Original Article

JOURNAL OF ONCOLOGY PHARMACY PRACTICE

J Oncol Pharm Practice
0(0) 1–7

DOI: 10.1177/1078155220968613
journals.sagepub.com/home/opp
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Actual body weight dosing of temozolomide and overall survival in patients with glioblastoma

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Abstract

Background: Adult glioblastoma patients receiving standard radiation therapy and concurrent temozolomide chemotherapy have a median survival of 14.6 months. Based on the pivotal trial data by Stupp et al., temozolomide doses were calculated based on body surface area. However, no details regarding the weight used to calculate body surface area was included in the study. As a result, temozolomide doses have been variable across the province.

Methods: This retrospective chart review was conducted to determine the correlation between dose of first line temozolomide with overall survival. Patients between January 1st, 2009 and December 31st, 2014 who were newly diagnosed, pathology confirmed glioblastoma treated first line with temozolomide within Alberta Health Services were included in the study. Temozolomide doses above and below determined cut points were compared through the Kaplan-Meier method, then assessed using the log-rank test.

Results: A cut point of 97.8% of actual body weight calculated body surface area dosing was determined for concurrent phase temozolomide. At doses above this cut point, there was a statistically significant ($p = 0.0158$) increase of 0.3 years in median overall survival. As for toxicity concerns, there was a statistically significant increase in the proportion of temozolomide dose reductions due to toxicity in patients dosed above the cut point.

Conclusion: Temozolomide doses at full actual body weight calculated body surface area dosing during the concurrent phase is required to achieve a similar median OS as seen in the pivotal trial by Stupp et al.

Keywords

Glioblastoma, temozolomide, overall survival, actual body weight, dosing

Date received: 1 June 2020; revised: 25 August 2020; accepted: 17 September 2020

Introduction

Adult glioblastoma is one of the most challenging malignant solid tumours to treat in oncology. The median survival of these individuals with standard radiation and chemotherapy is 14.6 months (1.22 years).[1] The current standard of care for adult glioblastoma as per the Alberta Health Services (AHS) Clinical Practice Guideline for adult glioblastoma consists of surgery, radiotherapy (RT) and concurrent temozolomide (TMZ), followed by six cycles of adjuvant TMZ.[2]

Temozolomide is an alkylating agent of deoxyribonucleic acid (DNA). Patients with glioblastoma receive a dose of TMZ 75 mg/m^2/day based on body surface area (BSA) for 6 weeks from the first day of RT until the last day of RT, to a maximum of 49 days. Four weeks following the last RT dose, patients are started on adjuvant chemotherapy, with TMZ being administered in the first 5 days of a 28-day cycle for a total of 6 cycles. For the first cycle, TMZ is dosed at 150 mg/m^2/day, and subsequent cycles are dose escalated at

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200 mg/m^2/day. See Figure 1 for the Treatment Schema. Dose adjustments are made for toxic hematologic and non-hematologic effects.

The abovementioned treatment regimen is based on the pivotal trial by Stupp et al. that showed an adjusted hazard ratio for death in the RT plus TMZ group as compared with the RT alone group to be 0.62 (95% CI 0.51 to 0.75).[1] In the study, doses of TMZ were based on BSA, but details regarding the weight used to calculate BSA (actual body weight (ABW) versus ideal body weight (IBW)) and whether or not doses were capped were not included.

In Alberta, concurrent and adjuvant TMZ therapy has been delivered at two sites since 2005. Both the Tom Baker Cancer Centre (TBCC) and the Cross Cancer Institute (CCI) utilize the Mosteller formula to calculate BSA (Figure 2). However, differences in application of the Mosteller formular to temozolomide dosing occurred at the two sites. At the CCI, because of concerns for toxicity, IBW was used for BSA calculation. However, if ABW was less than IBW, then ABW was used for BSA calculation. Ideal body weights were calculated using the Devine formula. At the TBCC, based on concerns for toxicity as well, the dosing of TMZ followed ABW dosing, but with BSA dose cap of 2.0 or 2.2 m^2. Temozolomide is supplied as 5 mg, 20 mg, 100 mg, 140 mg, or 250 mg capsules. For the most part, doses were rounded down to the nearest 5 mg. Each patient's weight was recorded at diagnosis, then again prior to starting concurrent TMZ. During the concurrent phase, TMZ doses were not adjusted. Then, prior to each adjuvant TMZ phase, each patient's weight was recorded again and changed in response to whether their body weight changed during each adjuvant cycle.

