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ORIGINAL ARTICLE

Temozolomide desensitization followed by metronomic dosing in patients with hypersensitivity

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Abstract

Purpose Temozolomide is the most effective chemotherapy for malignant glioma. Hypersensitivity requiring interruption of therapy may significantly impact patient survival. We have successfully employed temozolomide desensitization followed by metronomic dosing of temozolomide. Our purpose was to report patient characteristics and outcomes in patients with glioma (Grade 2–4) and temozolomide hypersensitivity managed by desensitization and metronomic dosing.

Methods We performed an observational study of 15 patients at Mayo Clinic (Rochester) with a diagnosis of glioma who underwent temozolomide desensitization with subsequent metronomic dosing from May 2012 to January 2017. We calculated overall and progression-free survival using the Kaplan–Meier method, and log-rank analyses to assess for differences in survival by WHO Grade or treatment initiation.

Results Median age at time of desensitization was 49.3 years (26.8–64.7 years). Median follow-up after desensitization was 35.5 months. One patient (6.7%) was unable to resume temozolomide due to recurrent allergy. The median time from first desensitization to discontinuation of metronomic temozolomide was 4.2 months (0–15.2 months). Median OS and PFS for the whole sample were 181.7 months and 44.9 months. For Grade 4, OS was 100% at 1 year, 40% at 3 years, 20% at 5 years; and PFS was 60% at 1 year, 40% at 3 years, and 20% at 5 years.

Conclusion Our results suggest that rapid-desensitization followed by metronomic temozolomide should be considered in patients with glioma who experience hypersensitivity. This strategy provides comparable outcomes to therapy with standard protocols, with the majority of patients able to tolerate temozolomide after desensitization with favorable disease control.

Keywords Temozolomide hypersensitivity · Glioma · Desensitization · Metronomic dosing · Survival

Introduction

Temozolomide (TMZ) is an alkylating chemotherapeutic used in the treatment of malignant glioma. TMZ is cytotoxic through alkylation of guanine nucleotides after non-enzymatic conversation to its active form (5-(3-methyltriazen-1-yl)imidazole-4-carboxamide or MTIC) [1–3]. Per the Stupp protocol, TMZ is administered at 75 mg/m^2/day for 42 days concurrently with radiotherapy followed by adjuvant therapy for 6 cycles at higher doses (150–200 mg/m^2/day) [1, 2]. The most common adverse effects associated with TMZ include alopecia, fatigue, rash, nausea, vomiting, constipation, headache, and anorexia. More severe adverse effects are leukopenia, thrombocytopenia, and pneumonitis [1, 4, 5]. The United States Food and Drug Administration data regarding delayed-type hypersensitivity reactions to TMZ with radiation therapy describe 19% of patients with rash, 4% with pruritus, and 5% with skin erythema. Only 1% of patients had a rash that was severity of Grade ≥ 3. The incidence of delayed hypersensitivity reactions are similar in patients on maintenance TMZ with 13% of patients experiencing rash, 5% pruritus, 1% erythema; and only 1% of patients having a rash that was severity of Grade ≥ 3 [1]. Other immunologic adverse reactions to TMZ have been reported, including: anaphylaxis, erythema multiforme [1], Stevens-Johnson syndrome-toxic epidermal necrolysis

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overlap (SJS-TEN) [6], and other hypersensitivity reactions [7–9].

TMZ is the standard of care for newly diagnosed GBM. It is often also used in recurrent GBM and for initial or salvage therapy in other infiltrating gliomas [2]. Hypersensitivity reactions requiring discontinuation or interruption of TMZ chemotherapy therefore may have a significant impact on tumor control and patient survival. There are several reports on the desensitization of hypersensitivity to TMZ [10–13]. We have described our desensitization protocol from a group of patients at Mayo Clinic [14], in which patients are administered low dose TMZ that is sequentially increased every 30 min prior to continuation of daily therapy at lower or metronomic dosing of TMZ (mTMZ). Previous studies have used mTMZ, most notably in recurrent malignant gliomas [15–19], as it was hypothesized to improve efficacy in treatment resistant malignancy, and would be not inferior to standard dosing schedules [20]. Here we report patient characteristics and therapeutic outcomes in a cohort of patients with glioma (WHO Grade 2–4) and concurrent TMZ hypersensitivity managed by desensitization and subsequently treated with metronomic dosing of TMZ.

