



## Review

# Extended Duration of Adjuvant Temozolomide in Glioblastoma Multiforme – A Review of Trials

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### Abstract

Surgical resection followed by concurrent radiation therapy and temozolomide (TMZ) chemotherapy then adjuvant TMZ is the current standard treatment for glioblastoma multiforme (GBM). There is a lot of controversy regarding the duration of adjuvant TMZ. The standard guidelines recommend 6 months of adjuvant treatment, however in clinical practice in a lot of centers around the world, TMZ therapy is continued beyond 6 months duration. In this review article we will discuss both favorable and unfavorable trials regarding extended TMZ therapy and try to analyze in whom extended TMZ therapy is beneficial and whether or not it should be offered.

**Keywords:** Adjuvant, Glioblastoma Multiforme, Extended duration, Temozolomide

**Cite This Article:** Pruthi DS, Nagpal P, Pandey M. Extended Duration of Adjuvant Temozolomide in Glioblastoma Multiforme – A Review of Trials. EJMO 2021;5(3):217–221.

Gliomas are the most common brain tumor in adults.<sup>[1]</sup> Glioblastoma Multiforme (GBM) is associated with the worst prognosis among the various grades of gliomas. The median overall survival in GBM despite various advancements in medicine still remains poor.<sup>[2]</sup> The standard treatment of glioblastoma multiforme is surgical resection followed by concurrent radiotherapy and chemotherapy in the form of oral Temozolomide (TMZ).<sup>[3]</sup> The treatment has evolved over the last decade from surgery alone to surgery followed by post-operative radiotherapy and currently post-operative chemo radiotherapy followed by adjuvant TMZ.<sup>[4]</sup>

There are a lot of prognostic factors which affect the outcome of treatment in GBM. The extent of resection, performance status and addition of chemotherapy are some well-known prognostic factors.<sup>[5]</sup>

The major landmark study which showed the benefit of

concurrent as well as adjuvant chemotherapy – Temozolomide was done by Stupp et al.<sup>[3]</sup> This is one of the most often quoted study in GBM. They randomized 573 patients who had undergone surgery to receive adjuvant radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) and radiotherapy plus daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. Since the publication of this trial the standard of care for GBM has been surgery followed by adjuvant chemoradiation with TMZ for a period of 6 months. The 5 year update of this trial revealed that the benefits of adjuvant temozolomide with radiotherapy lasted throughout 5 years of follow-up. A few

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**Submitted Date:** May 01, 2021 **Accepted Date:** June 14, 2021 **Available Online Date:** September 24, 2021

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patients in favorable prognostic categories (with MGMT methylation positive) survived longer than 5 years hence showing benefit from the addition of temozolomide.<sup>[6]</sup>

Adjuvant treatment with TMZ for 6 months has become standard of care in GBM cases according to Stupp trial. However in clinical practice in a lot of centers around the world, TMZ therapy is continued beyond 6 months duration. If the duration of this treatment is increased then two aspects need due importance. Firstly whether there is an actual benefit in giving extended duration of TMZ in terms of Progression Free Survival (PFS) or Overall Survival (OS) and secondly whether giving an extended duration of TMZ treatment is leading to an increased level of side effects or toxicity. The guidelines like National Comprehensive Cancer Network (NCCN) state that the duration of adjuvant temozolomide should be 6 months and they also mention that the benefit of extended duration of TMZ is unknown.<sup>[7]</sup> We will discuss various trials in which extended duration of TMZ was given and discuss both these aspects for each trial.