The American Society of Clinical Oncology (ASCO) clinical practice guideline addresses the concern surrounding dosing patients with larger body weights, specifically the obese population. The guideline includes the recommendation that "full weight-based chemotherapy doses be used in the treatment of the obese patient with cancer," particularly when the goal of treatment is cure, because dose-response relationships are common for many malignancies.[3] They acknowledge that most of the evidence is from early-stage diseases and that evidence supporting full weight based dosing in advanced diseases is limited.[3] While the guideline makes reference to breast cancers, other gynecological cancers, and other solid tumours, there was no specification for neuro-oncology patients. In the case of glioblastoma, the goal of treatment is not cure and usually, once a glioblastoma lesion is identified through imaging, the tumour is already at an advanced state.[4] Literature and other practice guidelines provide no guidance on TMZ dosing with IBW, ABW, or dose capping. This study will aim to determine whether full weight based dosing is warranted in the glioblastoma patient population as well.

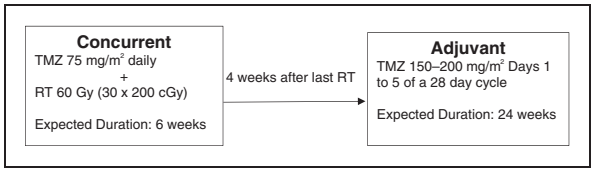

Figure 1. Treatment schema of concurrent therapy.

$$BSA\ (m^2) = \sqrt{ht\ (cm) \times wt\ (kg) \div 3600}$$

Figure 2. Mosteller formula.

Objectives

The primary objective of this study was to determine the association between the dose of first line TMZ, represented as a proportion of ABW based BSA dose, with overall survival (OS). OS is defined as the time from TMZ initiation until death from any cause.

Clinically significant or high grade adverse events, as well as disease progression, result in dose delays, dose reductions, or discontinuations. Therefore, the secondary objective of the study is to determine the incidence of TMZ dose delays, dose reductions, and discontinuations due to toxicities.

Methods

Study design and time frame

A retrospective chart review was performed of patients that were newly diagnosed with glioblastoma between January 1, 2009 and December 31, 2014 and received at least one dose of concurrent TMZ therapy. Data was collected until death from any cause. The concurrent period of treatment was defined as time from day one of RT until 28 days after the last day of RT, or until the first day of adjuvant TMZ therapy. Adjuvant TMZ period was defined as time from the first day of adjuvant TMZ therapy until 35 days after day one of the last cycle of TMZ. Overall survival was defined as time from first day of adjuvant TMZ until death from any cause. Patients alive at the end of the study were calculated from the first day of adjuvant TMZ until the last date of follow-up. Patients alive at the end of the study were censored. Time of death was as indicated in the Alberta Cancer Registry (ACR). Dose delays were defined as TMZ therapy that was rescheduled to 7 days

or later than the original day planned due to toxicity; dose reductions were defined as TMZ dose reductions greater than 10% from the ABW calculated BSA dose because of toxicity; and discontinuations were defined as TMZ discontinuation due to toxicity.

Data sources and collection

Data was accessed from the ACR and electronic medical records (EMRs) including the ARIA® Medical Oncology database and Cancer Control BDM®. Physician documentation was accessed if confirmation of surgery extent or reason for delays, reductions, and discontinuations of concurrent therapy was required.

Inclusion and exclusion criteria

The inclusion criteria for eligible patients included a new glioblastoma diagnosis confirmed through pathology and first line treatment with at least one dose of concurrent TMZ at CCI or TBCC. Patients enrolled in a clinical trial at any point were excluded to minimize confounding, as well as patients less than 18 years of age. Patients with missing data (unknown date of death, unknown dose of TMZ, unknown number of adjuvant cycles) were excluded as well.

Statistical analysis

Descriptive statistics were used to describe the study variables including mean and standard deviations for normally distributed continuous variables, and median and range for non-normally distributed continuous variables. Categorical variables were described using frequency and proportions. To assess the strength of the monotonic relationship between proportions of ABW calculation of BSA dosing of TMZ and OS, and because the data was not normally distributed, Spearman's Rho was used. While the correlation coefficient from Spearman's Rho provided information in terms of unit increase or decrease associated with OS, the applicability of this into clinical practice is limited. Hence, an optimal stratification method based on minimum p-value (maximum chi-square) method was used to dichotomize the continuous data. The dichotomizing of a continuous scale allows for translation of the data into clinical practice by providing a hypothetical cut point. The cut point determined was based on the TMZ dose that provided the minimum p-value or maximum chi-square results. Overall survival and the 95% confidence interval were calculated based on TMZ doses above and below the determined cut point using Kaplan-Meier method. Log rank tests were used to compare the survival curves between the groups. Cox's proportional hazard model were used to determine the factors associated with overall survival. Hazard ratio (HR) and the 95% confidence interval were reported. Multivariate Cox analysis was conducted to study the association of dichotomized TMZ dose with overall survival when accounted for confounding variables. Variables that were expected to confound OS include age, sex, and extent of surgical resection. Two-tailed test of proportions was utilized to determine whether the proportion of TMZ dose delays, reductions, and discontinuations when dosed above the cut point versus below or equal to the cut point are significantly different from each other. A p value less than 0.05 was used for all statistical significant and two-tailed tests were used. All data analyses were conducted using SAS (SAS Institute Inc., Cary, NC) version 9.3 software.