Materials and methods

We analyzed the clinical course of all patients with a diagnosis of glioma who underwent TMZ desensitization and subsequent metronomic dosing (mTMZ) after intolerable hypersensitivity to TMZ at standard dosing at our institution. Patients who underwent desensitization followed by mTMZ as part of either first-line therapy or after progression were included. The desensitization protocol has been previously published [14] and includes escalation of administered doses of TMZ (0.01–128 mg) given every 30 min prior to the initiation of a metronomic TMZ (50 mg/m^2/day) dosing schedule thereafter to limit potential for recurrent hypersensitivity. There was no specific premedication regimen utilized outside of patient's home medications.

All patients were treated at Mayo Clinic (Rochester, MN) from May 2012 to January 2017, with follow-up extending until October 2019. We considered data on demographics, tumor characteristics, time from TMZ exposure to hypersensitivity, duration of TMZ therapy after desensitization, and reasons for eventual TMZ discontinuation. IDH1-R132H (IDH) status was determined by immunohistochemical staining in a subset of patients. We calculated overall survival (OS) and progression-free survival (PFS) using the Kaplan–Meier method. OS was calculated as time from initial diagnosis to death. PFS was calculated as time from initial diagnosis (if mTMZ was started in initial therapy) or time from initiation of mTMZ (if mTMZ was started after progression) to radiologically/clinically determined progression. We also performed analyses to assess for any differences in survival by WHO Grade and timing of mTMZ initiation (first line or after progression). For these analyses, log rank test was performed to assess for survival differences between groups. All analyses were performed on SAS-University Edition. Our Institutional Review Board approved this single-institution retrospective study; and informed consent was waived given minimal risk to included participants.

Results

A total of 15 patients were included in the study. See Table 1 for patient demographics, tumor characteristics and survival data; and Table 2 for details regarding hypersensitivity reaction for each patient. Median age of our sample at time of desensitization was 49.3 years (26.8–64.7 years), with median time from initial TMZ exposure to hypersensitivity reaction of 8.6 months (0.6–98.7 months). All patients had symptoms of rash, with 10 having urticarial rash, 1 having measles-like rash, and the remaining 4 having a "non-urticarial" rash. No patients experienced SJS or TEN overlap. Median time from documentation of hypersensitivity reaction to TMZ discontinuation was 22 days (0–60 days), while median time from documentation of hypersensitivity reaction to desensitization and mTMZ initiation was 1.5 months (0.5–113.3 months). Median follow-up after desensitization was 35.5 months (62 months from time of initial diagnosis). Five patients underwent desensitization during first-line treatment and 10 were treated following progression. One patient developed a severe rash soon after desensitization and TMZ was permanently discontinued. Six patients completed their planned course of mTMZ therapy, and five eventually discontinued TMZ due to progression. Of the remaining three patients, one each stopped treatment due to hematologic toxicity, remained on treatment as of last follow-up, and was lost to follow-up. Three patients underwent a second desensitization either due to recurrent hypersensitivity or because of an interruption in daily mTMZ unrelated to hypersensitivity. Of the 14 patients with complete follow-up, the median time from first desensitization to final discontinuation of mTMZ was 4.2 months (0–15.2 months).

Median OS and PFS for the whole sample were 181.7 months and 44.9 months. Of the total 15 patients, 5 each had initial WHO Grade pathology of 2, 3, and 4. Median OS was 181.7, 311.3, and 24.7 months for Grade 2, 3, and 4. Median PFS was 58.9, 35.5, and 20.8 months for Grade 2, 3, and 4. For Grade 4 only, OS was 100% at 1 year, 40% at 3 years, 20% at 5 years; and PFS was 60% at 1 year, 40% at 3 years, and 20% at 5 years. There were no statistically significant differences in OS or PFS based on WHO Grade.

