Concomitant (without adjuvant) temozolomide and radiation to treat glioblastoma: A retrospective study

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Abstract

Between November 2004 and August 2006 we treated 35 patients with concomitant temozolomide (TMZ) and radiotherapy. Twelve patients had very large or multi-centric glioblastoma multiforme (GBM) with a poor performance status and received TMZ plus radiation doses of 45 to 50.4 Gy. Median survival of these patients was only 3.8 months and any benefit from treatment was small. Twenty three patients would have been eligible for randomisation in the EORTC/NCIC trial comparing combined and adjuvant TMZ plus radiation against radiotherapy alone. This group of patients received 60 Gy in 30 fractions plus concomitant TMZ (75mg/m^2) but no adjuvant chemotherapy. At a median follow-up of 26 months, 5 out of 23 patients are alive. The median survival time was 17 months (1.43 years 95% CI 0.96 to 1.55 years). 18% were alive at 2 years. Toxicity from temozolomide was infrequent. This series adds to indirect evidence that the concomitant rather than the adjuvant is the most efficacious part of the EORTC/NCIC schedule for this type of patient. Further trials should include a concomitant chemoradiotherapy regimen as well as a concomitant plus adjuvant chemotherapy

Key words: Brain tumours, Glioblastoma Multiforme, Radiotherapy, Temozolomide

Introduction

Glioblastoma Multiforme (GBM) is the most common and devastating form of brain tumour in adults. Following surgery and postoperative radiotherapy median survival is less than 1 year. Although resection of visible tumour may be possible in up to half of patients, [1] the infiltrative nature of this tumour means complete surgical eradication is rarely possible. The value of postoperative radiotherapy was unequivocally demonstrated by the Brain Tumour Study Group in 1980 [2] but for the next 25 years there was little or no progress in the treatment of this disease. The lack of new treatments contrasts with the very substantial progress seen in the treatments of other cancers, particularly breast cancer, [3] during this time period. In 2002 [4] a meta-analysis of 12 trials of either adjuvant, neoadjuvant or concomitant chemotherapy plus radiotherapy showed a modest but significant survival increase when chemotherapy was combined with radiotherapy. The most common agent used was lomustine. This study showed a significant prolongation in survival associated with chemotherapy with a hazard ratio of 0.85 (95% CI 0.78 to 0.91 $p = <0.001$). This was equivalent to a 2 month's increase in median survival time. The authors' conclusion was the small but clear improvement in survival from chemotherapy encouraged further studies of drug treatment for these tumours.

The most influential study was carried out by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) [1]. This was a randomised trial of treatment of GMB by radiotherapy alone compared with radiotherapy plus concomitant and adjuvant temozolomide (TMZ). TMZ is an oral alkylating agent which previously has been shown to have significant activity when used to treat recurrent high grade glioma [5]. In the EORTC/NCIC trial 573 patients were randomised either to radiotherapy alone (60 Gy in 30 fractions) or radiotherapy plus TMZ. Temozolomide was given in 2 phases; initially at a dose of 75mg/m^2 for 7 days a week from the first to the last day of radiotherapy. This was followed by 6 cycles of adjuvant TMZ ($150 - 200\text{mg/m}^2$) for 5 days during each 28 day cycle. This trial showed a significant advantage for the combination of radiation and TMZ compared to radiation alone. At a median follow-up of 28 months the median survival was 14.6 months with

radiation and TMZ and 12.1 months for radiation alone. The two year survival rate was 26.5% with radiation plus TMZ versus 10.4% with radiation alone.

Although the trial design did not allow a distinction between the relative contribution of the concomitant and maintenance components of the schedule, information in the study and in a paper published simultaneously [6] suggested that the concomitant phase was the most important. Benefit from TMZ seems to be restricted to patients suffering from a GBM with epigenetic silencing of the methylguanine methyl transferase gene (MGMT) by methylation following TMZ treatment. MGMT is a DNA repair enzyme and is a cause of resistance both to alkylating agents and radiation therapy [7]. In total 45% of 206 assessable cases were shown to have epigenetic silencing of the MGMT gene using methylation specific polymerase chain reaction analysis. Clinical benefit was restricted to this group of patients and was not seen in those without methylation of MGMT. Silencing of MGMT gene leads to diminished DNA repair and is likely to make radiotherapy more effective. Almost three quarters (72%) of patients with tumour progression after radiotherapy alone received chemotherapy and in most cases (84%) the agent used was TMZ. However TMZ administered on relapse did not substantially alter survival. Although 85% of patients completed the planned combined radiotherapy and TMZ, many patients failed to complete the adjuvant part of the schedule. The median number of cycles given was 3 (range 0 – 7).

