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Adjuvant Temozolomide Therapy Tolerance in Geriatric Glioblastoma Multiforme Patients

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Abstract

Objective: Glioblastoma multiforme (GBM) is a significant health issue in older patients. In recent years, there has been an increase in the number of studies on radiotherapy and concomitant temozolomide administration. However, there is not enough research on the tolerance of adjuvant temozolomide after this intensive therapy procedure.

Materials and Methods: Patients with GBM who were followed up between 2010 and 2020 were included. Patients were retrospectively screened. Side effect grading of patients was performed using the common terminology criteria for adverse events version 5.0.

Results: In patients ≤65 years old, 79.1% (121) received adjuvant temozolomide treatment for six months or more, whereas this rate decreased to 48.4% (15) in patients >65 years old (p<0.001). In the comparison of hematological toxicities arising during adjuvant temozolomide treatment in the ≤65 years old and older patient groups, no significant differences were found. The rates of patients experiencing grade 2 and above hematologic toxicity (p=0.91) and treatment discontinuation due to hematologic toxicity (p=0.53) were found to be similar in both groups. The median progression-free survival (p=0.004) and the median overall survival were (p<0.001) determined longer in the younger group.

Conclusion: Cancer and aging are dynamic, multidimensional processes that pose challenges to older patients and require multidisciplinary evaluation. Our study showed that although age-related differences in treatment completion and survival outcomes were observed, it is necessary to approach especially older patients individually, considering a comprehensive assessment of their general health status, comorbidities, and treatment tolerance, emphasizing the importance of geriatric oncology.

Keywords: Glioblastoma, temozolomide, geriatrics, older patient, adverse events

Introduction

Glioblastoma multiforme (GBM) is the most common and letal brain tumor in adults. Approximately 50% of newly diagnosed cases occur in patients aged 65 and older (1). Therefore, GBM is a significant health issue in older patients. Despite the use of surgery, radiotherapy, and chemotherapy, the median survival, which is approximately 15 months in the general population, can decrease to 9 months in this older patient group (2,3). Age and the patient's performance status can be listed among the most important negative prognostic parameters (4). The incidence of GBM in patients aged 65 years and older is 2.63 times higher than that in the general adult population (5). Moreover, the prognosis becomes less favorable than the patient's age increases (6). The current standard for GBM treatment is to continue adjuvant monotherapy with temozolomide for six months following adjuvant chemoradiotherapy after surgery. However, studies from population-based cancer registries have shown that older patients with glioblastoma (GBM) are less likely to undergo multiple types of treatment. Data from the surveillance, epidemiology, and end results cancer registry, including 4,137 GBM patients aged 65 years and older who were diagnosed between 1994 and 2002, revealed a median

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overall survival (mOS) of 4 months. Among these patients, 61% underwent surgical resection, 65% received radiotherapy, but only 10% received chemotherapy within 3 months of their diagnosis (7). In recent years, there has been an increase in the number of studies on radiotherapy methods and concomitant temozolomide administration or temozolomide monotherapy for older patients (8). Although phase III randomized studies have shown improved survival in older patients with O6-methylguanine DNA methyltransferase (MGMT) promoter methylation treated with temozolomide, at present, there is insufficient evidence to recommend temozolomide as monotherapy in older patients with GBM who are fit for multimodality treatment as there have been no randomized trials comparing standard chemoradiotherapy to temozolomide monotherapy alone (9). However, there are not enough research available on the tolerance of adjuvant temozolomide treatment after adjuvant chemoradiotherapy intensive therapy procedure (10).

As of today, studies have yet to provide a definitive answer to the questions of whether there is a difference in the tolerance of older GBM patients who have tolerated and completed surgery and adjuvant chemoradiotherapy and whose performance status is between 0-2 to adjuvant temozolomide treatment compared with younger patients, and whether this difference affects survival.

