

Update on Therapeutic Advances in Brain Tumors – Impact of a Phase III Trial of Temozolomide with Radiotherapy for Newly Diagnosed Glioblastoma

a report by

Warren P Mason, MD, FRCPC

Staff Physician, Princess Margaret Hospital, and Associate Professor, University of Toronto



Warren P Mason, MD, FRCPC, is a Staff Physician at Princess Margaret Hospital, Toronto, and an Associate Professor of Medicine at the University of Toronto. He co-chairs the Brain Disease Site Group of the National Cancer Institute of Canada Clinical Trials Group. His main research interest is in the treatment of brain tumors, particularly glioma, with an emphasis on novel drug evaluation for glioblastoma. He received an MD from the University of Toronto in 1987, and trained in medicine and neurology at McGill University, Montreal, and the University of Toronto, and in neuro-oncology at Memorial Sloan-Kettering Cancer Center in New York.

Introduction

Primary brain tumors are uncommon neoplasms that represent only 2% of all cancers. Glioblastoma multiforme (GBM), the most common of these neoplasms, is a devastating and intractable cancer.¹ Survival for patients with GBM has been brief, with most patients not surviving more than nine to 12 months following diagnosis. This is a dismal outcome that had not changed significantly until recently, despite decades of intense research. Optimal management of GBM includes maximal surgical resection followed by conventional radiotherapy. The use of adjuvant chemotherapy, usually nitrosourea-based, has been controversial because most large phase III trials have failed to demonstrate a statistically significant survival advantage for patients who receive chemotherapy as part of their initial treatment.² However, some studies have shown that long-term survival is greater for patients who received adjuvant chemotherapy (a 5% increase in survival at two years, from 15% to 20%).³ Such interpretations of results that explore the value of adjuvant chemotherapy have resulted in a geographic divergence of practice patterns. In the US, chemotherapy has been routinely administered adjuvantly; in Europe and elsewhere, it has been reserved for recurrence.

Until recently, first-line chemotherapy for GBM has been nitrosoureas, usually carmustine or lomustine.

For the past seven to eight years, a novel methylating agent, temozolomide, has been commercially available for malignant gliomas, including GBM.⁴ Structurally similar to dacarbazine, temozolomide is an oral agent with excellent penetration into the central nervous system (CNS). It is very well tolerated with few significant side effects – the most common of which is dose-dependent myelosuppression – usually thrombo-cytopenia, and fatigue. The absence of known long-term side effects including cumulative myelo-suppression, are features that makes extended exposure feasible. Until recently, temozolomide was only approved for the treatment of recurrent malignant gliomas. In the US, approval was granted only for anaplastic astrocytoma, while in Europe and most other developed countries, the agent was also approved for recurrent GBM. The reasons for variable approved indications were complex and based on divergent interpretations of registration trials that incorporated a novel end-point, progression-free survival at six months, which was not universally accepted as a valid outcome.^{5–7} Nonetheless, temozolomide has been widely used in the US and elsewhere, and is currently the most commonly prescribed drug for GBM and other gliomas. A recent study that explored temozolomide concurrently and adjuvantly with radiotherapy for newly diagnosed GBM has been recently reported by investigators in Europe and Canada.⁸ This trial is the first to show a statistically significant and clinically meaningful

1. DeAngelis L, "Brain tumors", *N. Engl. J. Med.* (2001);344, pp. 114–123.
2. Medical Research Council Brain Tumor Working Party, "Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial", *J. Clin. Oncol.* (2001);19, pp. 509–518.
3. Stewart L, "Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomized trials", *Lancet* (2002);359, pp. 1,011–1,018.
4. Stupp R, Gander M, Leyvraz S, Newlands E, "Current and future developments in the use of temozolomide for the treatment of brain tumors", *Lancet Oncol.* (2001);2, pp. 552–560.
5. Yung W K A, Albright R E, Olson J et al., "A phase II study of temozolomide versus procarbazine in patients with glioblastoma multiforme at first relapse", *Br. J. Cancer* (2000);85, pp. 588–593.
6. Yung W K A, Prados M D, Yaya-Tur P et al., "Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse", *J. Clin. Oncol.* (1999);17, pp. 2,762–2,771.
7. Brada M, Hoang-Xuang K, Rampling R et al., "Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse", *Ann. Oncol.* (2001);12, pp. 259–266.
8. Stupp R, Mason W P, van den Bent M J et al., "Radiotherapy plus concomitant and adjuvant temozolomide for newly diagnosed glioblastoma", *N. Engl. J. Med.* (2005); 352, pp. 987–996.

survival advantage for patients who received temozolomide chemotherapy as part of their initial treatment. This trial, the results of which will be presented in detail, has provided sufficient evidence for approval of this regimen for newly diagnosed GBM in the US and is likely to become the new standard of care (SOC) for this disease worldwide.

