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# Temozolomide Alone in Elderly GBM Patients with Poor Performance Status: Is there any Benefit?

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## ABSTRACT

GTR followed by post-op RT with concurrent TMZ followed by adjuvant TMZ is standard of care in GBM. Introduction of TMZ was based on a pivotal study in which patients were mostly 70 years or younger; increasing age was found to be a negative prognostic factor. Efficacy of this adjuvant treatment decreased with advanced age and poor performance status, as they have poor prognosis and do not tolerate this treatment well. In this population, RT alone or RT plus best supportive care or supportive care only or TMZ only tried with varied results. There is always a debate that which of these is better and should be recommended. As radiotherapy comes with the logistic problem of daily visit to hospital, we have reviewed relevant studies to see whether TMZ alone should be recommended to these patients.

**Keywords**: GBM; Temozolomide; Radiotherapy; Kanamycin; Radiation therapy oncology

## INTRODUCTION

### What is Temozolomide?

TMZ is an oral second-generation imidazotetrazine derivative with antitumor activity by methylation of specific DNA sites. Its therapeutic efficacy depends on the methylation of the N-7 or O-6 positions of guanine residues. Besides direct antitumor effect, TMZ is a major radiosensitizing agent. In some tumor cells, resistance to TMZ is driven by the O(6)-Methylguanine-DNA-Methyltransferase (MGMT) enzyme, which is involved in the reparation of alkylating damages. Therefore, epigenetic silencing of the MGMT promoter is predictive of response to TMZ [1].

## CASE PRESENTATION

### Recursive Partitioning Analysis

Prognostic classification of glioblastoma patients is shown in Table 1. In 2005, a study conducted by EORTC-NCIC, showed that addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit in all subgroups in their study except the patients with poor performance status.

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**Table 1:** Prognostic classification of glioblastoma patients.

| RPA class | RTOG (original) | EORTC (adapted) |
|---|---|---|
| | **III** | |
| Age, years | <50 | <50 |
| Tumor type | Anaplastic astrocytomas | Glioblastoma multiforme |
| Mental status | Abnormal | - |
| Performance status | - | WHO PS 0 |
| Age, years | <50 | - |
| Tumor type | Glioblastoma multiforme | - |
| Performance status | KPS 90-100 | - |
| | **IV** | |
| Age, years | <50 | <50 |
| Tumor type | Glioblastoma multiforme | Glioblastoma multiforme |
| Performance status | KPS<90 | WHO PS 1-2 |
| Age, years | ≥ 50 | ≥ 50 |
| Tumor type | Anaplastic astrocytomas | Glioblastoma multiforme |
| Performance status | KPS 70-100 | - |
| Treatment status surgery | ≤ 3 months from time of first symptom to start of treatment | Complete/partial surgery |
| Mental status | - | MMSE ≥ 27 |
| Age, years | ≥ 50 | - |
| Tumor type | Glioblastoma multiforme | - |
| Mental status | Good neurologic function | - |
| Treatment status | Surgical resection | - |
| | **V** | |
| Age, years | ≥ 50 | ≥ 50 |
| Tumor type | Glioblastoma multiforme | Glioblastoma multiforme |
| Performance status | KPS 70-100 | - |
| Mental status | Neurologic function that inhibits the ability to work | MMSE < 27 |
| Treatment status | Surgical resection or biopsy only followed by at least 54.4 Gy radiotherapy | Biopsy only |
| Age, years | ≥ 50 | - |
| Tumor type | Glioblastoma multiforme | - |
| Performance status | KPS<70 | - |
| Mental status | Normal | - |

## RESULTS AND DISCUSSION

### Surgery Followed by Adjuvant RT+TMZ

In 2009, the 5 year follow up data of EORTC-NCIC trial showed that all prognostic subgroups benefit from combined treatment, including patients with impaired performance status or recursive partitioning analysis prognostic class V. Their data suggested that patients with good prognoses benefit most from combined treatment of radiotherapy and temozolamide. The median survival for RPA class III was 14.8 months, for RPA class IV was 13.3 months whereas for RPA class V, it was 9.1 months only. However, these subgroup analyses on few patients lack statistical power and do not justify drawing definitive conclusions [2].