Therefore, our study aimed to compare adjuvant temozolomide treatment tolerance in young and older patients with GBM who have undergone surgical treatment and completed adjuvant chemoradiotherapy and who have ECOG performance scores of 0-2. We will evaluate parameters such as patients' completion of treatment, the most commonly observed hematological side effects, and treatment discontinuation due to side effects in this study. Additionally, the secondary objective of our study was to examine the impact of age on recurrence and survival in a similar patient group with comparable performance status.

Materials and Methods

Patients with GBM who were followed up in the Clinic of Medical Oncology at University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital and Gazi University Hospital between 2010 and 2020 were included in the study. Patients were retrospectively screened. Patients diagnosed with GBM who successfully completed post-surgical adjuvant chemoradiotherapy and continued adjuvant temozolomide treatment were included in the study. Patients with an ECOG performance score of 0-2 before starting adjuvant temozolamide treatment were included in the study. One hundred eighty-six patients were divided into two groups using a cut-off age of 65 years. Follow-up data were obtained from the hospital medical records. Our study has received approval from the Ethics Committee of University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (approval number: 2024-04/45, dated: April 4, 2024).

Toxicities were classified according to the National Cancer Institute common terminology criteria for adverse events (CTCAE) version 5 as follows:

- Grade 1: Mild - Characterized by either no symptoms or mild symptoms that only require observation without any intervention.
- Grade 2: Moderate - Requires minimal or local treatment, which may slightly restrict daily activities and necessitate some help with instrumental activities.
- Grade 3: Severe or medically important but not immediately life-threatening; could lead to hospitalization or extended stay and may affect self-care activities.
- Grade 4: Life-threatening events that require urgent intervention.
- Grade 5: Death caused by adverse events.

According to CTCAE, leukopenia, thrombocytopenia, and anemia are defined as values that are below the lower limit of normal laboratory values.

Statistics

Statistical evaluations were performed using SPSS version 21.0. The chi-square method was used to examine the binary relationships of categorical variables. Kaplan-Meier survival analysis was employed for survival analyses. A p-value of <0.05 was considered statistically significant.

Results

Out of 186 patients, 154 were 65 years or younger while 32 were older than 65 years old. Both groups had similar distributions in terms of the gender of patients, tumor size, and the types of surgeries performed (Table 1). All patients in both groups successfully completed adjuvant chemoradiotherapy and subsequently started adjuvant temozolomide treatment.

In patients ≤65 years old, 79.1% (121) received adjuvant temozolomide treatment for six months or more, whereas this rate decreased to 48.4% (15) in patients >65 years old ($p<0.001$) (Table 2). Although 56.2% of patients under 65 could receive treatment after recurrence, only 40% of older patients could receive treatment. Although there is a numerical difference, no statistically significant difference was observed (Table 2). Of the 48 patients who could not complete the adjuvant temozolomide treatment, 32 (66%) were young, and 16 (33%) were older. It was determined that 18 out of 48 patients could not complete

their treatment due to disease progression or death. Although 11/16 (69%) of older patients could not complete the treatment due to hematological adverse events, it was found that 19/32 (59%) of the young patients had the same reason for treatment discontinuation.

The comparison of hematological toxicities arising during adjuvant temozolomide treatment in the ≤65 years old and older patient groups is provided in Table 3. No significant differences were found between the patient groups in terms of hematologic side effects, including anemia (p=0.72), leukopenia (p=0.82), and thrombocytopenia (p=0.34). The rates of patients experiencing grade 2 and above hematologic toxicity (p=0.91) and treatment discontinuation due to hematologic toxicity (p=0.53) were found to be similar in both ≤65 years old and older patients.

The median progression-free survival (mPFS) was determined to be 16 (min-max: 13.9-18) months in patients under 65 years old and 10 (min-max: 8.4-11.5) months in older patients (p=0.004) (Figure 1). The mOS was determined to be 22 (20-24) months in patients under 65 years old and 11 (6.8-15.1) months in older patients (p<0.001) (Figure 2).