Table 1 Patient/tumor characteristics and survival data

#	Grade	mTMZ (months)	OS (months)	PFS (months)	Age (years)	Sex	Censor (OS/PFS)	Histology	IDH1	1p/19q	MGMT	TERT	Reason mTMZ discontinued	Subsequent therapies
1	2	10.62	138	58.9	32.3	M	Yes/no	Oligodendroglioma	Mutant	Co-deleted	Methylated	Mutant	Completion	Lomustine
2		0.85	115.3	91	26.8	F	Yes/yes	Oligodendroglioma	–	Co-deleted	–	–	Completion	–
3[a]		1.12	181.7	53.7	34.8	M	No/no	Oligodendroglioma	–	Co-deleted	–	–	Progression	Lomustine, bevacizumab, procarbazine, vincristine
4[b]		1.51	111.1	16.1	35.7	F	No/no	Oligodendroglioma	–	Co-deleted	–	–	Completion	Lomustine, bevacizumab, procarbazine, carboplatin
5		12.1	232.6	165.4	47.6	M	Yes/no	Diffuse astrocytoma, NOS	–	Intact	–	–	Completion	–
Mean (SD)		5.24 (5.6)	155.74 (51.3)	77.02 (56.1)	35.44 (7.6)	…								
6	3	14.76	311.3	60.8	61.7	F	No/no	Anaplastic astrocytoma	–	–	–	–	Hematologic	–
7		6.28	61.2	50.9	42.8	F	Yes/yes	Anaplastic astrocytoma	–	–	–	–	Completion	–
8		4.34	43.8	8.5	62.2	F	No/no	Anaplastic astrocytoma	Wildtype	–	Methylated	–	Progression	Lomustine, bevacizumab
9[c]		3.65	54.9	10.2	64.7	F	Yes/no	Anaplastic astrocytoma	–	–	–	–	Progression	Lomustine, bevacizumab
10[A]		1.97	45.9	2.4	49.3	M	Yes/yes	Anaplastic astrocytoma	Wildtype	Intact	–	–	Continuing	–
Mean (SD)		6.2 (5.0)	103.42 (20.1)	26.56 (27.1)	56.14 (9.6)	…								

Table 1 (continued)

#	Grade	mTMZ (months)	OS (months)	PFS (months)	Age (years)	Sex	Censor (OS/PFS)	Histology	IDH1	1p/19q	MGMT	TERT	Reason mTMZ discontinued	Subsequent therapies
11[d]	4	1.87	22.4	10.1	30.8	F	No/no	Glioblastoma	–	–	–	–	Progression	Lomustine, bevacizumab, procarbazine
12		4.54	67.7	67.7	60.4	M	Yes/yes	Glioblastoma	Mutant	–	Methylated	–	Completion	–
13		0.03	24.7	20.8	60.1	F	No/no	Glioblastoma	–	–	–	–	Hypersensitivity	Bevacizumab, lomustine
14		7.5	21.2	7.8	52.6	F	No/no	Glioblastoma	Wildtype	–	Unmethylated	–	Progression	Bevacizumab, lomustine
15		3.81	44.8	36.1	64.3	M	Yes/no	Glioblastoma	Wildtype	–	Methylated	–	Continuing	–
Mean (SD)		3.55 (2.8)	36.16 (20.1)	28.5 (24.6)	53.64 (13.5)	…								

Table separated by WHO Grade. Presented histology and molecular data represents tumor characteristics at initial diagnosis

[A]Lost to follow-up, at least completed 60 days, a: found to be IDH mutant on re-resection on recurrence, b: with focal anaplasia on histology at initial diagnosis, on recurrence was found to be IDH wildtype (IDH status not available on initial diagnosis), c: small cell type, d: with PNET-like features. '–' denotes unknown molecular status. Mean (standard deviation) included for included measures by WHO Grade