Study Design, Results and Safety

A large randomized phase III trial involving 573 patients from 15 countries and 85 medical centers has recently been reported by the European Organisation for the Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).⁸ This trial randomized patients with newly diagnosed GBM to either radiotherapy alone or radiotherapy with concurrent and adjuvant temozolomide. This trial was undertaken to confirm favorable but preliminary phase II results using this regimen.⁹ The basis of the regimen itself, which involves continuous and prolonged exposure to temozolomide during and after radiotherapy, was based on *in vitro* evidence that temozolomide acts synergistically with radiotherapy, and the observation that chronic temozolomide exposure depletes the cellular enzyme responsible for alkylator/methylator resistance, O⁶-methylguanine methyltransferase (MGMT).^{10,11}

Patients were enrolled within six weeks of the diagnosis of a newly diagnosed histologically confirmed GBM. Treatment was initiated within one week of randomization. The characteristics of both groups were well balanced at baseline. Median age was 56 years (range 18 to 70 years); World Health Organization (WHO) performance status was 0–2, and 84% of patients had surgical resection.

The control group received fractionated focal irradiation at a dose of 2Gy daily for five days each week for a period of six weeks (total dose 60Gy in 30 daily fractions). The group randomized to the experimental therapy received radiotherapy as prescribed above with concomitant temozolomide chemotherapy administered at a dose of 75mg/m²/day for the duration of radiotherapy (42 consecutive days, but not to exceed 49 days if radiotherapy was interrupted). Following a four-week hiatus, patients were treated with up to six cycles of

adjuvant temozolomide according to the standard five-day schedule administered every 28 days. Temozolomide was given at 150mg/m²/d for the first cycle and increased to 200mg/m²/d for the second and subsequent cycles if the first cycle had no serious toxicity.

In the group receiving concomitant radiotherapy/temozolomide, 85% completed treatment as planned. Concomitant temozolomide was stopped prematurely in 37 patients (13%). Adjuvant monthly chemotherapy was initiated in 223 patients (78%) who received a median of three cycles; 47% of patients completed six cycles of adjuvant temozolomide. The main reason for failure to start or complete adjuvant temozolomide was disease progression. The primary end-point was overall survival while secondary end-points were progression-free survival, safety, and quality of life (QOL).

The data were analyzed at a median follow-up of 28 months, at which time 480 patients (85%) had died. Median survival for patients randomized to radiotherapy alone was 12.1 months compared with 14.6 months for those randomized to radiotherapy with temozolomide. The addition of temozolomide to radiotherapy reduced the risk of death by 34%. The two-year survival rate was 26.5% in patients randomized to radiotherapy/temozolomide compared with 10.4% in the control group. Median progression-free survival was 6.9 and five months, respectively. All survival data were highly statistically significant ($p < 0.001$) and strongly favoured the group randomized to radiotherapy plus temozolomide. The only patients who received limited benefit from combined modality treatment were those who had biopsy only or who had poor performance status.

Both concurrent temozolomide/radiotherapy and adjuvant temozolomide were well tolerated. Severe grade 3 or 4 myelosuppressive toxicity occurred in less than 5% of patients in the combination arm. Adverse events were analyzed during radiotherapy (with or without concomitant temozolomide), adjuvant therapy, and the entire study period from entry until disease progression or last follow-up. No grade 3 or 4 hematologic toxicity was reported in the group treated with radiotherapy alone. Overall, grade 3 and 4 hematologic toxicity was reported in 19 patients (7%) during concomitant temozolomide/radio-

9. Stupp R, Dietrich P-Y, Kraljic S O et al., "Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide", *J. Clin. Oncol.* (2002);20, pp. 1,375–1,382.
10. Tölcher A, Gerson S, Denis L et al., "Marked inactivation of O⁶-alkylguanine-DNA alkyltransferase activity with protracted temozolomide schedules", *Br. J. Cancer* (2003);88, pp. 1,004–1,011.
11. Wedge S, Porteous J, Glaser M, Marcus K, Newlands E, "In vitro evaluation of temozolomide combined with X-irradiation", *Anticancer Drugs* (1997); 8, pp. 92–97.

therapy; grade 3 or 4 neutropenia was seen in 12 patients (4%), and grade 3 or 4 thrombocytopenia in nine patients (3%).

During adjuvant chemotherapy, grade 3 or 4 hematologic toxicity was reported in 14% of patients, 4% had grade 3 or 4 neutropenia, and 11% had grade 3 or 4 thrombocytopenia.

Severe infections were reported in six patients (2%) in the radiotherapy group and in nine patients (3%) receiving concomitant temozolomide/radiotherapy. Severe infections were reported in 12 patients (5%) receiving adjuvant temozolomide therapy.