Discussion

The Central Brain Tumor Registry of the United States statistical report showed that GBM is the most common malignant central nervous system tumor in adults. The incidence rates of GBM increase with age, and the median age at diagnosis is 65 years (11). The management of older GBM patients is challenging. This is primarily due to comorbidities, reduced bone marrow reserve, and the potential for decreased treatment tolerance due to worsening performance status, which can be concerning for clinicians. Therefore, the guidelines recommend that the standard STUPP (radiotherapy:total 60 Gy, 2 Gy per daily fraction (Monday to Friday) over 6 weeks and temozolomide: during radiotherapy: 75 mg per square meter of body-surface area per day, 7 days per week,post-radiotherapy (adjuvant) 6 cycles consisting of 150-200 mg per square meter for 5 days during each 28-day cycle) protocol be accessible to older patients with good physical condition. In general, there is no consensus on treatment plans for older patients with glioma and little is known about the standardization of diagnosis and treatment guidelines for older GBM (12).

A decline in performance scores in older patients is an expected outcome. However, as far as we know from the literature, there is no information regarding whether there is a difference

Table 1. General characteristics of the patients

Age (years)	<65	≥65	p
Gender % (n) Female Male	 37.7% (58) 62.3% (96)	 40.6% (13) 59.4% (19)	0.75
Type of surgery % (n) GTR STR Bx	 82.5% (127) 13% (20) 4.5% (7)	 84.4% (27) 15.6% (5) 0%	0.45
Patients who completed adjuvant CRT % (n)	100% (154)	100% (32)	
Patients who received adjuvant temozolamide % (n)	100% (154)	100% (32)	
Tumor size % (n) <5 cm 5-10 cm Undefined	 65.6% (101) 27.3% (42) 7.1% (11)	 58.1% (18) 35.5% (11) 6.5% (2)	0.65

GTR:Gross total resection, STR: Subtotal resection, Bx: Biopsy, CRT: Chemoradiotherapy

Table 2. Patients› survival outcomes

Age (years)	<65	≥65	p
Adjuvant treatment duration (temozolamide)% (n) Treatment for 6 months and above Incomplete treatment	 79.1% (121) 20.9% (32)	 48.4% (15) 51.6% (16)	 <0.001*
Chemotherapy after relapse % (n) Yes No	 56.2% (68) 43.8% (53)	 40% (10) 60% (15)	 0.139
PFS (median month) - (95% CI)	16 (13.9-18)	10 (8.4-11.5)	0.004 (logrank)*
OS (median month) - (95% CI)	22 (20-24)	11 (6.8-15.1)	<0.001 (logrank)*

*statistically significant. PFS: Progression-free survival, CI: Confidence interval, OS: Overall survival

in treatment tolerance between older patients with good performance status and younger patients. Therefore, in our study, we attempted to standardize the impact of the pre-adjuvant treatment performance score on treatment selection and continuation in both groups by comparing older and young patients with good ECOG performance status. Our study found that although older patients tolerated and completed surgery and adjuvant chemoradiotherapy, their completion rates for adjuvant temozolomide treatment were lower than those of younger individuals. One of the key findings of our study was the notable disparity in the duration of adjuvant temozolomide treatment between the two age groups. In most older patients, discontinuation of adjuvant temozolomide treatment was attributed to performance status hematological toxicities (9).

