CLINICAL-PATIENT STUDIES

Toxicity and efficacy of protracted low dose temozolomide for the treatment of low grade gliomas

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Abstract Protracted low dose temozolomide (75 mg/m^2/day on days 1–21 of 28 days) offers potential advantages over standard temozolomide schedules (200 mg/m^2/day on days 1–5 of 28 days) including greater cumulative drug exposure and depletion of O^6-alkylguanine DNA alkyltransferase levels, theoretically overcoming intrinsic chemoresistance. We retrospectively review our experience in 25 patients with pathologically proven low grade gliomas (LGG) treated with protracted low dose temozolomide to primarily quantify its toxicity and secondarily to assess efficacy. None had previously received radiation. Tumor response was graded based on changes in tumor size, steroid requirements, and clinical exam. About 243 cycles of protracted low dose temozolomide were administered. Three patients (12%) were changed to standard temozolomide dosing due to side effects, including intractable nausea ($n = 2$) and multiple cytopenias ($n = 1$). The most frequent toxicities were fatigue (76%), lymphopenia (72% [48% high grade]), constipation (56%), and nausea (52%). High grade toxicities (other than lymphopenia) included secondary malignancy, pruritis, hyponatremia, neutropenia, leukopenia, and cognitive decline ($n = 1$ for each). Tumor response rate was 52% and and disease control rate was 84%. Six month PFS was 92% and 12 month PFS was 72%. Response rates and PFS were independent of pathological subtype, deletion status, and indication for chemotherapy. Protracted low dose temozolomide has a distinct spectrum of toxicities compared to standard dosing but is well tolerated in most patients and may provide improved response rates compared to standard dosing. The results of larger randomized trials are needed to assess its potential advantages over other management schemes.

Keywords Chemotherapy · Glioma · Low grade glioma · Temozolomide · Toxicity

Introduction

Temozolomide (TMZ) is an oral alkylating with excellent bioavailability and a favorable toxicity profile that induces DNA damage by methylating the O^6 position of guanine. It has been shown to be efficacious for the treatment of anaplastic gliomas and glioblastomas [1–3]. Encouraging results have also been obtained in low grade gliomas (LGG) using a standard dosing regimen (200 mg/m^2 for 5 days every 28 days) [4–10]. Despite the emphasis on the standard regimen (based on early phase I studies [11]), experimental and in vivo studies suggest that the antitumor activity of TMZ is schedule-dependent and that continuous or protracted dosing may be more effective than the standard schedule commonly used [12].

Protracted low dose TMZ is theorized to have improved efficacy as a result of a combination of

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increased cumulative drug exposure and depletion of O^6-alkylguanine DNA alkyltransferase (AGAT) [13–16]. AGAT (which is synonymous with O^6-methylguanine-DNA methyltransferase [MGMT]) is a DNA repair enzyme that is irreversibly inactivated when it removes alkyl groups from the O^6 position of guanine. Because it is irreversibly inactivated and de novo AGAT synthesis is required to replenish AGAT function, protracted low dose TMZ results in greater AGAT depletion than less frequent administrations [17]. The depletion of AGAT may be critical since AGAT expression has been implicated in chemoresistance; tumoral AGAT expression is inversely related to chemosensitivity [18–22]. Based on these considerations, a joint study of the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumor Group, EORTC Radiotherapy Group, and the National Cancer Institute of Canada's Clinical Trials Group (NCIC-CTG) is underway to compare continuous low dose TMZ (75 mg/m^2 daily for 21 days every 28 days) with radiotherapy (50.4 Gy) in patients with LGG who require treatment due to either tumor progression, uncontrolled symptoms, or unfavorable prognostic factors [23].

Despite the potential advantages, reports of clinical investigations using protracted low dose TMZ have been limited [15, 16, 24–26]. The toxicity and chemotherapeutic efficacy of protracted low dose TMZ still need further elucidation before widespread use can be advocated. The objective of this study was primarily to evaluate the toxicity and secondarily to assess the efficacy of protracted, low dose TMZ (75 mg/m^2 on days 1–21 of 28 days) in a series of patients with LGG treated at the University of Virginia using this dosing regimen.

