

Treatment of Newly Diagnosed Glioblastoma with Concomitant and Adjuvant Temozolomide and Radiotherapy

UK Experience

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Abstract

Background and aim: In the UK, the current management of high-grade gliomas consists of maximal surgical debulking, where possible, followed by radiotherapy. A large, randomized, multicenter trial assessing the addition of temozolomide to radiotherapy found a significant increase in median survival of the order of 2.5 months in favor of the combined treatment (14.6 vs 12.1 months; $p < 0.001$). Our center has considerable experience with temozolomide and has treated patients with a regimen similar to that used in the above trial. The aim of this study was to confirm whether these results are translated into a benefit when used in clinical practice in the UK.

Material and methods: We present a retrospective study of 86 patients treated for glioblastoma with radiotherapy with or without temozolomide between 1998 and 2003. A search of our radiotherapy database was undertaken and patient records were accessed for histopathology, chemotherapy, and radiotherapy information. Patients who were diagnosed with glioblastoma and who did not receive radiotherapy or only received a palliative dose were excluded from the study. Radiotherapy was administered at a dosage of 60–65Gy in 30–37 fractions over 6 weeks. Temozolomide was administered orally at a dosage of 75 mg/m² daily for 6 weeks throughout the radiotherapy, followed by adjuvant temozolomide given for 6 cycles on days 1–5 of a 28-day cycle (150–200 mg/m²/day).

Results: Eighty-six patients (59 male and 27 female; mean age = 55.1 years, range 25–72) with glioblastoma were planned to receive treatment with a radical dosage of radiotherapy. Forty-eight patients (56%) underwent surgical debulking. Forty-nine patients (57%) received concurrent temozolomide and radiotherapy followed by adjuvant temozolomide (median number of cycles received was three). Thirty-seven patients (43%) initially received radiotherapy alone, although nine of those received chemotherapy on further disease progression. Three patients died before treatment was completed. The decision to treat with temozolomide was influenced by the availability of the drug. There were no identifiable patient factors influencing the decision for radical radiotherapy alone or combined radiotherapy and temozolomide. Patients treated with concurrent temozolomide and radiotherapy had a significantly better median survival of 13 months compared with 8 months for those treated with radiotherapy alone ($p < 0.003$).

Conclusion: The addition of temozolomide to the standard treatment of radiotherapy for glioblastoma improved overall survival. This study shows that the published phase III results in a selective group of patients can be replicated in everyday practice and that the combined regimen is both practical and effective.

In the UK, the current management of high-grade gliomas (WHO grades III and IV) consists of maximal surgical debulking,

where possible, followed by radiotherapy. This achieves a median overall survival of 11–36 months for grade III and 5–12 months

for grade IV tumors.^[1,2] There is clearly interest regarding whether these poor survival figures can be further improved with the development of adjuvant therapy. Meta-analyses suggest adjuvant (particularly nitrosourea-based) chemotherapy is associated with improved survival.^[3]

Temozolomide is an orally active alkylating agent, derived from dacarbazine, with a good safety profile.^[4] There are numerous phase I and II studies to suggest efficacy in patients with WHO grade IV glioma, with response rates as high as 30–40%.^[5,6] A randomized phase II study of temozolomide versus procarbazine in patients with recurrent glioblastoma showed a significantly improved 6-month progression-free survival in favor of temozolomide (21% vs 8%; $p = 0.008$),^[7] although procarbazine is rarely used alone in the UK. Observations such as these have led the National Institute for Health and Clinical Excellence (NICE) in the UK to issue guidance on the use of temozolomide as second-line chemotherapy in high-grade gliomas at the point of first relapse, recurrence, or progression in patients expected to live for longer than 12 weeks.^[8]

In 2002, Stupp et al.^[9] reported on the use of temozolomide as adjuvant treatment with radiotherapy. A phase II trial revealed that concomitant radiotherapy and temozolomide followed by 6 months of adjuvant temozolomide potentially conferred a survival advantage in patients with glioblastoma. This led to a multicenter, phase III, randomized trial of combined treatment versus radiotherapy alone involving 573 patients and 85 centers. After a median follow-up of 28 months, a significant increase in median survival was demonstrated, of the order of 2.5 months, in favor of the combined treatment (14.6 vs 12.1 months, $p < 0.001$; hazard ratio for death in the combined group was 0.63 [95% CI 0.52, 0.75]).

Our center, the Neuro-oncology Group, Charing Cross Hospital, London, UK, has considerable experience with temozolomide and has treated patients with a regimen similar to that used by Stupp et al.^[9] We present here the results of a retrospective study of 86 patients treated with radiotherapy with or without temozolomide for glioblastoma in our center between 1998 and 2003.