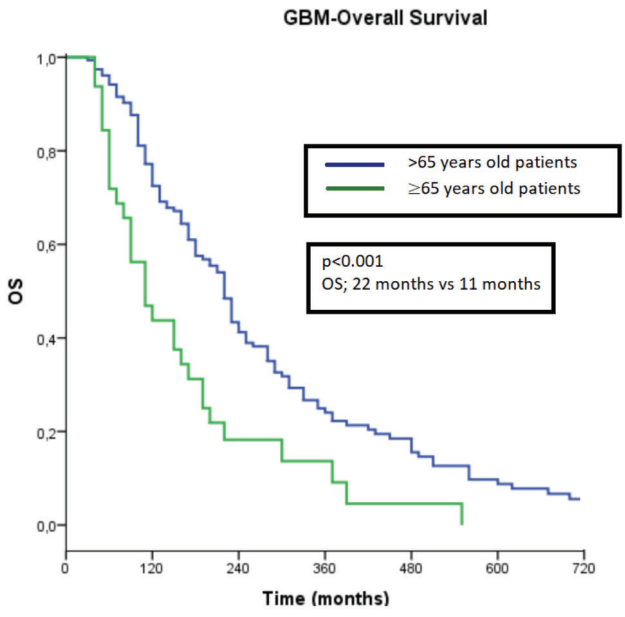

Figure 1. GBM and overall survival (OS)

GBM: Glioblastoma multiforme

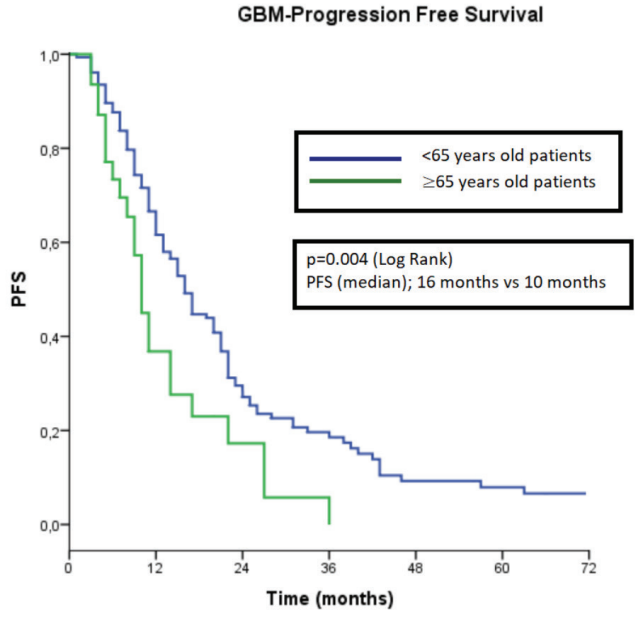

Figure 2. GBM and progression free survival (PFS)

GBM: Glioblastoma multiforme

Table 3. Temozolamide-related hematologic toxicity

Age (years)	<65	≥65	p
Anemia % (n)			
No	71.4% (110)	75% (24)	0.72
Grade 1	22.1% (34)	21.9% (7)	
Grade 2	2.6% (4)	3.1% (1)	
Grade 3	3.9% (6)	0%	
Grade 4	0%	0%	
Leukopenia % (n)			
No	64.5% (98)	62.5% (20)	0.82
Grade 1	19.1% (29)	25% (8)	
Grade 2	8.6% (13)	6.3% (2)	
Grade 3	5.3% (8)	6.3% (2)	
Grade 4	2.6% (4)	0%	
Thrombocytopenia % (n)			
No	64.4% (96)	64.5% (20)	0.34
Grade 1	23.5% (35)	19.4% (6)	
Grade 2	4.7% (7)	12.9% (4)	
Grade 3	2.7% (4)	3.2% (1)	
Grade 4	4.7% (7)	0%	
≥ Grade 2 hematological adverse events % (n)	19.6% (30)	18.8% (6)	0.91
Patients who cannot complete adjuvant treatment due to hematological adverse events	59.4% (19)	68.8% (11)	0.53

Regarding hematological toxicities arising from adjuvant temozolomide treatment, our analysis revealed no significant differences between the two age groups in terms of anemia, leukopenia, and thrombocytopenia. Additionally, the rates of grade 2 and above hematologic toxicity, as well as treatment discontinuation due to hematologic toxicity, were similar in both age groups. The rates of grade 3-4 hematologic toxicity in older patients with GBM are between 10% and 25% in the literature, and in our study, a rate of 19.6% was found for grade 2 or higher hematologic toxicity (13,14). However, although some studies have defined a difference in hematologic toxicity between older and young patients, no statistically significant difference was found in our analysis (15). These conflicting results suggest that age alone may not be a definitive predictor of susceptibility to hematologic side effects and that other individual patient factors, such as performance status, may also play an important role. Although there was no significant difference in hematologic toxicity rates, the percentage of treatment discontinuation due to hematologic toxicity was higher in the older patient group, albeit statistically insignificant. The main reason for this may be that older patients are more fragile and tend to terminate their treatment earlier according to the physician's choice due to treatment-related side effects, and the return of hematologic toxicity takes longer.

