved in patients with LGG, and prolonged disease stabilization can be observed even in the absence of significant neuroimaging variations. In adults, chemotherapy activity has been demonstrated clearly, particularly in pure oligodendrogliomas and mixed oligo-astrocytomas [10, 11], even if more substantial therapeutic activity has been observed in anaplastic oligodendrogliomas [12]. The scarce data on chemotherapy in adult LGG reported in the literature [13, 14] reveal that LGG seems to be less chemosensitive than anaplastic forms, but that chemotherapy may induce long-term stabilization of the disease and important clinical benefits, including control of epilepsy.

Genetic alterations, such as loss of the heterozygosity of chromosomes 1p and 19q, have been shown to be powerful predictors of survival and chemosensitivity in oligodendroglial tumors [15, 16]. At present, the role of molecular changes in astrocytoma is less clear, but many authors suggest that genetic alterations may help to identify chemosensitivity in low-grade astrocytomas as well [17]. Furthermore, the evaluation of therapeutic response to chemotherapy in patients affected by indolent, infiltrating and
often non-enhancing tumors, is not easy using common neuroimaging response criteria.

Temozolomide (TMZ) is a methylating agent that has shown clinical activity in the treatment of recurrent anaplastic astrocytoma and glioblastoma multiforme. Recent data have suggested a possible role of TMZ chemotherapy in LGG [18]. The primary aim of this study was to assess the activity of TMZ chemotherapy in patients with progressive LGG, evaluated with conventional clinical and neuroimaging response criteria. A further aim was to evaluate the patients' clinical benefits, in terms of seizure control and improvement in quality of life (QoL).

Patients and methods

Objectives

A prospective phase II study was performed between April 2000 and September 2002, with the aim of determining the antitumor activity of TMZ in the treatment of adult progressive LGG and evaluating TMZ toxicity in this patient population. The primary end point of the study was response to treatment. Secondary end points included clinical benefits in terms of modification of seizure frequency, QoL and toxicity.

Eligibility criteria

Patients with grade II (WHO) histologically confirmed glioma (astrocytoma, oligodendrogliomas and mixed oligo-astrocytoma) entered the study at the moment of clinically and radiologically documented progression. All patients were required to present measurable disease on pretreatment contrast-enhanced magnetic resonance imaging (MRI), Karnofsky performance status (KPS) >60 and Barthel index (BI) >80. The study was approved by our ethics committee and all patients were required to provide signed informed consent.

Treatment schedule

TMZ was administered orally, once a day, for five consecutive days every 4 weeks, at a starting dose of 200 mg/m²/day if not pretreated, or 150 mg/m²/day September 2002, with the aim of determining the antitumor activity of TMZ in patients affected with LGG (29 astrocytoma, four oligodendroglioma and 10 mixed oligo-astrocytoma), showing a response rate of at least 25%.

Table 1 shows the patient population characteristics. Forty-three patients affected with LGG (29 astrocytoma, four oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with TMZ, at the time of documented clinical and radiological progression (median time from first histological diagnosis to TMZ treatment 61 months, range 5–144); 16 patients were submitted for re-operation after recurrence and histology showed the presence of anaplastic focal areas in eight cases and a grade II astrocytoma in the other eight cases. Seventeen patients (39.5%) presented non-enhancing lesion on MRI, while 26 (60.5%) presented focal enhancing areas in the context of non-enhancing lesion; 30 patients (69.7%) had previously received radiotherapy; 16 (37.2%) were pretreated with a PCV regimen (mostly affected by oligodendroglioma or mixed oligo-astrocytoma), showing a response rate (CR or PR) of 69%.

Table 1. Patient characteristics

| Age, median (range) | 39.5 (21–69) |
| Karnofsky performance status, median (range) | 90 (70–100) |
| Barthel index, median (range) | 95 (85–100) |
| Histology |  |
| Astrocytoma | 29 |
| Oligodendroglioma | 4 |
| Mixed oligo-astrocytoma | 10 |
| Enhancing lesion on MRI | 26 |
| Non-enhancing lesion on MRI | 17 |
| Prior chemotherapy (PCV) | 16 |
| Prior radiotherapy | 30 |
| Surgery |  |
| Biopsy | 11 |
| Resection | 32 |
| Second resection | 16 |
| Anaplastic progression | 8 |
| No histological progression | 8 |

MRI, magnetic resonance imaging; PCV, procarbazine–lomustine–vincristine.

day 1 of treatment to the radiographical or clinical evidence of disease progression.

Statistical analysis

We used a single-stage design for the trial. A response rate of 10% was considered of no interest, while the study would be considered as positive if the responses rate was of at least 25%. At a significance level of 5% with a power of 80%, 40 patients were required to enter the study, and eight objective responses needed to be observed to consider the study as positive, χ²-test was used to study the association between response and variables. Survival curves were estimated by the Kaplan–Meier method and differences were evaluated by the log-rank test.