Methods

Between 1998 and 2003, we treated 86 patients with a radical course of external beam radiotherapy following a diagnosis of glioblastoma. Patient records were accessed and demographic data, original histopathologic diagnosis, and chemotherapy and radiotherapy information were obtained, along with the dates of diagnosis and death and any available toxicity data, including blood results. The original histologic sections were retrieved from

the files of the Department of Histopathology and reviewed by an experienced neuropathologist to update grade and histologic diagnosis according to criteria of the current WHO classification.^[10]

Patients who were diagnosed with glioblastoma and who did not receive radiotherapy or those who received only a palliative dose were excluded from the study. There were no intended deciding factors as to which patients should receive radiotherapy alone and which should receive combined treatment. Patients who were fit for radical radiotherapy were deemed fit enough for combination treatment (all patients had WHO performance status 0, 1, or 2). The choice of treatment options was made principally according to the availability of temozolomide for adjuvant use, but was also influenced by patient choice. Surgical debulking or diagnostic biopsy was performed at the discretion of the treating neurosurgeon and was chiefly influenced by tumor site and accessibility.

Radiotherapy was administered at Charing Cross Hospital, typically at a dosage of 60Gy in 30 fractions over 6 weeks. A minority of patients (24%) received 65Gy in 37 fractions. External beam radiotherapy was delivered conformally, either conventionally simulated or CT planned. Temozolomide was administered orally at a dosage of 75 mg/m² daily for 6 weeks throughout radiotherapy. This was followed by a planned course of adjuvant temozolomide given for six cycles on days 1–5 of a 28-day cycle. The dosage of the first cycle was 150 mg/m²/day and 200 mg/m²/day for the five further cycles. Patients receiving temozolomide were given prophylactic cotrimoxazole 480mg twice a day on Mondays, Wednesdays, and Fridays during concomitant chemoradiation.

Statistical Analysis

Kaplan-Meier survival curves were plotted for both treatment groups. Survival data were calculated from the date of initial tissue diagnosis. Log-rank testing was performed to assess the equivalence of survival in both groups. Survival was also assessed by primary surgical procedure, which is a possible confounding factor of known prognostic significance. Patients were grouped into those undergoing initial surgical debulking versus those undergoing only diagnostic biopsy.

Results

Eighty-six patients entered this study. The mean age was 55.1 years (range 25–72) with 59 males and 27 females. Thirty-eight patients (44%) underwent a surgical biopsy and 48 (56%) underwent a debulking procedure prior to the planned radiotherapy. Table I shows the baseline patient and tumor characteristics and treatment schedules received. It can be seen from table I that the

Table I. Patient and tumor characteristics

Characteristic	Overall (%)	Chemoradiotherapy group (%)	Radiotherapy group (%)
No. of patients	86	49	37
Age (y)			
Mean	55.1	51.8	58.4
Range	25–72	28–71	25–72
Gender			
Male	59	35	24
Female	27	14	13
WHO performance status			
0	51 (59.3)	29 (59.2)	22 (59.5)
1	18 (20.9)	11 (22.4)	7 (18.9)
2	17 (19.8)	9 (18.4)	8 (21.6)
3–4	0	0	0
Surgery			
Biopsy	38 (44.2)	21 (42.9)	17 (45.9)
Debulking	48 (55.8)	28 (57.1)	20 (54.1)
Radiotherapy dosage			
60Gy in 30 fractions	50 (58.1)	34 (69.4)	16 (43.2)
65Gy in 37 fractions	21 (24.4)	7 (14.3)	14 (37.8)
Other fractionations	15 (17.4)	8 (16.3)	7 (18.9)

distributions of performance status and surgical procedures do not vary between treatment groups.

The reviewed histologic sections confirmed the diagnosis of glioblastoma in 69 cases. Seventeen cases (all stereotactic biopsies) showed an astrocytic tumor with lower-grade features (WHO grade II or III). In all these cases, neuroimaging features were consistent with glioblastoma, indicating a sampling error. Of these 17 patients, eight were in the chemoradiation group, eight in the radiotherapy only group, and one died before commencing treatment.

Of the 86 patients planned to undergo radiotherapy, three deteriorated such that they were unable to receive the full planned treatment. Nine patients underwent radical radiotherapy followed by chemotherapy on further disease progression. In this group the second-line chemotherapy used included irinotecan, procarbazine, or temozolomide. These patients were classified as receiving radiotherapy alone for purposes of the survival analysis by intention-to-treat. Forty-nine patients (57%) received combined chemoradiotherapy and 37 (43%) received radical radiotherapy alone as the initial treatment. Of the patients treated with adjuvant temozolomide, 17 (35%) completed the six cycles. Reasons for stopping included disease progression, bone marrow suppression, and patient choice. The median number of cycles received was three.