Although we did not observe a statistically significant difference, we found that the ability to receive treatment for recurrence was 16.2% higher in the young patient group than in the older group. Similar results have been obtained in studies conducted in the literature on this subject (16). In this result, it has been observed that the performance score at the time of recurrence is influential (16). After adjuvant temozolomide, although the ability to receive treatment after recurrence is statistically equivalent, these numerical differences are reflected in the OS data.

In two key phase studies published in 2012 on older patients with GBM, PFS and OS were found to be shorter than in our study (17,18). The reason for this is that the STUPP protocol was used in the treatment of the patients we analyzed, which is different from the two studies. The evaluation of mPFS and mOS yielded significant distinctions between the two age groups, and these findings are consistent with the literature (19). The mPFS was notably longer in patients under 65 years old (16 months) than in older patients (10 months) ($p=0.004$). Similarly, the mOS was substantially higher in the younger cohort (22 months) than in the older group (11 months) ($p<0.001$). This result was already expected, given that in many studies, a negative impact of age on PFS has been observed (20,21). These findings underscore the potential impact of age on glioblastoma prognosis. One of the main reasons leading to this result is particularly the lower treatment tolerance of older patients after first-line treatment compared with young patients. In addition, publications indicate that the changing tumor microenvironment with increasing age can also impact these outcomes (19,22).

Study Limitations

The present study has multiple limitations. The data collection was conducted retrospectively, and the patients were not randomized. Regarding molecular markers, isocitrate dehydrogenase (IDH) mutations are less common in the older with GBM. Meanwhile, MGMT promoter methylation has been identified in approximately half of patients with GBM (23). The inability to access the retrospective data of molecular analyses of patients such as MGMT and IDH in our study was also another limiting factor that could have affected survival. Nevertheless, the strength of the present work is the standardized collection of patient characteristics, especially the standardization of patients' ECOG performance scores is crucial.

Conclusion

For older patients with newly diagnosed GBM, current management includes surgery, RT, and chemotherapy; however, survival is significantly worse than that observed in younger patients. Cancer and aging are dynamic multidimensional processes that pose challenges to older patients and require multidisciplinary evaluation. Therefore, the results of our study also emphasize the importance of evaluating the general health status of geriatric oncology patients because it suggests that additional factors such as performance status and comorbidities, which change with age as well as age progression, may be at least as important as age in the treatment tolerance of patients. While age-related differences in treatment completion rates and survival outcomes were observed, it is essential to approach each patient individually, considering a comprehensive assessment of their overall health, comorbidities, and treatment tolerance. Research in this area, particularly where geriatric assessment is performed prior to treatmentş, may facilitate the development of more specialized treatment strategies for older patients with glioblastoma.

Ethics

Ethics Committee Approval: Our study has received approval from the Ethics Committee of University of Health Sciences Turkey, University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (approval number: 2024-04/45, dated: April 4, 2024).

Informed Consent: Due to the retrospective character of our study, the 'informed consent form' of the patients was not requested by the clinical research ethics committee.

Footnote

Authorship Contributions

Surgical and Medical Practices: N.Ö., A.Ö., O.Y., C.K., Concept: B.K.İ., O.Y., C.K., Design: B.K.İ., F.G., P.K.T., Data Collection or Processing: B.K.İ., İ.K., G.D.İ., V.B.T., F.G., P.K.T., O.S., İ.Ö., N.Ö., A.Ö.,

O.Y., C.K., Analysis or Interpretation: B.K.İ., F.G., P.K.T., Literature Search: B.K.İ., Writing: B.K.İ., C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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