When the results of the EORTC/NCIC trial were presented at ASCO in June 2004 we asked the Primary Care Trust (PCT) to fund TMZ. This was not possible in the absence of National Institute of Clinical Excellence (NICE) guidance. This was not forthcoming until June 2007. However as the concomitant part of the schedule seemed to be the most important component, the hospital cancer directorate agreed to fund concomitant TMZ (but not the adjuvant cycles). The money was found from existing resources. As the treatment we could offer patients was significantly different from the full EORTC schedule, we planned to audit the results of this policy. This retrospective study examines the results of treatment of GBM patients treated by concomitant TMZ and radical radiotherapy.

Materials and Methods

A retrospective review was carried out of pharmacy, radiotherapy and departmental registry databases to identify patients with GBM treated by concomitant TMZ and radiotherapy under the local policy between November 2004 and August 2006.

During that time, if the tumour was either multicentric or extremely large, patients received whole brain or very large field radiotherapy with treatment doses of 45 – 50.4 Gy in 25 – 28 fractions. In those with less extensive disease, received a tumour dose of 60 Gy in 30 fractions given over 6-weeks using 6mV X-rays. The volume irradiated was the contrast enhanced tumour volume plus a 3 cm margin of apparently uninvolved brain. All patients began radiotherapy within 6 weeks of surgery or biopsy if inoperable. TMZ was given at a dose of 75mg/m² by mouth starting on the first day of radiotherapy and ending on the last day of therapy. The antiemetic metoclopramide was prescribed at 10mg three times a day. Patients were reviewed along with the previous day's full blood count and serum biochemistry at least once a week during chemo radiation therapy, and toxicity was recorded using the common toxicity scale.

Overall survival (OS) was calculated from the date chemo radiation started to the date of death. For those patients still alive, their OS was censored at the date they were last known to be alive. Kaplan-Meier estimates of OS survival curves, median survival times and 95% confidence intervals were obtained [8]. The hazard ratio for comparing between the extent of disease groups was estimated using Cox proportional hazards regression [8].

Results

A total of 35 patients were identified who were suffering from a GBM and received radiotherapy plus TMZ and their survival data were updated in April 2008. In 12 cases the volume of brain requiring irradiation would not tolerate a dose of 60 Gy as used in the EORTC trial. The 23 patients with less extensive disease received the trial dose of 60 Gy. Amongst those with

extensive disease patients, 8 (67%) had a performance status (PS) of 2 or more whilst in those with less extensive disease 16 (70%) had a PS of 1 (Table 1). It is noteworthy that 21 (91%) of the less extensive were treated by debulking surgery, while for those with extensive disease more than half (58%) had biopsy only mainly due to their large, multicentric disease.

The combined treatment was remarkably well tolerated with 85% of patients showing no evidence of toxicity. No patients suffered nausea and vomiting, perhaps in part due to prophylactic metoclopramide and concomitant steroid administration. Two patients had raised liver transaminases (raised ALT), grade 2 and 3 respectively. This was more likely due to anticonvulsant medication than TMZ. Haematological toxicity was confined to two patients one who developed grade 2 thrombocytopenia which led to a dose reduction. The second patient (who had very extensive tumour) had grade IV thrombocytopenia. This was of sudden onset and the TMZ was discontinued immediately. Five weeks elapsed before the plate count returned to >100 and during this time period the patient developed a grade III anaemia requiring transfusion.

Of the 35 patients treated, 5 remain alive all with the less extensive disease at diagnosis (Table 1). Amongst those with very extensive disease the median survival time is 3.8 months (95% CI 0.7 to 8.1) none are alive beyond 13.8 months. For those with less extensive disease the median is 17.1 months (11.5 to 18.6) with an estimated proportion alive beyond 2 years of 18%. The survival curves are shown in Fig 1 and the hazard ratio reflecting the relatively poorer outcome in those with very extensive disease is 7.4 (95% CI 2.9 to 18.1, $p < 0.001$).

