

Surgery, radiotherapy and temozolomide in treating high-grade gliomas

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1. ABSTRACT

Temozolomide (TMZ) a recent, oral, second generation alkylating agent is a chemotherapeutic with demonstrated efficacy for the treatment of high-grade gliomas. The efficacy of TMZ has been demonstrated in both pre-clinical and phase I and II studies. The goal of this study is to determine the activity and safety of temozolomide in improving overall survival (OS), progression-free survival (PFS) and health-related quality of life (HQL) in patient with malignant gliomas treated by surgery, radiotherapy and temozolomide. Twelve patients with newly diagnosed glioblastoma (GBM), and anaplastic astrocytoma (AA) were studied. The mean follow-up period was 12 months. The overall response rate for all histological groups was 33% (4 patients), 6 patients (50%) showed a stabilization of disease. The median progression-free survival (PFS) and overall survival (OS) was respectively 8.35 and 14.1 months; time to progression was 36 week ranging from 20 to 46 In all patients, treatment with temozolomide was associated with improvement of

performance status including the patient showing disease progression; Karnofski score improved in all patients by a minimum of 10, with a median of 20 at 6 months. No patient stopped the treatment due to side-effects, no major adverse events were recorded. In two cases of glioblastoma, we observed complete response and after three years, the quality of life is optimal. Surgery allows to establish a histopathological diagnosis, to improve signs and symptoms which are attributable to intracranial hypertension or tumour topography, and to reduce the number of target cells for adjunctive therapies. Radiotherapy improves survival and TMZ chemotherapy that is given after radiotherapy adds survival benefit for patients. Because of its favourable pharmacokinetic and pharmacodynamic properties and improved tolerability. Temozolomide appears to be an ideal, first-line, single-agent, with a safe profile and demonstrated HQL benefits in patients with high-grade gliomas.



Figure 1. MRI of a patient with a right frontal glioblastoma before surgery.



Figure 2. MRI of the same patient after surgery.

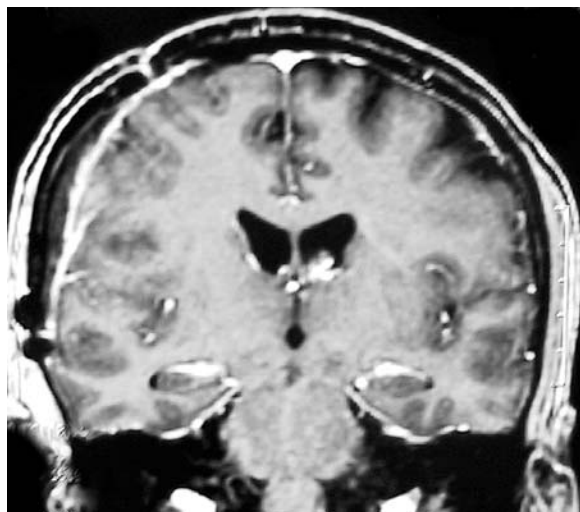


Figure 3. MRI of the same patient after radiotherapy and chemotherapy at follow-up of 18 months.

2. INTRODUCTION

The treatment of high-grade gliomas is still problematic, and there are no clearly established and universally accepted chemotherapeutic regimens available at this time. Although, nitrosoureas are considered the most effective first-line agents despite the lack of reliable data; there is indeed no evidence at this time of any advantage for combination treatment versus single agent chemotherapy nor there is any indication about which one is the best treatment to start with (1-3).

Temozolomide a new orally administered agent, is an imidazotetrazine derivative; its mechanism of action is methylation of guanine residues in the tumour cell DNA, thus creating a mismatch that the repairing enzyme system cannot fix since it cannot find a base complementary to methylated guanine; this ultimately leads to cell cycle arrest. Temozolomide exerts a good anti-tumour effect in a wide variety of cancers, particularly in the forms resistant to conventional drugs. Its effect is dose dependent and the most frequent minor side-effect is nausea (4-7).

3. MATERIAL AND METHOD

12 patients with newly histologically-diagnosed high-grade glioma (GBM and AA), were enrolled into this clinical trial. Histopathological diagnosis was obtained after surgical resection, the purpose of surgical treatment was cytoreduction of tumour mass to the maximum extent consistent with optimal preservation of neurologic function. In phase I of the study, TMZ (75 mg/m²/day per 7 days/wk for 6 weeks) was orally administered to patients concomitantly with radiotherapy (RT) (2 Gy per fraction once daily, per 5 days/wk for 6 weeks). In phase II of the study, four weeks after completion of RT, a monochemotherapy using TMZ was administered orally in a fasting manner at the dosage of 200 mg/m²/day for the first 5 days and then repeated every 28 days for 6 cycles. Primary end-points were the safety and tolerability profile of this two-phase combined treatment and secondary end-points were the objective response, survival rates expressed as overall survival and progression-free survival and improvement of performance status measured by Karnofski score.

Baseline assessments including medical history, physical and neurological examination, haematological and clinical chemistry and KPS evaluation, were performed both at admission and repeated immediately before initiation of treatment as well as at 4 weeks, 3 and 6 months thereafter and at any time of disease progression (DP). The objective tumour assessment (mass-volume) was done by a gadolinium-enhanced MRI which was taken at baseline, and then at 3, 6 and 12 months and at any time of DP. The assessment of tumour response was based on MRI scan supported by neurological examination and KPS determination in the context of steroids use. The initiation of a new treatment cycle was based on haematological criteria (absolute neutrophilic cells count $>1.5 \times 10^9/l$, platelet $>100 \times 10^9/l$).