The most common non-hematologic toxicity during radiotherapy was moderate–severe fatigue in 26% of the control group and 33% of those who received concomitant temozolomide. Thromboembolic events occurred in 16 patients in the control group and 12 in the radiotherapy/temozolomide group, for a total of 28%. Pneumonia was reported in five patients and three patients, respectively; opportunistic infections occurred in one patient in each group.

At a median follow-up of two years, no evidence of treatment-induced, late-toxic effects has been seen, including cognitive deficits and the development of secondary hematologic malignancies.

At study completion, 512 patients (268 in the radiotherapy-alone group and 244 in the temozolomide/radiotherapy group) had disease progression. In both groups, 23% of patients underwent further resection, and 72% of the control group and 58% of the radiotherapy/temozolomide group received further chemotherapy. Response to salvage chemotherapy was not recorded.

Who Benefits from Treatment

Despite the excellent results obtained from this trial, not all patients with GBM responded to temozolomide and benefited from the combined treatment. A companion study to the randomized trial has reported that methylation of the MGMT promoter (i.e. MGMT silencing) in GBM tumor samples of patients enrolled in the study was a strong and independent prognostic factor for prolonged survival, and an independent predictor of benefit from the combined modality treatment.¹² The main

mechanism of cellular resistance to temozolomide is believed to be expression of MGMT, and silencing of the MGMT promoter in a tumor cell results in low expression of this enzyme.¹³ In the author's study, the MGMT promoter was methylated in 45% of 206 evaluable cases. For patients whose tumors had a methylated MGMT promoter, median survival was 21.7 months for patients who received temozolomide compared with 15.3 months for those who only received radiotherapy as part of their initial treatment. More impressively, two-year survival was 46% for patients with heavily methylated MGMT who received temozolomide concomitantly and adjuvantly with radiotherapy. MGMT promoter methylation status therefore appears to be the first molecular genetic determinant of outcome and treatment response for GBM.

Limitations of the Study and Future Directions

While concomitant and adjuvant temozolomide chemotherapy with radiotherapy is likely to become an SOC for most patients with newly diagnosed GBM, it is not a cure, and further therapeutic advances are required. The author's study was not designed to examine the relative benefits of the concurrent compared with the adjuvant phase of temozolomide therapy, and given the gravity of this disease, it is unlikely that a trial will be conducted to investigate directly this issue. More importantly, it is not clear at this time whether this regimen has been optimized for maximal benefit, and perhaps better results can be achieved by prolonging and intensifying the duration of the adjuvant phase of temozolomide treatment. Future trials for GBM will determine whether treatment intensification of temozolomide can improve upon the striking results obtained in this study. Treatment intensification by administering more temozolomide for a longer duration has two goals – firstly, it may provide further benefit to patients whose tumors have a methylated MGMT promoter, and are already benefiting from temozolomide exposure, and secondly, it may prove to be of particular benefit to those patients whose tumors do not express methylated MGMT promoter and who are currently not receiving much benefit from temozolomide as it was administered in the author's study.

Methylation status of the MGMT promoter was a strong and independent prognostic factor for survival and a predictor of treatment response in the phase III

12. Hegi M, Diserens A-C, Gorlia T et al., "MGMT gene silencing and benefit from temozolomide in glioblastoma", *N. Engl. J. Med.* (2005);352, pp. 997–1,003.

13. Esteller M, Hamilton S, Burger P, Baylin S, Herman J, "Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia", *Cancer Res.* (1999);59, pp. 793–797.

trial conducted by the EORTC and NCIC. These results were obtained retrospectively, and were based on results from 206 of 573 patients who were enrolled. For these reasons, methylation status of the MGMT promoter needs further evaluation, and plans are underway to incorporate this molecular marker as a stratification factor in future phase III trials of GBM. Moreover, MGMT promoter status is not the only marker of response and resistance to temozolomide chemotherapy. In the author's study, a number of patients whose tumors had methylated MGMT promoter had a poor outcome even when treated with combined chemoradiotherapy. Future trials for GBM will have translational research strategies integrated into their design to identify other potential molecular markers for favorable outcome and response to therapy.

Conclusions

The phase III trial of temozolomide with radiotherapy for newly diagnosed GBM conducted by the EORTC and NCIC has defined a new SOC for this disease. It represents a major advance in the management of GBM, and will serve as the touchstone for subsequent studies that will build on these promising results. It is likely that this regimen will also be studied in some way in other malignant gliomas such as anaplastic astrocytoma and oligodendroglioma. While this trial justifies the use of temozolomide chemotherapy for GBM, a great deal more work is required if this disease is ever to be curable or even controllable, and new agents with activity against GBM will need to be identified for such advances to occur. ■