Ethics approval

Ethics approval was received from the Health Research Ethics Board of Alberta Cancer Committee.

Results

Patient enrollment

As seen in Figure 3, a total of 400 patients were newly diagnosed with glioblastoma between January 1st, 2009 and Dec 31st, 2014. Of these 400 patients, 90 patients were excluded and 310 patients qualified for inclusion.

Patient characteristics

Patient characteristics are described in Table 1. Among these patients, there were 202 males (65.1%). The median age was 59 years, with 254 patients (81.9%) being equal to or older than 50 years old. Of the patients with known extent of surgery, a subtotal resection was the most common (39.7%). Only 88 patients (28.4%) had MGMT methylation, while the majority of IDH 1/2 status was unable to be determined.

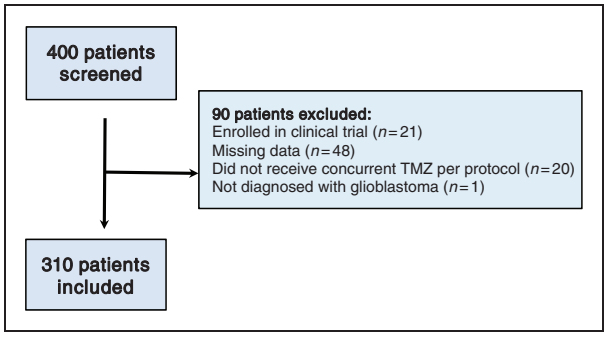

Figure 3. Patient enrollment.

Table 1. Patient characteristics.

Characteristics	Overall (n = 310)	
Sex		
Male	n = 202	65.1%
Female	n = 108	34.8%
Median age, years	59 (range 18-83)	
Age, years		
<50	56	18.1%
≥50	254	81.9%
Extent of surgery		
Biopsy	86	27.7%
Subtotal resection	123	39.7%
Gross total resection	73	23.5%
Unknown	28	9.0%
MGMT methylation		
Methylated	88	28.4%
Unmethylated	75	24.2%
Unavailable	147	47.4%
IDH 1/2 status		
Wild type	108	34.8%
Mutated	8	2.6%
Unavailable	194	62.6%

Table 2. Delivery of therapy.

Characteristics	Overall (n = 310)
Concurrent (Mean)	37.4
TMZ, doses	(SD: 10.4)
RT, weeks	5.3 (SD: 1.6)
Adjuvant, TMZ cycles	
Median	3
Range	0–30
# of dose delays	
Median	0
Range	0–8
# of dose reductions	
Median	1
Range	0–3

Delivery of therapy

As outlined in Table 2, the mean number of concurrent TMZ doses that patients received was 37.4, along with a mean of 5.3 weeks of RT. During the adjuvant phase, the number of adjuvant TMZ cycles ranged from 0 to 30, with a median of 3 cycles.

Overall survival

The correlation between TMZ dose and OS based on Spearman's Rho was poor (−0.02). For this reason, the minimum p-value and maximum chi-square method was used to determine an optimal cut point to dichotomize the TMZ dose and help with interpretation of the TMZ dose. The results of OS with concurrent TMZ divided into % ABW BSA dose groups are described in Table 3. Based on the optimal cut point method, the cut point was determined as 97.8% for ABW calculated BSA dose and the relevant cut point BSA was determined to be 73.4 mg/m^2.

Table 3. OS with concurrent TMZ.