### RT Alone

In 2004, Roa, et al. did a prospective randomized clinical trial to compare standard Radiation Therapy (RT) with an abbreviated course of RT in older patients (≥ 60 yrs) with Glioblastoma Multiforme (GBM). Overall survival measured from randomization were 5.1 months for standard RT versus 5.6 months for the shorter course RT. They concluded that there is no difference in survival between standard RT or short-course RT. In view of the similar KPS scores, decreased increment in corticosteroid requirement and reduced treatment time, the abbreviated course of RT is a reasonable treatment option for older patients with GBM.

In 2005, a retrospective study by Marijnen CA, et al showed that in RPA group V, the median survival for irradiated patients was 9.4 *vs.* 2.1 months for non-irradiated patients. They concluded that for patients with a poor prognosis (*i.e.,* RPA group V), radiotherapy improves survival significantly.

In 2007, Florence did a randomized controlled trial of supportive care only or supportive care plus radiotherapy in patients with 70 year or more and KPS 70 or higher. This study showed that the addition of radiotherapy to supportive care prolongs survival and does not reduce the health-related quality of life or cognitive function of patients. The median survival with radiotherapy plus supportive care was 29.1weeks (7 months) as compared with 16.9 weeks (4 months) with the supportive care alone [3].

In 2012, the Nordic Clinical Brain Tumour Study Group (NCBTSG) did a randomised trial to compare survival, health-related quality of life and safety in post surgery glioblastoma patients with ≥ 70 yrs with single-agent temozolomide chemotherapy, hypofractionated radiotherapy or standard radiotherapy. In comparison with standard radiotherapy, median overall survival was significantly longer with temozolomide 8 years 3 months *vs.* 6 years 0 months with standard RT but not with hypofractionated radiotherapy 7 years 5 months. For age older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy. Patients treated with temozolomide who had tumour MGMT promoter methylation had significantly longer survival than those without MGMT promoter methylation (9 years 7 months *vs.* 6 years 8 months p=0.02), but no difference was noted between those with methylated and unmethylated MGMT promoter treated with radiotherapy. They concluded that standard radiotherapy was associated with poor outcomes, especially in patients older than 70 years. Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma. MGMT promoter methylation status might be a useful predictive marker for benefit from temozolomide [4].

### TMZ alone

In 2003, Glantz et al. did a retrospective review of a cohort of 86 elderly (defined as 70 year age or older) malignant glioma patients who received monthly TMZ in lieu of radiation. Authors concluded that TMZ is as effective as radiation as a treatment of elderly patients with malignant glioma. It is an alternative and perhaps, a superior therapeutic option to irradiation, based on its ease of administration and low morbidity.

In 2010, a study by Florence Laigle-Donadey et al. showed the effect of upfront temozolamide in elderly patients with good performance status. They retrospectively analyzed all patients who were eligible for the Florence Keime-Guibert et al. trial, but who refused to participate and were finally treated with TMZ alone. Overall Median Survival (MS) was 36 weeks and median Progression-Free Survival (PFS) was 20 weeks for the whole group. These preliminary results supported further randomized studies comparing TMZ with RT [5].

In 2011, tried temozolamide alone in elderly patients with poor performance status in ANOCEF phase II trial. Median PFS was 16 weeks and median OS was 25 weeks comparing favorably with a 12-to16-week OS expected from a purely supportive approach. Overall quality of life and cognition improved over time before disease progression. O6-Methylguanine-DNA Methyltransferase (MGMT) promoter methylated status indicated longer PFS (26 months 11 weeks; P=0.03) and OS (31 months 19 weeks; P=0.03) [6].

In 2012, Neurooncology working group (NOA) of the German cancer society conducted a randomized trial (NOA-08) comparing efficacy and safety of RT to Temozolomide (TMZ) in patients with anaplastic astrocytoma or glioblastoma. Patients >65 years with a Karnofsky performance score>60 were randomized without stratification to receive standard RT (60 Gy in 30 fractions) or TMZ in a one week on/one week off schedule. Median OS 8 years 6 months versus 9 years 6 months of TMZ versus RT. Non-inferiority of TMZ compared with RT was significant (p=0.033). Also median Event-Free Survival (EFS) 3 years 3 months versus 4 years 7 months indicating non-inferiority (p=0.043). DNA repair protein O6-Methylguanine DNA-Methyltransferase (MGMT) promoter methylation in tumor tissue tested was associated with prolonged OS 11 years 9 *versus* 8 years 2 months. Patients with MGMT promoter methylation had longer EFS when treated with TMZ 8 years 4 months versus 4 years 6 months with RT, whereas patients without MGMT promoter

methylation had longer EFS when treated with RT 4 years 6 months versus 3 years 3 months with TMZ [7].