Methods

Patient selection and evaluation

After receiving Human Investigation Committee (HIC) approval, we retrospectively reviewed the University of Virginia NeuroOncology database to identify all patients with pathologically proven LGG treated with protracted low dose TMZ between October 2003 and June 2006. Twenty-five patients were identified. Diagnoses included oligodendroglioma ($n = 15$), oligoastrocytoma ($n = 6$), astrocytoma ($n = 1$), and unspecified LGG ($n = 3$). Patient charts were retrospectively reviewed to identify relevant clinical history, past medical history, details of pathology, and details of treatment.

Treatment

Patients received TMZ 75 mg/m^2/day orally for 21 days every 28 days. The original plan in each patient was to administer between 12 and 15 cycles of TMZ. Patients were evaluated every two to three cycles. Dosing was reduced in the setting of some high-grade toxicities, as described in the results. The treatment was discontinued in the presence of disease progression or due to unacceptable toxicity (as described in the results). Patients were maintained on prophylaxis against Pneumocystis carinii with trimethorpim–sulfamethoxazole. Antiemetics and stool softeners were prescribed as needed.

Toxicity evaluation

Toxicity was assessed at each clinical follow-up by patient history and laboratory examination. Laboratory examination included complete blood counts with differentials and comprehensive metabolic panels. Toxicities were graded according to the NCI Common Toxicity Criteria v3.0 (http://ctep.cancer.gov/forms/CTCAEv3.pdf).

Tumor response criteria

Tumor responses were evaluated according to established response criteria that incorporate changes in tumor size, steroid requirements, and patient neurological status [27]. Complete MRI (including T1 without and with contrast, T2, and FLAIR sequences) were obtained every 2–3 months in all patients as part of routine neuro-oncological follow-up. For this study, we retrospectively measured the maximum perpendicular cross-sectional diameters of each patient's tumor as it appeared on FLAIR sequences before and after treatment. A complete response (CR) was defined as complete disappearance of all enhancing and nonenhancing tumor, with the patient not receiving steroid and being neurologically stable or improved. A partial response (PR) was defined as ≥50% reduction in FLAIR tumor volume from baseline and maintained for at least 8 weeks with the patient using stable or reduced steroids and being clinically stable or improved. A minor response (MR) was defined as ≥25% but less than 50% reduction in tumor volume or no change in volume but disappearance of tumor enhancement and maintained for at least 8 weeks, with the patient using stable or reduced steroids and being clinically stable or improved. Progressive disease (PD) was defined as ≥25% increase in tumor volume, any new

distant tumor, or tumor-related neurological progression while on stable or increased steroids. Stable disease (SD) was defined as any other clinical status that does not meet any of the above criteria.

Statistical analysis

Survival was measured from day 1 of treatment. Progression free survival (PFS) was measured until the first sign of radiological or clinical progression (whichever came first) or last follow-up visit if no progression was noted. Survival was estimated by the Kaplan–Meier method and differences were evaluated by the log-rank test. The overall response rate and its 95% confidence intervals (95% CI) were calculated by pooling CR, PR, and MR rates.

Results

From October 2003 to June 2006, 25 patients were treated with protracted low dose TMZ (75 mg/m^2/day on days 1–21 of a 28 day cycle) for a pathologically proven diagnosis of low grade glioma, including 15 oligodendrogliomas (WHO grade II), 6 oligoastrocytomas (WHO grade II), 1 astrocytoma (WHO grade II), and 3 low grade gliomas, not otherwise specified. Of these 25 patients, 10 were treated for progressive disease and 15 were treated at the time of initial diagnosis. Further pretreatment patient characteristics are provided in Table 1. On MRI FLAIR images, the median and range of maximum tumor diameters were 47 mm and between 19 and 98 mm. Gadolinium enhancement was noted in 24% of patients' pretreatment MRIs.