The radiotherapy dosage received was predominantly 60Gy in 30 fractions (58%), although a proportion (24%) received 65Gy in 37 fractions. The choice of dosage schedule was in line with the departmental policy of the time. Fifteen patients (17.4%) received different radiotherapy doses because treatment had to be cut short as a result of toxicity (seven patients), patient deterioration (three patients), or patient choice (five patients). Six of these were in the combined chemoradiotherapy group and nine in the radiotherapy only group. For the purpose of analysis, these patients were included in the original intention-to-treat category.

Patients with poor performance status were offered palliative doses of radiotherapy, chemotherapy alone, or best supportive care and were not included in this analysis. The same clinical oncologist planned all the radiotherapy, and either the clinical oncologist or a single medical oncologist was responsible for prescribing and overseeing the temozolomide treatment. Figure 1 shows the Kaplan-Meier survival curves for the radiotherapy alone versus concurrent therapy groups. Those patients treated with concurrent temozolomide and radiotherapy followed by adjuvant temozolomide had a significantly better median survival of 13 months compared with 8 months for those treated with radiotherapy. Log-rank tests gave a hazard ratio of 0.52 in favor of the combined treatment group (95% CI 0.30, 0.88, $p < 0.003$).

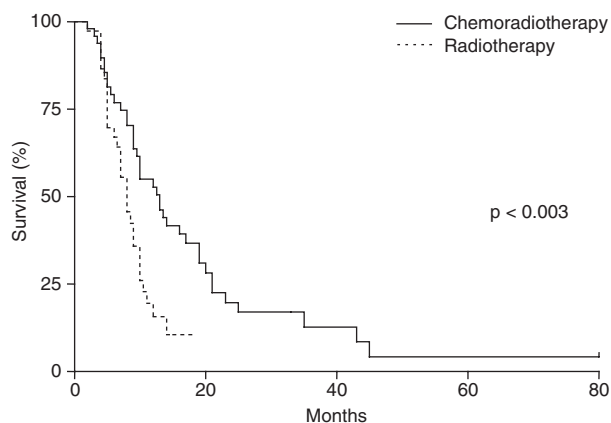


Fig. 1. Kaplan-Meier survival curves for patients with glioblastoma treated with combined temozolomide and radiotherapy vs radiotherapy only.

Overall survival by primary surgery is shown in figure 2 (debulking surgery [n = 48] vs biopsy only [n = 38]). Median survival for patients who underwent debulking surgery was 10 months compared with 9.5 months for those who had a biopsy alone (hazard ratio of 1.16 for the debulked group [95% CI 0.72, 1.89; $p = 0.53$]).

Table II shows the hematologic toxicity data by treatment group. Toxicity grades are in accordance with the Common Terminology Criteria for Adverse Events (CTCAE version 3.0).^[11] Because of the retrospective nature of the study, the toxicity data are incomplete, but from the information available there appear to be no significant differences in the rates of leukopenia, neutropenia, lymphopenia, anemia, or thrombocytopenia between patients receiving chemoradiotherapy and those receiving radiotherapy alone. There were insufficient data available to report on other measures of toxicity.

Discussion

The presentation of data from a randomized study of concomitant and adjuvant temozolomide with radiotherapy, conducted by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada Clinical Trials Group, has widened the interest in the use of temozolomide as an adjuvant treatment for grade IV astrocytomas.^[12] There appears to be a significant improvement in both progression-free and overall survival compared with that achieved by the standard treatment of radiotherapy alone. However the current UK guidelines do not recommend the use of temozolomide as adjuvant treatment.^[8] Many centers treating brain tumors will have had little experience with temozolomide in this role. The purpose of this retrospective study was to determine whether the impressive results seen in the EORTC study are translated into a benefit when used in standard clinical practice in the UK. Our center has had

considerable experience with temozolomide since the early phase I studies and has been treating patients with combined temozolomide and radiotherapy in the adjuvant setting for the past 7 years.

It is recognized that this is a retrospective review, so the choice of radiotherapy alone versus radiotherapy plus temozolomide is clearly open to bias. There were no identifiable factors in the decision between the two treatment groups except for the availability of temozolomide. Patient factors such as performance status did not bias the choice of one modality of treatment over another, and this is confirmed by the distributions shown in table I.