Table 2 Details of hypersensitivity reaction and timing of therapy

#	mTMZ initiation	Symptoms	Time relapse to re-treatment (days)	Time exposure to allergy (months)	Time allergy to discontinuation (days)	Time allergy to mTMZ (months)	Allergy recurrence
1	Progression	Rash, non-urticarial	6	68.3	19	0.5	No
2		Hives	130	23.6	41	1.6	No
3		Hives	161	4.9	0	42.3	No
4		Hives	7	15.5	60	1.4	No
5		Rash, non-urticarial	140	1.1	22	111.7	No
6		Hives, leg edema	9	88.4	0	38.6	Yes
7		Hives	190	15.3	31	0.7	No
8		Hives	15	29.7	22	1	Yes
9		Hives	117	37.5	47	1.1	Yes
	Mean (SD)		86.11 (75.7)	31.59 (29.2)	26.89 (20.2)	22.1 (37.7)	
10[a]	First-line	Rash, non-urticarial	–	4.6	39	3.9	No
11		Rash, non-urticarial	–	1.1	4	6.1	No
12		Hives	–	1.1	3	1.4	No
13		Measles-like rash	–	0.6	52	2.6	Yes
14		Hives	–	2.7	1	0.9	No
15		Hives	–	8.5	6	0.6	No
	Mean (SD)		–	3.1 (3.0)	17.5 (22.1)	2.58 (2.1)	

Table separated by time of mTMZ initiation (first-line vs. after progression)

[a]Lost to follow-up, at least completed 60 days. Mean (standard deviation) included for included measures by mTMZ initiation

Median OS was 24.7 months for initiation as first-line and 181.7 months for initiation after progression. Median PFS was 20.8 months for initiation as first-line and 58.9 months for initiation after progression. There were no statistically significant differences in OS or PFS based on timing of mTMZ initiation. See Fig. 1a–f for Kaplan–Meier curves (OS, PFS) for the whole sample, by pathologic grade, and by treatment initiation. Molecular analysis was limited by lack of data (seen in Table 1) on all patients such that we were unable to draw meaningful conclusions from the data.

Discussion

In patients who develop a hypersensitivity reaction to TMZ, desensitization with subsequent metronomic dosing allows most patients to successfully resume therapy with comparable outcomes relative to patients without hypersensitivity. Only one patient (6.7%) was unable to resume TMZ due to recurrent allergy. Most patients were able to continue TMZ at metronomic dosing until disease progression or the completion of planned therapy, this coupled with the comparable outcomes to patients without hypersensitivity demonstrates that this is an effective strategy and a viable option for patients who experience hypersensitivity to TMZ in the form of rash during standard treatment. To our knowledge this is the largest case series of patients with glioma and TMZ hypersensitivity successfully treated with TMZ desensitization and subsequent metronomic dosing. Our results support the tolerability and efficacy of our protocol relative to standard therapy.

Patients in our small cohort had a relatively favorable outcome compared to previous reports of patients treated with metronomic dosing of TMZ. We found median OS of 181.7 months, median PFS of 44.9 months for our entire cohort ($n=15$); and of interest OS was 100% at 1 year, 40% at 3 years, 20% at 5 years for patients with Grade 4 pathology ($n=5$). Analyses (log rank test) by tumor Grade showed no statistically significant differences between Grade despite patients with Grade 4 pathology at diagnosis having a lower OS and PFS. This was likely secondary to the small sample size ($n=5$ in each group). We also found the median OS was larger for Grade 3 (311.3 months) than for Grade 2 (181.7 months). This is unexpected and driven by this being a small sample size—3/5 of the Grade 3 participants were censored, with the lengthy survival (311.3 months) from participant #6 likely skewing the survival estimates based on the Kaplan–Meier method. Thus, stratified survival results must be interpreted with caution.