### **Trials**

One of the earlier trials for extended TMZ was done by Hau et al in 2007. They gave temozolomide for at least 12 cycles or 12 months in adjuvant setting and analyzed 128 patients. Patients receiving first-line temozolomide for a median 13 cycles had a median PFS of 14 months. Median OS was 30.6 months with 2 year OS being 68%. TMZ. Median Time to Progression (TTP) was 14 months. A small percentage of patients experienced grade III to IV toxicity. Overall the extended duration of TMZ was well tolerated with a low incidence of TMZ. Major adverse events of patients included grade III or IV thrombocytopenia (10%), leukopenia (7%), gastrointestinal toxicity (5%), and infection (4%). They suggested that long-term treatment with temozolomide was feasible and well tolerated.<sup>[8]</sup>

Barbagallo et al. conducted a retrospective study of 37 patients who underwent surgery and post-operative chemoradiotherapy as per Stupp regimen. Patients were segregated based on duration of adjuvant TMZ therapy duration. Kaplan-Meier curve analysis showed that patients treated with more than six TMZ cycles had OS and PFS that was significantly longer than patients receiving standard treatment (median OS 28 months vs. 8 months); (median PFS 20 months vs 4 months). MGMT methylation status and number of TMZ cycles appeared to be prognostic factors relating to survival in patients with glioblastoma. Prolonged therapy did not confer hematological toxicity or opportunistic infections in either patient group.<sup>[9]</sup>

A study done by Malkoun et al was a retrospective study

assessing prolonged adjuvant temozolomide for more than 6 months after chemoradiotherapy completion in patients with glioblastoma along with the impact of molecular prognostic factors. 37 out of 45 patients were eligible for continuation of extension of TMZ therapy. They found that p53 overexpression was the only significant prognostic factor for PFS, with a median PFS of 9.3 months versus 7 months for patients without p53 overexpression. Overall survival (OS) was 84.8% at 6 months, 54.3% at 12 months, 26.1% at 18 months, and 21.7% at 24 months. Progression-free survival (PFS) was 73.9% at 6 months, 34.8% at 12 months, 15.2% at 18 months and 10.4% at 24 months. 13 patients had grade 3–4 hematological toxicities, including 7 lymphopenia (18.9%) and 4 thrombocytopenia (10.8%). No treatment disruption was needed to be done however 8 patients required dose modification. In terms of molecular analysis they found that p53 overexpression was the only significant prognostic factor for PFS, with a median PFS of 9.3 months versus 7 months for patients without p53 overexpression. The authors suggested that delivering adjuvant TMZ therapy for more than 6 months is feasible in patients with GBM.<sup>[10]</sup>

Darlix et al. conducted a retrospective study of 58 patients comparing survival and toxicity in GBM according to the number of cycles of adjuvant TMZ. Twenty out of fifty eight patients received 9 or more cycles. Prolonged treatment improved PFS and OS without increased toxicity. Extent of resection was found to be a significant prognostic factor. They also found out that the risk of recurrence was significantly higher in the group receiving six cycles of adjuvant TMZ.<sup>[11]</sup>

Bhandari et al. in 2017 assessed 40 patients of GBM in post-operative setting and randomized 20 each to receive RT with concurrent TMZ followed by adjuvant TMZ to either 6 or 12 months. Median OS was 15.4 months and 23.8 months respectively. Median PFS was 12.8 months and 16.8 months respectively. In terms of toxicity analysis 15% in the extended TMZ arm developed grade 3 hematological toxicity. They concluded that extended TMZ leads to an improvement in DFS and OS. In terms of tolerability and safety, the authors interpreted that it does not depend on the cumulative doses of TMZ cycles and in patients who tolerate it well for initial 6-12 cycles continue to tolerate it well.<sup>[12]</sup>

Skardelly et al. also did a study in which they divided patients into groups: those who completed six TMZ maintenance cycles and those continued with TMZ treatment after six cycles. They showed a statistically significant benefit in terms of PFS but not in OS in those patients who received more than 6 cycles of TMZ.<sup>[13]</sup> Median TTP was 13.7 months

in the 6 month group and 20.9 months in the > 6 months group. Prognostic factors included MGMT gene promoter methylation, extent of resection and age at diagnosis. Adverse events were observed more often in the groups that received less than six cycles of TMZ maintenance, intrinsically inverted in correlation to the number of TMZ cycles.<sup>[13]</sup>