The trial by Stupp et al.^[12] was restricted to glioblastomas, and, although we have treated some grade III patients with a similar regimen, for the purposes of this analysis we present the data for patients initially diagnosed with glioblastoma only. All cases had neuroimaging features consistent with glioblastoma. Although our expert review of the histologic sections confirmed glioblastoma in only 69 of the 86 cases (80.2%), this is not unusual. Previous studies have shown stereotactic biopsy and surgical resection specimens to differ in tumor grading in up to 49% of cases.^[13] We show that the patients receiving the combined treatment have a significantly improved overall survival compared with those receiving radiotherapy alone ($p < 0.003$). The survival benefit is of a similar magnitude to that seen in the large multicenter trial, although the absolute survival figures are lower. It should be noted that in the study by Stupp et al. more patients received maximal debulking surgery (84%) compared with our study (55.8%). However, in our group of patients, we found no differences in survival by primary surgical procedure.

Given the retrospective nature of this study, the toxicity data are incomplete and confined to those reported in the patient records. We report the available hematologic toxicity data, but there was insufficient information for any reasonable comment on other

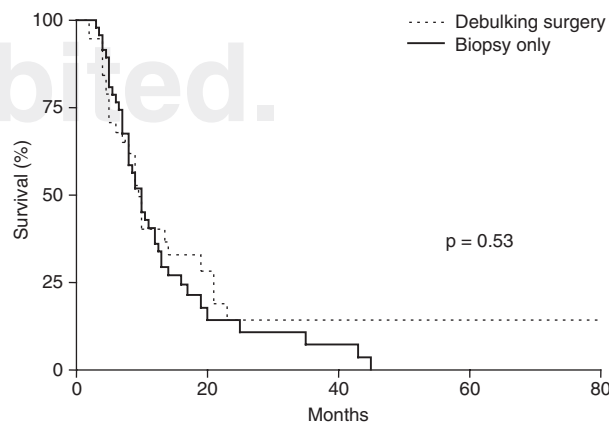


Fig. 2. Kaplan-Meier survival curves for patients with glioblastoma undergoing maximal debulking surgery vs those undergoing biopsy only.

Table II. Incidence of hematologic toxicity data by treatment group. Toxicity grades are in accordance with the Common Terminology Criteria for Adverse Events (CTCAE version 3.0^[11])

Toxicity	Chemoradiotherapy group – concurrent period (%; n = 49)	Chemoradiotherapy group – adjuvant period (%; n = 49)	Radiotherapy alone (%; n = 37)
Leukopenia			
Grade 1–2	1 (2.0)	5 (10.2)	0
Grade 3–4	0	3 (6.1)	0
Unknown	10 (20.4)	3 (6.1)	8 (21.6)
Neutropenia			
Grade 1–2	1 (2.0)	3 (6.1)	0
Grade 3–4	0	3 (6.1)	0
Unknown	10 (20.4)	3 (6.1)	8 (21.6)
Lymphopenia			
Grade 1–2	26 (53.0)	18 (36.7)	18 (48.6)
Grade 3–4	5 (10.2)	9 (18.4)	1 (2.7)
Unknown	10 (20.4)	3 (6.1)	8 (21.6)
Anemia			
Grade 1–2	7 (14.2)	8 (16.3)	7 (18.9)
Grade 3–4	0	1 (2.0)	0
Unknown	10 (20.4)	3 (6.1)	8 (21.6)
Thrombocytopenia			
Grade 1–2	11 (22.4)	15 (30.6)	11 (29.7)
Grade 3–4	0	2 (4.1)	0
Unknown	10 (20.4)	3 (6.1)	8 (21.6)

measures such as nausea, fatigue, headaches, erythema, or convulsions. It is our experience, however, that the patients receiving concurrent temozolomide and radiotherapy generally tolerate treatment well, without significant treatment delays. We observed extremely low rates of leukopenia and neutropenia, and the incidence of lymphopenia, anemia and thrombocytopenia was very similar in both the chemoradiotherapy and radiotherapy groups. We acknowledge that the toxicity data may be underestimated in a retrospective study, but our observations are in line with feasibility studies by groups such as Schonekaes et al.,^[14] who found only occasional grade I and II toxicities and no grade III or IV toxicities with combined treatment. Although in the Schonekaes et al. study the radiation dosage was lower (20–30Gy) and the tumors treated were recurrent, the authors found that the patients treated with the combined modality suffered no more adverse effects than patients receiving temozolomide alone.

Conclusion

Our experience with temozolomide is in agreement with the recently reported data from the EORTC and other randomized studies. We agree that temozolomide administered concomitantly

with radiotherapy followed by adjuvant temozolomide appears to confer a survival advantage over the current standard treatment for glioblastoma, although we accept the limitations of a non-randomized retrospective study. The importance of our observations is that they show that the survival advantage in large, multicenter, randomized phase III studies with highly selected patients can be repeated in everyday practice, hence giving further support for combined treatment as the standard of care. We have found temozolomide to be both safe and practical to use in conjunction with radiotherapy for treatment of glioblastoma in a UK cancer center.

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