Previous data from the EORTC-NCIC trial showed OS was 27.2% at 2 years, 16% at 3 years, 12.1% at 4 years, and 9.8% at 5 years in patients with glioblastoma treated with concurrent TMZ and RT [21]. Moreover, results from the second interim and first molecular analyses of the CANTON

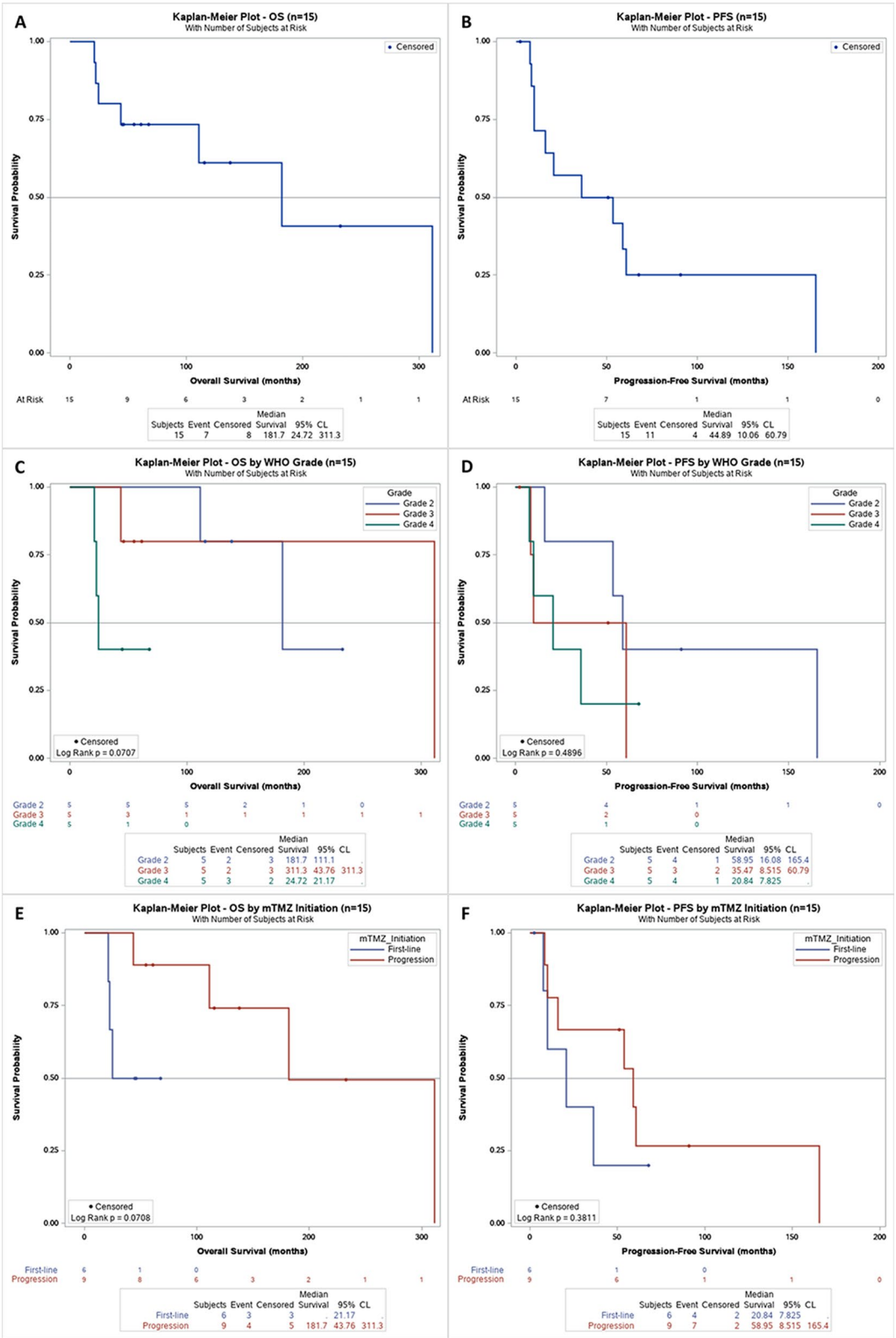

Fig. 1 Survival outcomes using the Kaplan–Meier method for whole sample and by pathologic grade, treatment initiation. **a** OS and **b** PFS of the whole sample (unstratified), **c** OS and **d** PFS by pathologic WHO Grade, **e** OS and **f** PFS by time of initiation of mTMZ therapy. All OS and PFS are in months (*x* axis). Censored participants indicated by 'dots' on the curve. *P* value from log rank tests included where indicated when assessing for surival differences. Data from **a**–**f** are from the whole sample ($n = 15$)

trial suggest that the median OS after TMZ concurrent with RT in patients with IDH wildtype was 19 months and 116 months in patients with IDH mutation [22]. While our results are not directly comparable to previous reports of survival data, patients in our small sample had similar outcomes with desensitization and mTMZ as part of their management.

We found previously published desensitization protocols in patients with TMZ hypersensitivity are similar in design to ours and have been generally successful in allowing patients to continue higher-dose TMZ therapy. One distinction between our protocol and others is that there was no targeted premedication regimen administered in our patients. Previously published protocols include: combined sequential increases of TMZ (0.025–110 mg, 30 min between doses) with premedication of corticosteroids and antihistamines [13]; sequential increases of TMZ (0.035–80 mg, 12 steps, 30 min between doses) without premedication [10]; premedication with corticosteroids and antihistamines followed by one of two protocols, (1) 0.05–60 mg over 12 steps then continuation of 20–60 mg per day over 4 additional days or (2) 5–60 mg over 7 steps with the same continuation plan as the first protocol [11]; and premedication with methylprednisolone, ranitidine, cetirizine, montelukast 30 min prior to administration of a sequential desensitization protocol of 5 mg TMZ with increasing doses of TMZ every 30 min [12].