Table 1. Patient characteristics and survival

Characteristics	Value (%)
Population	
Age 21-50	4 (33.4)
Age >50	8 (66.6)
Sex	
Male	9 (75)
Female	3 (25)
Outcome	
Complete response	2 (16.66)
Partial response	2 (16.66)
Stabilization of disease	6 (50)
Progression of disease	2 (16.66)
Survival	
median progression-free survival	8.35 months
overall survival	14.1 months
time to progression	36 weeks

4. RESULTS

The overall response rate (only responsive patient) for all histological type was 33% (4 patients), 6 patients (50%) showed a stabilization of disease (Table 1). The median progression-free survival and overall survival was respectively 8.35 and 14.1 months; time to progression was 36 week ranging from 20 to 46. Among the patients treated with temozolomide two cases of complete response (figure 1, figure 2, figure 3), 2 partial response and 2 progressive disease were observed. In 6 cases the disease stabilized and out of them in 27% a significant neurological improvement was detected by Karnofski score. In all patients, surgical and adjuvant treatment with radiotherapy and chemotherapy with temozolomide was associated with improvement of performance status including the patient showing disease progression; Karnofski score improved in all patients by a minimum of 10, with a median of 20 at 6 months. Concomitant RT plus TMZ (phase I) followed by adjuvant TMZ (phase 2) were well-tolerated; indeed, nonhematological adverse events were rare and mild in severity; we have registered only two case of drug related nausea and vomiting, successfully managed by pharmacological therapy. The combination of radio- and chemo-therapy, in phase I of the study did not significantly increase the incidence and severity of hematological toxicity caused by radiotherapy and during the adjuvant TMZ-based chemotherapy administered in phase II of the study we didn't record any neutropenia or piastrinopenia as described in other series.

5. DISCUSSION

Anaplastic astrocytomas and glioblastomas are the most frequent and most malignant hemispherical tumours. Unfortunately, astrocytic tumours are of infiltrative character and radical removal is not possible. Recurrent malignant gliomas are rarely suitable for reoperation. In most of the cases of recurrent gliomas chemotherapy is the last choice (8-11).

Continuous research into new strategies and chemotherapy agents for the treatment of malignant high-

grade gliomas have led to the synthesis of a new chemotherapy drug, temozolomide (TMZ), with a lower toxicity profile compared to conventional chemotherapy agents, such as nitrosoureas. Temozolomide is an oral alkylating chemotherapy agent licensed for the treatment of recurrent high-grade gliomas, anaplastic astrocytoma and glioblastoma multiforme. Because of its favourable pharmacokinetic and pharmacodynamic properties and improved tolerability, TMZ is has been the subject of several trial for its use as chemotherapeutic agent in newly-diagnosed GBM (12-16).

Nowadays, the aim of chemotherapy in patients with high-grade gliomas is palliation in the attempt of improving neurological function or preventing neurological and globally health-related quality of life (HQL) deterioration (17,18). During this study, we evaluated the activity and safety of temozolomide as single first-line agent. The primary end-points were PFS and function benefits assessed by a validated instrument such as KPS. A review of the literature suggests that an agent demonstrating 6 months PFS of 10% or more should be considered active. In our series we observed a PFS at 8.35 months and OS was 14.1 months, being higher than observed in other reports following various combination regimens. Twelve patients with large lesion area underwent debulking surgery; and then they were selected for early radiation and chemotherapy; it did not make any difference in the outcome and globally in the functional status. Considering that the goal of palliative treatment is to reduce disease burden and improve or avoid HQL deterioration we found that all patients had benefits independently from the objective response rate tested by gadolinium-enhanced MRI including the patients who showed a DP. Surgery alone does not result in a higher survival rate for GBM and AA patients. However, surgery allows to establish a histopathological diagnosis, to improve signs and symptoms which are attributable to intracranial hypertension or tumour topography, and to reduce the number of target cells for adjunctive therapies. Radiotherapy improves survival and TMZ chemotherapy that is given after radiotherapy adds survival benefit for patients (19-22).

Temozolomide is effective in treating anaplastic astrocytomas and glioblastomas independently of debulking surgery and/or radiotherapy. The response rates obtained using temozolomide were at least comparable if not better than those reported after first- and second-line treatments using for example procarbazine, irinotecan, topotecan, taxans, idarubicin, etc. as a single-agent or in various and different association regimens (23,24). Temozolamide treatment was also associated with a relatively prolonged PFS, substantial improvement of HQL tested by KPS, safe and well-tolerated profile that makes patients able to sustain intense and continuous cycles of therapy (25). The use of this drug should be explored more extensively as single-agent or in combination regimens starting as front-line settings in consideration of already clinically proven effectiveness and promising the possibility of employment in different ways and doses possibly by continuous administration to achieve better and prolonged results by increasing its therapeutic level (26).

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Abbreviations: TMZ: Temozolomide; OS: overall survival; PFS: progression-free survival; HQL: health-related quality of life; GBM: glioblastoma; AA: anaplastic astrocytoma; RT: radiotherapy; KPS: Karnofski performance score; DP: disease progression

Key Words: Surgery, Chemotherapy, Radiotherapy, High-Grade Gliomas, Temozolomide

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