Rechallenge with temozolomide in recurrent glioma

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Abstract Despite a confirmed survival benefit associated with adjuvant radio- and chemotherapy, the majority of patients with malignant glioma relapse after initial therapy. Recurrent malignant glioma treatment has not been standardised and usually the response rate to standard chemotherapy protocols for recurrent malignant glioma is less than 30%. The growing body of evidence demonstrating the clinical importance of O6-methylguanine methyltransferase (MGMT) has generated a considerable interest in the exploration of strategies to overcome MGMT-mediated resistance to alkylating agents; for example protracted administration of Temozolomide (TMZ) may result in more extensive and sustained depletion of MGMT; for this reason a variety of dosing schedules that increase the duration of exposure and the cumulative dose of TMZ are being investigated for the treatment of patient with recurrent malignant glioma after standard treatment. The most widely studied regimens in this setting include (1) 21 of 28-day schedule at a dose of 75–100 mg/m²/day; (2) 7 of 14-day schedule at a dose of 150 mg/m²/day, also referred to as the “one week on/one week off” schedule; (3) Continuous daily schedule at a dose of 50 mg/m²/day. An alternative dosing schedule of TMZ may be a reasonable option in patients having high-grade gliomas with recurrence after standard therapy.

Keywords Temozolomide · Recurrent glioma · Salvage chemotherapy · Dose-dense

Malignant gliomas are very aggressive tumors and, despite recent improvements in their treatment, almost always relapse after a first-line therapy.

Treatment of recurrent malignant gliomas has not been standardised. In fact there is no consensus on the optimal approach for this group of patients, especially nowadays that recurrence occurs after the use of Temozolomide (TMZ) as first-line chemotherapy, in patients treated with many cycles (often more than six) of adjuvant therapy.

Temozolomide is an oral alkylating agent with established antitumor activity in patients with primary brain tumors and melanoma. It was shown to significantly improve survival in patients with newly diagnosed glioblastoma (GBM), when administered in concomitance with radiotherapy (RT) and as maintenance therapy [1]. Several studies have suggested that resistance to alkylating agents is primarily mediated by O6-methylguanine methyltransferase (MGMT) that repairs the DNA damage caused by TMZ. It has also been showed that methylation of the MGMT promoter may correlate with improved survival in patients treated with RT plus TMZ, suggesting that tumors with low levels of MGMT protein (caused by epigenetic gene silencing) may respond better to TMZ than do tumors with high MGMT levels [2]. MGMT can effectively repair TMZ-mediated DNA damage, but in this process the enzyme is consumed.

The growing body of evidence demonstrating the clinical importance of MGMT has generated an interest in the exploration of strategies to overcome MGMT-mediated resistance to alkylating agents. In fact, it has been demonstrated that TMZ could decrease MGMT activity in
peripheral mononuclear cells, and that protracted administration of TMZ results in more extensive depletion of MGMT [3].

Many patients with high-grade glioma receive TMZ as part of their initial treatment and typically experience disease progression during or within a few months after completing first-line therapy. Rechallenge is defined as the re-use of a therapeutic agent that had been used previously in the same patient. In the recurrence setting, the repeated administration of TMZ with the same schedule of the first line has not generally been recommended because of the risk of cumulative toxicity and for the possibility of chemoresistance. However, alternative dosing schedules may increase the duration of exposure and the cumulative dose of TMZ are being investigated for the treatment of recurrent glioma, with the goal of improving antitumor activity and overcoming resistance. This has focused the attention on alternative therapeutic regimens with prolonged application of increased doses of TMZ per 28-day cycle to overcome resistance to the conventional regimen. Alternative dosing schedules may result in higher cumulative doses than the standard 5-day regimen and may deplete tumour-derived O6-methylguanine DNA methyltransferase (MGMT) in tumour cells, thus sensitizing tumor cells to the toxic effects of TMZ.

The most widely studied regimens in this setting include,

- 21 of 28-day schedule at a dose of 75–100 mg/m²/day.
- 7 of 14-day schedule at a dose of 150 mg/m²/day (also referred to as the “one week on/one week off” schedule).
- Continuous daily schedule at a dose of 50 mg/m²/day.

Franceschi et al. [4] in 2005 reported the results in 14 glioma patients who received a second course of TMZ for the treatment of disease progression or recurrence after an initial course of TMZ. Objective response or stable disease was achieved in six patients, and the 6-month progression-free survival (PFS) was 36%; no significant cumulative toxicity or hematologic malignancy was observed in this cohort of patients.

Several studies have tested the 21/28-day schedule at doses ranging from 75 to 100 mg/m²/day. Strick et al. [5] reported the data of 21 patients with recurrent malignant gliomas pre-treated with TMZ (18 GBM and 3 grade III gliomas), treated at progression with TMZ 100 mg/m²/day on 21/28 schedule; PFS at 6-months (PFS-6) was 39% and in particular, 2/7 patients with unmethylated MGMT promoter were progression-free for more than 6 months. As toxicity concerned generally, patients tolerated this dose-dense regimen quite well and in particular hematological toxicity was mild and manageable.

The RESCUE study has hypothesized that a continuous regimen of 50 mg/m² TMZ could overcome resistance to standard therapy. The authors treated 120 patients with malignant glioma (GBM and AA) at progression after standard chemotherapy with TMZ 5/28 with continuous dose-intensive TMZ 50 mg/m²/day for up to 1 year or until progression occurred. The PFS-6 was 23.9% in GBM patients and 35.7% in AA patients, and grades 3 and 4 hematologic toxicities were uncommon [6].

Wick et al. [7] conducted a retrospective review of patients with recurrent glioma during TMZ therapy re-treated with different alternative TMZ regimens (standard 5/28 schedule, 75 mg/m²/day on days 1–21/28, 1 week on–1 week off, metronomic at 40 mg/m²/day). The PFS-6 was 48% in patients with anaplastic astrocytoma and 27.7% in those with GBM. All TMZ-based regimens were well tolerated and in particular, toxicity in patients treated with the 40 mg/day continuous schedule was grade 1 or 2.

Concerns have emerged regarding an increase in infections with these alternative schedules of treatment. The dose intensity achieved in this case does not appear to significantly increase the frequency of thrombocytopenia or neutropenia, but in some studies the reported incidence of selective lymphopenia is high, particularly in patients treated with the 21/28-day schedule.

For this reason, patients treated with dose-dense TMZ regimens are at increased risk for opportunistic infections such as Pneumocystis carinii pneumonia (PCP). It is not clear if the high rate of lymphopenia could be directly correlated to a high rate of infections. For example, Tosoni et al. [8] reported a 12% rate of infection due to lymphopenia during a 21/28-day regimen for recurrent malignant glioma. However, a similar rate of infection was not observed by other authors [9].

In conclusion, alternative dosing schedules of TMZ may be a reasonable option in patients with high-grade recurrent gliomas after standard therapy. In particular, intensive and prolonged TMZ schedules could be considered for patients with unmethylated MGMT to overcome the possible drug resistance.

Conflict of interest The authors declare that there is no actual or potential conflict of interest in relation to this article.

References