The metronomic dosing of chemotherapeutics has been hypothesized to potentiate established agents [20]; with several published reports on mTMZ as a therapeutic strategy in gliomas. It is important to note that metronomic dosing of TMZ in our study was used to maintain tolerance to TMZ and not to determine if this regimen had increased efficacy relative to standard dosing. Previous trials include a Phase I trial of patients with recurrent glioblastoma ($n=6$) and anaplastic glioma ($n=3$), mTMZ at two doses (25, 50 mg/m^2/day) in continuous 42-day cycles was found to be tolerated with mainly grade 1–2 adverse events. Median PFS was 8.5 months and median OS was 12.7 months in this series [18]. A Phase II trial of patients with recurrent glioblastoma studied mTMZ dosing in two cohorts, the first ($n=10$) received daily dosing at 40 mg/m^2/day and increased to 50 mg/m^2/day, while the second ($n=28$) received daily mTMZ only at 50 mg/m^2/day. The 6-month PFS for the whole cohort was 32.5% and OS at 6 months was 56% [16]. In another trial, 30 patients with recurrent glioblastoma after standard therapy were administered mTMZ (50 mg/m^2/day) daily for a median of 8 weeks. Results showed median PFS of 2 months and OS of 6 months from the start of therapy [19]. Lastly, a Phase II trial of 37 patients with glioblastoma and 10 patients with WHO Grade 3 glioma showed 6-month PFS of 19% and median OS of 7 months in the glioblastoma group, while 6-month PFS was 30% and median OS was 18 months in the Grade 3 glioma group [17].

In conclusion, our findings suggest that rapid-desensitization followed by mTMZ should be considered in patients with glioma who experience TMZ hypersensitivity. This strategy provides comparable outcomes to therapy in patients treated with TMZ per standard protocols with the majority of patients able to tolerate TMZ after desensitization with favorable disease control.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest pertaining to this study.

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