Year	OS probability if >97.8% of ABW BSA dosing	OS probability if ≤97.8% of ABW BSA dosing
1	63.9%	45.8%
2	30.3%	19.0%
3	14.3%	8.4%
Median	1.25 years	0.95 years
(95% CI)	(1.08–1.47)	(0.80–1.11)
p value (Log-Rank)		0.0158

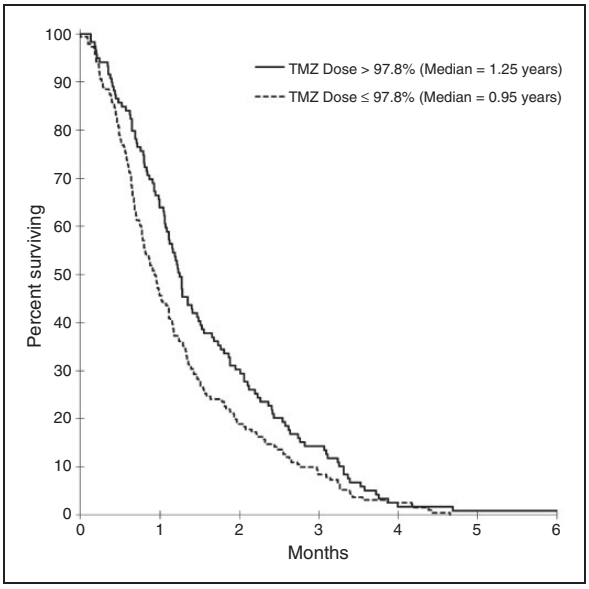

Figure 4. Kaplan Meier curve.

The median OS was 1.25 years (95% CI: 1.08–1.47) for the ABW BSA dosing greater than 97.8% compared to the median OS of 0.95 years (95% CI: 0.80–1.11) for the group with ABW BSA dosing less than or equal to 97.8%. The median OS was statistically different between the two groups ($p = 0.0158$). Table 3 also provides 1 year, 2 year, and 3 year survival probabilities between the two groups. Figure 4 presents the Kaplan-Meier curve for the ABW BSA dosing for the two groups, showing that higher ABW BSA dosing is shown to have better survival as compared to the less than or equal to 97.8% group.

The association of ABW BSA dose with overall survival adjusted for age, gender, and extent of surgical resection was conducted using multivariate Cox's

Table 4. Multivariate Cox regression analysis.

Adjusted for age, sex, extent of surgical resection	*p* Value	Hazard ratio (95% CI) for death
Concomitant TMZ 97.8%	0.0179	0.75 (0.60–0.95)

Table 5. Incidence of delays and reductions.

TMZ	>97.8%	≤97.8%	*p*-value (Test of Proportion)
Delay	38/119 = 31.9%	49/191 = 25.7%	0.23
Reduction	46/119 = 38.7%	48/191 = 25.1%	0.01
Discontinuation	7/119 = 5.9%	14/191 = 7.3%	0.62

proportional hazard model. As seen in Table 4, the results of the adjusted analysis of ABW BSA dose indicated that it was an independent predictor of overall survival. HR was 0.75 (95% CI: 0.60–0.95, $p = 0.0179$).

Incidence of delays, reductions, discontinuations due to toxicities

As seen in Table 5, dose reductions due to toxicity occurred in 38.7% of the group dosed above the cut point and 25.1% in the group dosed at or below the cut point. Dose reductions were the only toxicity occurrence that were statistically significantly different between the two cut point groups ($p = 0.01$). The difference between the two groups in terms of dose delays or discontinuations was not statistically significant.

Discussion

Since the approval of temozolomide use in glioblastoma patients in Alberta, there have been various dosing methods that have been employed. For patients with larger body weights, there was often the concern of toxicity should they be dosed at full ABW based BSA doses. To compensate, dose capping was employed or IBW was utilized for calculating BSA doses. This study demonstrates that higher ABW BSA dosing has better outcomes in terms of median OS. In other words, the group of patients that were dosed closer to 100% of the ABW calculated BSA dose of TMZ had improved median OS. Based on these results, AHS has consolidated how BSA is calculated for TMZ dosing, using ABW in the Mosteller formula and without any dose capping.

Consistently, in the literature, there is evidence that dose reductions may result in poorer survival rates. In a large clinical trial looking at the relationship between toxicity and obesity in women receiving adjuvant chemotherapy for breast cancer, the authors found that patients who received less than 95% of the expected chemotherapy (based on full ABW-based dosing) were found to experience worse failure-free survival.[5] And more recently, in a study conducted by the International Breast Cancer Study group, patients with estrogen receptor negative breast cancer who received less than 85% of the expected dose had significantly worse outcome for disease free survival, with a higher relapse rate and a lower survival rate.[6] Then, in a cohort study looking at patients with primary invasive epithelial ovarian cancers, the authors concluded that dose reduction of paclitaxel and carboplatin was also associated with poorer survival.[7]

The baseline characteristics of patients included in this study coincide with the characteristics of glioblastoma patients in Stupp's trial in terms of sex, age, and extent of surgery.[1] In the study by Stupp et al., the median survival was 14.6 months (1.22 years) in the RT plus TMZ group.[1] Our study's finding that median OS is 14.9 months (1.25 years) with concurrent TMZ and RT similarly coincide with the findings of Stupp et al., but only when patients are dosed above the cut point. Otherwise, for patients who are dosed below or equal to the cut point, the median OS becomes 11.4 months (0.95 years) and is thus, inferior to the findings in the literature. Due to the small number of patients who were still alive at cycle 6 of the adjuvant phase, no analysis or conclusions could be drawn with regards to 2 year survival rate.