Discussion

The survival of patients with very large or multi-centric GBM often with a poor performance status was poor with a median survival of only 3.8 months. It is doubtful whether they benefited from treatment. Our experience again emphasises the value of performance status in predicting outcome following treatment of brain tumours. By contrast, the group of 23 patients who would

have been eligible for randomisation for the EORTC trial seem to have benefited from TMZ, as their survival was superior to our previous experience when patients were treated by only radiotherapy. Survival is also compatible with that seen in the two randomised trials published so far. The EORTC/NCIC [1] study of 287 patients treated by concomitant TMZ and radiotherapy followed by adjuvant TMZ reported a median survival of 14.8 months and a 2-year survival of 26.5% with a median follow-up interval of 28 months. A large Greek randomised phase 2 study [9] reported a similar median survival of 13.4 months in a group of 57 patients receiving a standard dose of 75mg/m² during radiotherapy followed by an intensified adjuvant schedule of 150mg/m² TMZ day 1 – 5 and 15 – 19 every 28 days. As response and subsequent improvement in survival following radiotherapy is so reliant on epigenetic silencing of the MGMT gene, increased survival in a small series may be heavily influenced by the number of patients with methylation of the MGMT gene. Clearly we do not know our patients' MGMT status. In the EORTC/NCIC series 45% of patients had MGMT promoter methylation. Clearly if the number in our series was more than 45% it could explain the median survival of 17 months. However, this small retrospective series suggests that the concomitant component of the EORTC/NCIC chemoradiotherapy regimen is the most important. Currently we are following the NICE Guidelines and giving suitable patients both concomitant and adjuvant TMZ. However the results of this small retrospective series would suggest that a concomitant chemoradiotherapy arm should be compared with patients treated by chemoradiotherapy plus adjuvant therapy in any future randomised trials.

Conflict of interest statement

None of the authors have any conflict of interest.

Table 1 Patient characteristics and current survival status

Extent of disease		Very Extensive	Less Extensive (satisfy EORTC protocol criteria)
Number	n	12	23
Age (years)	Median (range)	68 (19 – 81)	61 (23 – 75)
Gender	Male (%)	9 (75)	16 (70)
WHO	0	2	5
performance	1	2	16
status	2	5	-
	3	1	-
	4	2	-
	Not recorded	-	2
Extent of	Biopsy only (%)	7 (58)	2 (9)
surgery	Debulking (%)	5 (42)	21 (91)
Alive (%)		0 (0)	5 (22)

Fig 1 Actuarial survival curve of patients treated with concomitant temozolomide and radiotherapy (EORTC – patients eligible for the EORTC trial. Non EORTC – ineligible patients)

References

1. Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Eng J Med* 2005; 353:987-96
2. Walker MD, Green SB, Byar DP et al. Randomized comparison of radiotherapy and nitrosoureas for the treatment of malignant gliomas after surgery. *N. Eng J Med* 1980;303:1323-9
3. Blamey RW, Ellis IO, Pinder SE et al. Survival of invasive breast cancer according to the Nottingham Prognostic Index in cases diagnosed in 1990-1999. *Eur J Cancer* 2007;43:1548-1555
4. Stewart LA. Chemotherapy in adult high grade glioma: A systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002;359:1011-8
5. Stupp R, Gander M, Leyvraz S et al. Current and future developments in the use of temozolomide in the treatment of brain tumours. *Lancet Oncol* 2001;2:522-60
6. Hegi ME, Disereus AC, Gorlia T et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Eng J Med* 2005;352:997-1003
7. Stupp R, Hegi ME, Gilbert MR et al. Chemoradiotherapy in malignant glioma: Standard of care and future directions. *J Clin Oncol* 2007;25:4127-4136
8. Machin D, Cheung Y-B and Parmar MKB (2006). *Survival analysis: a practical approach*. 2nd edn. Chichester, Wiley. Z

9. Athanassiou H, Synodinou M, Maragoudakis E et al. Randomised phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. J Clin Oncol 2005;27:2372-2377