Results

Table 1 shows the patient population characteristics. Forty-three patients affected with LGG (29 astrocytoma, four oligodendroglioma and 10 mixed oligo-astrocytoma) were treated with TMZ, at the time of documented clinical and radiological progression (median time from first histological diagnosis to TMZ treatment 61 months, range 5–144); 16 patients were submitted for re-operation after recurrence and histology showed the presence of anaplastic focal areas in eight cases and a grade II astrocytoma in the other eight cases. Seventeen patients (39.5%) presented non-enhancing lesion on MRI, while 26 (60.5%) presented focal enhancing areas in the context of non-enhancing lesion; 30 patients (69.7%) had previously received radiotherapy; 16 (37.2%) were pretreated with a PCV regimen (mostly affected by oligodendroglioma or mixed oligo-astrocytoma), showing a response rate (CR or PR) of 69%. Metabolic imaging with positron
emission tomography (PET) and/or single photon emission computed tomography (SPECT) was carried out in 10 patients previously treated with radiotherapy, with the aim of differentiating possible focal radionecrosis.

The age of patients ranged from 21 to 62 years, with a median of 39 years. Median KPS was 90 (70–100); median BI was 95 (85–100). Epilepsy resistant to anticonvulsant treatment with more than one drug was present in 31 patients (69.7%). Most of the patients were treated with carbamazepine–oxcarbazepine and/or topiramate. TMZ was administered for a median of 10 cycles (range 3–22); a total of 469 cycles was performed.

We observed an objective response rate of 47% [four CR plus 16 PR; 95% confidence interval (CI) 31% to 61%], a disease control rate of 86% [four CR plus 16 PR plus 17 SD, with four minor responses; 95% CI 76% to 96%] and six progressive disease (PD) (Table 2). Median duration of response was 10 months, with a PFS rate of 76% at 6 months and 39% at 12 months. The response rate in patients presenting non-enhancing lesions on MRI (17 patients) was lower than that observed in patients presenting enhancing lesions on MRI (26 patients): 29% (95% CI 8% to 51%) versus 58% (95% CI 38% to 76%), respectively.

The influence of TMZ treatment on seizure frequency in the 31 patients presenting with uncontrolled epilepsy was relevant, with CSC in six patients and PSC in nine, with steroid dose stable or reduced and no modification in anticonvulsant medication.

The clinical benefit was significantly higher in patients with non-enhancing lesions than in those with enhancing lesions, with 81% (nine of 11; 95% CI 59% to 100%) of seizure control (CSC in two cases, PSC in seven) and 30% (six of 20; 95% CI 10% to 50%) of seizure control (two CSC and four PSC), respectively (P <0.05) (Table 3).

Twenty-five patients completed a baseline QoL questionnaire and at least one follow-up questionnaire. The QoL baseline profile was similar for patients who showed a response (CR or PR) and for patients who did not. An improvement of QoL score in one or more items was more frequent in patients with CR or PR than in patients with SD or PD (Figure 1). Out of 16 patients receiving steroids at the beginning of chemotherapy, a reduction in steroid dose was observed in nine (56%). Eight patients (18%) showed an increase in KPS.

Responses to chemotherapy were observed after a median of four TMZ cycles. In five patients late response was observed after more than five cycles and in two cases a PR became a CR after more than 10 cycles (12 and 13 cycles, respectively). Four minor responses were observed after five to 12 cycles of chemotherapy.

The median PFS was 10 months for the whole population. Patients with a radiological response of SD showed a relevant clinical benefit during TMZ treatment, with 41% gaining seizure control (Table 3) and QoL improvement in five patients (29.4%). PFS at 6 and 12 months was not significantly different in patients with radiological response (CR plus PR) and in patients with SD (Table 4).

Drug-related toxicity was limited: 10 patients (23.2%) showed myelotoxicity and/or gastrointestinal toxicity WHO grade >3.

**Discussion**

LGGs represent a heterogeneous group of tumors with variable natural histories, in which the relative risks and benefits of aggressive treatment must be balanced for each individual patient. Mainly in the presence of relevant residual disease, an adequate surveillance program is justified after first-line treatment. Tumor evolution sometimes occurs with anaplastic progression; sometimes the histology remains unmodified at the time of recurrence. Anaplastic transformation may occur focally and seems to be closely correlated with the imaging characteristics of enhancing areas in the context of the tumor after contrast medium administration [21, 22]. In other cases, volumetric expansion cannot be correlated with MRI enhancement, and only metabolic imaging

<table>
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<tr>
<th>Table 2. Response to TMZ chemotherapy by histology</th>
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<tbody>
<tr>
<td>Histology</td>
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</tr>
<tr>
<td>Astrocytoma</td>
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<tr>
<td>Mixed + oligo</td>
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<tr>
<td>Total</td>
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CR, complete response; G3, gastrotoxicity grade 3 (WHO); M3, myelotoxicity grade 3 (WHO); PD, progressive disease; PR, partial response; SD, stable disease; TMZ, temozolomide.
demonstration of anaplastic progression in eight, but the radiological particularly epilepsy control, were significantly higher in patients suggested that new imaging modalities, such as PET and MRI objective tumor response by measuring its shrinkage. The response formation [23]. Furthermore, patients can present neurological reduction in steroid dosage, improvement in KPS and BI, and patients without enhancing lesions (29%).