Our study's final adjusted HR did not include MGMT methylation status. While we did test the association with MGMT methylation status, we were not able to include this in the final analysis as approximately 50% of the data for MGMT methylation status was not available. In previous literature, patients with MGMT promoter methylation demonstrated an 8 month improvement in median survival with the addition of TMZ, while unmethylated patients derived only a 1 month improvement in median survival.[8] Although MGMT promoter methylation status is a known prognostic factor, our study could not include this in the adjusted analysis as we were limited by the data available for extraction.

A number of patients in our study received greater than 6 cycles of adjuvant TMZ and thus, diverged from the original treatment schema. In a recent publication, the authors found that OS was not affected by continuing adjuvant TMZ beyond 6 cycles.[9] This was based on a study by Blumenthal et al., with Stupp as one of the co-authors and with a much larger sample size.[9] In addition, the belief during the design of Stupp's trial was that it was most important to administer chemotherapy early in the course of the disease, for a

sufficient time, and concurrently with RT.[1] Stupp et al. explained that the additional 6 cycles of adjuvant TMZ were only added in order to ensure sufficient exposure to the drug.[1] As a result, the number of adjuvant cycles was not considered to be a confounding factor and instead, the focus was directed on concurrent therapy.

In the study by Stupp et al., the most common reason (39%) for discontinuation was due to disease progression and only 8% discontinued TMZ due to toxic effects. Even in the retrospective study by Van Vugt et al., where their primary objective was to assess the toxicity profile of TMZ dosed at 300 mg/m^2 on a 3 days on/11 days off regimen in recurrent malignant gliomas, they found that the regimen was generally well tolerated.[10] They reported no adverse events higher than grade 3 and no patients experienced thrombocytopenia higher than grade 2.[10] The most common reason for the 53.3% patients who had a dose reduction was because of thrombocytopenia.[10] The small proportion of patients discontinuing TMZ due to toxicity found in these studies coincide with the recommendation by the ASCO clinical practice guidelines. Their recommendation is to provide full weight-based chemotherapy dosing, because there is no evidence of toxicity at these doses, because most data indicate that myelosuppression is the same or less pronounced at full weight-based doses, and because selecting reduced doses may result in poorer OS rates.[3]

Our study found that there was no statistically significant difference between delays and discontinuations due to toxicities when patients were dosed above versus below or equal to the cut point. However, we did find a statistically significant difference in the proportion of dose reductions due to toxicity between the 2 groups. Hematological toxicities that patients experienced in our study were thrombocytopenia and neutropenia. Non-hematological toxicities included decreased functional status, infections, rash, and elevated liver enzymes.

The study design as a retrospective chart review contributes an inherent risk of bias associated with incomplete patient data. Data collection was limited to the level of detail recorded in documentation notes. As such, quality of life assessment was unable to be determined and likely would require data from a prospectively designed study to assess adequately. Our study also relies on clinicians with regards to the accuracy and consistency at which they adhere to the definition of tumour progression and the interpretation of what determines a diagnosis of glioblastoma and tumour progression. In addition to MGMT methylation status and IDH 1/2 mutation data not being available, the use of corticosteroids, tumour location and volume, and performance status at diagnosis were potential confounding factors that our study did not record. Another point of consideration is that the patients in our study may have received various therapy regimens after discontinuing TMZ and this may have played a role in affecting survival, though this was not recorded in our study. However, overall, the literature has limited evidence for salvage chemotherapy and some clinicians believe that subsequent treatments following adjuvant TMZ are associated with shorter long term survival and potentially increased toxicity.[11] Perhaps a larger sample size may find a correlation between TMZ dose and OS via Spearman's Rho, but this was not feasible within the scope of this project.

Conclusion

In order to maintain a similar median OS as seen in the pivotal trial by Stupp et al., it seems that full ABW based BSA doses of TMZ are required during the concurrent phase. Toxicity concerns at higher doses of TMZ are unfounded.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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