Blumental et al conducted an analysis of patient data from 4 randomized trials (EORTC/NCIC 26981-CE.3; EORTC26071-CENTRIC; EMDCORE; RTOG 0525-Intergroup) for newly diagnosed glioblastoma. They investigated a total of 2214 GBM patients in these four trials. 624 patients met their inclusion criteria out of which 333 cases discontinued TMZ after 6 cycles, while 291 patients continued maintenance TMZ up to 12 cycles or until progression. They showed that extended TMZ therapy was associated with an improved PFS (which was more pronounced in patients with methylated MGMT) however there was not a relationship between OS and extended TMZ therapy.<sup>[14]</sup>

Refae et al. randomized 59 patients to 6 cycles of adjuvant TMZ (n=29) or >6 cycles of adjuvant TMZ (n=30). Both OS and PFS were statistically better in the patients receiving extended duration of TMZ (Median PFS of 12.1 months for patients with 6 cycles of adjuvant TMZ versus 18.8 months for patients with more than 6 cycles of adjuvant TMZ) (Median OS of 18.1 and 24.1 months for patients receiving 6 cycles and more than 6 cycles of adjuvant TMZ, respectively). In toxicity analysis almost all Grade 3-4 toxicity were encountered during concurrent chemoradiotherapy. Four patients encountered grade 3-4 hematological toxicity which imposed stoppage of TMZ. In univariate analysis, more than 6 cycles of adjuvant chemotherapy and KFS performance status showed improvement of survival, with no impact on of age or gender.<sup>[15]</sup>

Hsieh et al. conducted a study in Hong Kong in which 14 patients were assessed for outcomes after giving extended TMZ treatment. A significant improvement in PFS was observed in the extended TMZ arm (43.4 months vs. 17 months) with no significant increase in toxicity in the extended TMZ group.

Ehsan Alimohammadi et al. did a systemic review and meta-analysis studying the impact of extended adjuvant temozolomide in newly diagnosed cases of GBM. Seven articles involving 1018 patients were included. They found that overall survival was higher in the case group (>6 cycles TMZ) compared to the control group (6 cycles TMZ). The case group had higher progression-free survival compared with the control group.<sup>[16]</sup>

Seiz et al. showed that long term administration of TMZ in 114 patients affected TTP and OS and it directly correlated with the number of chemotherapy cycles. They also shows

that this long term administration of TMZ was safe and efficacious. Side effects were more prevalent in the early phase of administration and that there is benefit of extended TMZ treatment regardless of extent of surgery or other factors.<sup>[17]</sup>

Urgoiti et al. conducted a population-based analysis from the Alberta Cancer Registry and patient charts to determine the benefit of extended adjuvant TMZ treatment. They found a benefit in both PFS and OS with extended course of TMZ and found that the duration of TMZ treatment to be an independent prognostic factor. At the same time, extended therapy was not associated with increased toxicity.<sup>[18]</sup>

Rivoirard et al. recruited 53 patients who were given a median number of 10 cycles of adjuvant TMZ. The median PFS was 13 months and the median OS was 18.5 months. 41 patients had to stop the extended TMZ treatment with the main reason being tumor progression. Dose reduction had to be done beyond the second cycle of TMZ and the main reason was thrombocytopenia. They concluded that adjuvant TMZ should be continued for more than 6 months in those patients who are good responders.<sup>[19]</sup>

Results of the German RCT done by Herrlinger U et al. (CeTeG/NOA-09) reported that there is benefit with the addition of lomustine to TMZ in methylated GBM which lend further credence to the hypothesis that more intensive and aggressive alkylating chemotherapy is likely to benefit patients with methylated tumors.<sup>[20]</sup>