In 2013, ANOCEF group published a multicentric, prospective and non-randomised phase II trial evaluating the efficacy and safety of the combination of TMZ with Bevacizumab (BV) as an initial treatment for elderly patients with GBM and KPS<70. Treatment consisted of TMZ 130 mgs/$m^2$/d-150 mgs/$m^2$/d for 5 days every 4 weeks plus BV 10 mgs/kg every 2 weeks, until 12 cycles or tumoral progression. Neither surgical resection nor radiotherapy was performed. Median OS was 24 weeks and median PFS was 16 weeks. This study concluded that TMZ-based treatment is of help in elderly GBM patients with poor KPS. However, the addition of bevacizumab does not appear to be of benefit in term of PFS and OS [8].

In 2016, Ulrich Herrlinger, et al published the randomized glarius trial. They compared Bevacizumab (BEV) plus Irinotecan (IRI) versus temozolomide in newly diagnosed O6-methylguanine-DNA methyltransferase nonmethylated glioblastoma patients. In this phase II, unblinded trial 182 patients in 22 centers were randomly assigned 2:1 to BEV (10 mg/kg every 2 weeks) during Radiotherapy (RT) followed by maintenance BEV (10 mg/kg every 2 weeks) plus IRI (125 mg/$m^2$ every 2 weeks) or to daily TMZ (75 mg/$m^2$) during RT followed by six courses of TMZ (150 mg/$m^2$/d-200 mg/$m^2$/d for 5 days every 4 weeks). BEV+IRI resulted in a superior PFS-6 rate and median PFS compared with TMZ. However, BEV+IRI did not improve OS, potentially because of the high crossover rate. BEV+IRI did not alter QOL compared with TMZ (**Table 2**) [9].

**Table 2:** Patients with MGMT methylated tumours fair better with TMZ.

| Name of the trial | Median survival (months) |
|---|---|
| **RT+TMZ** | |
| EORTC-NCIC | 9.1 |
| **RT alone** | |
| Roa, et al. | 5.6 |
| Marjinen CA, et al. | 9.4 |
| Florence Keime-Guibert, et al. | 7 |
| Nordic trial | 6 |
| NOA trial | 9.6 |
| **TMZ alone** | |
| Glantz M, et al. | Full article to be accesses (Wiley) |
| Florence Laigle-Donadey, et al. | 9 |
| ANOCEF II | 6 (MGMT unmethylated) |
| | 7 (MGMT methylated) |
| NOA trial | 8.6 (MGMT unmethylated) |
| | 11.9 (MGMT methylated) |
| Nordic trial | 8.3 |
| Best supportive care alone | - |
| Florence Keime-Guibert, et al. | 4 |

The results of the studies discussed above suggests that overall survival of the elderly glioblastoma patients with poor performance status is similar with RT+TMZ *vs.* RT alone *vs.* TMZ alone (9 months) [10]. It is also clear that patients with MGMT methylated tumours fair better with TMZ alone. Nordic trial is a randomized trial which clearly shows that in these patients, standard fractionation RT is inferior that TMZ or short course RT. Though survival with best supportive care only is 4 months only as of now, there is no head on trial of TMZ alone *vs.* best supportive care. Though EORTC-NCIC trail updated results in 2009 shows that RT+TMZ has benefit of survival even in RPA V patients it comes with the inconvenience and cost of visiting hospital daily for radiotherapy, toxicity of both the treatment [11].

## CONCLUSION

So as of now, with the available evidences, we will advocate TMZ alone in elderly glioblastoma patients with poor performance status as it will improve the quality of life in such patients while getting the survival benefit similar to concurrent chemoradiation. On the basis of these results, a nihilist attitude toward elderly patients with GBM and a poor performance status is not warranted. Although randomized comparative trials are needed to determine the optimal therapeutic regimens temozolomide alone is a non-inferior option for this fragile population.

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