Another critical issue in this field is the criteria for evaluating treatment policy and a more intensive therapeutic strategy.

The patients included in our study presented an initial histological diagnosis of well-differentiated glioma, and in all cases showed clinical and neuroimaging documented progression. Histological restaging at recurrence was possible only in 16 patients, with demonstration of anaplastic progression in eight, but the radiological characteristics of enhancing lesion in 25 patients, and non-enhancing lesion in 17, probably reflects the variability of LGG, which may recur with or without histological progression.

Another critical issue in this field is the criteria for evaluating treatment efficacy. Chemotherapy response criteria are usually based on volumetric neuroimaging aspects that evaluate the objective tumor response by measuring its shrinkage. The response rate as evaluated by these classical criteria is considered a traditional end point in clinical trials, but it is also well known that there is not necessarily a correlation between objective response and other measures of clinical benefit, considered as beneficial effects on disease-related symptoms and QoL. It has been suggested that new imaging modalities, such as PET and MRI spectroscopy, may offer new possibilities for evaluating treatment results in brain tumors. Since LGG are characterized by reduced growth potential, and a very low proliferating cell population, which may recur with or without histological progression.

The radiological response rate in the whole population was 47%, but was higher, though not statistically significant, in the group of patients showing enhancing areas on MRI (58%) than in patients without enhancing lesions (29%).

In contrast, the clinical benefits of chemotherapy, such as a reduction in steroid dosage, improvement in KPS and BI, and particularly epilepsy control, were significantly higher in patients with non-enhancing lesions, who often showed an SD on radiological examination. In fact, in many cases seizures are the only symptom, which implies that performance status and neurological status may be well preserved even in the presence of voluminous tumors. Moreover, despite limitations due to the small size of this study, QoL measurements indicate an improvement of function scores in a larger proportion than patients who achieved an objective radiological response. The effect of chemotherapy differed between enhancing and non-enhancing tumors, with more prolonged PFS being achieved in the latter. PFS was similar in patients with CR/PR and with SD. Recent studies on recurrent anaplastic astrocytoma, anaplastic oligodendroglioma and mixed anaplastic oligo-astrocytoma [24–26] included patients with history of low-grade disease reporting variable response rates to TMZ chemotherapy ranging from 35% to 61%. The remarkable heterogeneity of LGG in biological behavior and response to treatment should be considered in patients’ selection criteria of clinical trials. The results of the present study seem to indicate that chemotherapy may produce a different response in LGG: a radiological ‘sprinter’ response or a ‘jogger’ response with long stabilization of disease often associated with considerable clinical benefits, particularly in patients presenting with epilepsy. Other reports support our observation of relevant clinical benefit induced by chemotherapy, often not related to radiological response, in the subgroup of patients with non-enhancing LGG [12, 27]. The different biological behavior of progressive LGG should be better identified taking into account radiological, pathological and genetic characteristics that will indicate the optimal treatment. In particular, it has already been suggested that indolent gliomas with low mitotic index may be treated with new schedules of administration of TMZ with chronic low-dose exposure [27, 28].

The results of our study indicate that TMZ is active in progressive LGG. The high response rate of 47% confirms that chemotherapy is a valid option in the treatment of this group of tumors. However, the role of TMZ chemotherapy in progressive LGG needs to be studied in larger series.

<table>
<thead>
<tr>
<th>Imaging response</th>
<th>Epilepsy</th>
<th>QoL</th>
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<tbody>
<tr>
<td>Non-enhancing tumors (17 patients)</td>
<td>1 CR, 4 PR, 11 SD</td>
<td>Seizure control 81% (9/11)</td>
</tr>
<tr>
<td>Enhancing tumors (26 patients)</td>
<td>3 CR, 12 PR, 6 SD</td>
<td>Seizure control 30% (6/20)</td>
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CR, complete response; PR, partial response; QoL, quality of life; SD, stable disease.

<table>
<thead>
<tr>
<th>Epilepsy</th>
<th>QoL</th>
<th>PFS-6/PFS-12</th>
<th>Radiotherapy</th>
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<tbody>
<tr>
<td>CR + PR (20 patients)</td>
<td>8/12 (66%), 5 CSC, 3 PSC</td>
<td>8 improved, 7 stable</td>
<td>85%/42%</td>
</tr>
<tr>
<td>SD (17 patients)</td>
<td>7/14 (50%), 1 CSC, 6 PSC</td>
<td>5 improved, 8 stable</td>
<td>88%/47%</td>
</tr>
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CR, complete response; CSC, complete seizure control; PFS-6/PFS-12, percentage of patients with progression-free survival at 6 and 12 months; PR, partial response; PSC, partial seizure control; QoL, quality of life (EORTC QLQ-C30 questionnaire); SD, stable disease.
References