Liu et al. published a case report of multifocal glioblastoma with deep structure involvement who showed significant benefit with long term adjuvant TMZ treatment. The treatment was well tolerated with no significant side effects.<sup>[21]</sup>

There have been a few studies which don't show significant benefit of extended TMZ treatment. In a study done by Gramatzki et al they found no significant benefit in terms of OS. There was a PFS benefit in the extended TMZ group of nearly 3 months however it was not statistically significant.<sup>[22]</sup>

In the GEINO – 014 study, 159 patients were randomized to extend or not TMZ treatment to 12 cycles after proving lack of progression of the disease in the MRI. The authors did not find any significant difference in 6 month PFS or OS in the extended TMZ group. Patients in the experimental arm had more toxicity (lymphopenia, thrombocytopenia and nausea and vomiting).<sup>[23]</sup> However there has been some criticism regarding this study which was described by Gupta et al. They argued that firstly a non-comparative randomized design with an intrinsic control arm was used which was not so different from the historical trials; secondly there were clear imbalances in baseline patient characteristics; thirdly there was under dosing of TMZ in the ex-

tended adjuvant phase and finally MGMT methylation was not used as a biomarker to enrich the patient population.<sup>[24]</sup>

## Discussion

There is a lot of disparity in the duration of adjuvant TMZ in case of GBM. What is recommended by the guidelines and what is practiced in the clinic seems to vary with a lot of clinicians advocating the use of extended TMZ (longer than 6 months duration). In clinical practice there seems to be a trend in a lot of clinicians across the world of giving an extended duration of TMZ. There is no large scale multicentric randomized control trial to address this discrepancy.

In this review article we have summarized both positive and negative trials. We can see that there is a lot of data supporting the use of extended TMZ and at the same time some trials showing no significant benefit.

The studies which have shown the clinical effectiveness of prolonged adjuvant TMZ for adult patients with high-grade gliomas are mostly small Randomized Control Trials (RCTs), few cohort and retrospective studies. When we look at the trials that lead to benefit of extension of TMZ treatment we need to see which patients actually derive a benefit. Some factors that point to an improved benefit include: MGMT methylation status, good performance status, those who are good responders to the overall treatment (assessed by MRI scan after 6 months) and those who did not have significant toxicity in the 6 months of adjuvant TMZ. In terms of toxicity one important we can see from these trials is that if side effects are to occur they would occur within the initial few cycles. In most of these trials, long term TMZ is generally well tolerated. If extension of TMZ is contemplated then it should be given for 10-12 months duration in total and side effects should be monitored regularly. Dose should be modified in case of side effects. Other factors which should be considered are age, performance status (KPS) and extent of surgical resection. Those patients who would actually derive benefit from long term administration of TMZ should not be denied that benefit. It seems naïve to assume that unmethylated tumors would derive benefit with >6 cycles of TMZ and it stands to reason that only patients with methylated MGMT should be considered for extended adjuvant regimens.

The limitations of these studies are compromised quality and small sample size which emphasizes the need to carry out a large multicentric randomized trial with a large sample size and a long follow up so as to determine the actual benefit in PFS or OS and to assess long term toxicity profile. We also need to take into account various prognostic factors that may help the clinicians to select patients which would derive a benefit of extended duration of TMZ. In this

regard TMH, Mumbai is currently accruing patients on a prospective trial of Biomarker-based Optimization of Adjuvant Therapy (BOAT) in newly-diagnosed glioblastoma (CTRI/2018/11/016349) that randomly assigns patients with methylated MGMT to standard 6 cycles of TMZ versus extended adjuvant TMZ.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – D.S.P.; Design – D.S.P., P.N.; Supervision – P.N., M.P.; Materials – D.S.P., P.N.; Data Collection &/ or processing – D.S.P., P.N.; Analysis &/or interpretation – D.S.P., P.N., M.P.; Literature search – D.S.P., P.N.; Writing – D.S.P.; Critical review – P.N., M.P.

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