About 243 cycles of chemotherapy were administered to the 25 patients. The number of cycles of protracted low dose TMZ administered per patient ranged from one to 16 (median = 12 cycles). Three patients did not complete their originally prescribed course of protracted low dose TMZ due to adverse effects of chemotherapy, including grade 2 nausea (two patients) and multiple combined high grade cytopenias (one patient). In these patients, chemotherapy was changed to standard dose TMZ (150–200 mg/m^2/day on days 1–5 of a 28 day cycle). In addition, four patients did not complete their originally prescribed course of chemotherapy due to disease progression on therapy. These patients were referred for radiation therapy. The median follow-up for all patients was 19.8 months (range 5.3–26.2 months).

Table 1 Patient characteristics

No. of patients	25
Gender	
Male	12
Female	13
Age, years	
Median	48
Range	21–76
Histology, n	
Oligodendroglioma	15
Oligoastrocytoma	6
Astrocytoma	1
LGG, NOS	3
Prior Surgery, n	
Biopsy only	11
Subtotal resection	14
Prior chemotherapy, n	2
Prior radiotherapy, n	0
Indication for chemotherapy, n	
Initial treatment	15
Progression	10
KPS at start of treatment	
Median	90
Range	70–100
Cycles of TMZ, n	
Total	243
Median	12
Range	1–16

LGG, NOS = low grade glioma, not otherwise specified

TMZ = temozolomide

Toxicity

The primary purpose of this study was to evaluate the toxicity and tolerability of protracted low dose TMZ for the treatment of LGG. Adverse events are summarized in Table 2. There were no deaths (grade 5 toxicity) associated with treatment. Lymphopenia was the most common high grade toxicity (grade 3), occurring in 48% of patients. No grade 4 lymphopenias were noted. Grade 3 lymphopenias occurred between cycles 4 and 16 (median was during cycle 6). In two patients, localized herpes zoster infections requiring antiviral therapy were noted associated with grade 3 lymphopenias. No other negative sequelae accompanied lymphopenias. In one patient, however, after experiencing combined grade 3 lymphopenia, grade 2 leukopenia, and grade 2 neutropenia during the 4th cycle of protracted low dose temozolomide, a patient was changed to standard dose TMZ due to the combination of multiple cytopenias. High grade cytopenias resolved with the change in regimen. Other high grade toxicities were uncommon; six events were identified in 5 patients including neutropenia, leucopenia, hyponatremia, cognitive disturbance, pruritis, and secondary malignancy (diffuse large B-cell lymphoma). The secondary malignancy and pruritis

Table 2 Toxicity of chemotherapy

Toxicity, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total
Blood/Bone Marrow					
Leukopenia	4	3	1	–	8 (32%)
Lymphopenia	–	6	12	–	18 (72%)
Neutropenia	1	2	1	–	4 (16%)
Thrombocytopenia	1	–	–	–	1 (4%)
Constitutional Symptoms					
Fatigue	17	2	–	–	19 (76%)
Weight loss	–	1	–	–	1 (4%)
Dermatology/Skin					
Pruritis	1	1	1	–	3 (12%)
Rash/Desquamation	1	1	–	–	2 (8%)
Gastrointestinal					
Constipation	14	–	–	–	14 (56%)
Nausea	10	3	–	–	13 (52%)
Vomitting	5	1	–	–	6 (24%)
Infection					
Opportunistic infection—Zoster	–	2	–	–	2 (8%)
Metabolic/Laboratory					
Alkaline phosphatase	3	–	–	–	3 (12%)
ALT	6	–	–	–	6 (24%)
AST	5	–	–	–	5 (20%)
Creatinine	2	–	–	–	2 (8%)
Hyperkalemia	2	–	–	–	2 (8%)
Hyponatremia	2	–	1	–	3 (12%)
Neurology					
Cognitive disturbance	–	–	1	–	1 (4%)
Depression	–	2	–	–	2 (8%)
Ocular/Visual					
Flashing lights	1	–	–	–	1 (4%)
Pain					
Arthralgia	1	–	–	–	1 (4%)
Secondary Malignancy					
Possibly related to cancer treatment	–	–	–	1	1 (4%)

were identified in the same patient during the 12th cycle of therapy.

The most frequent toxicities were fatigue (76%), lymphopenia (72%, as described above), constipation (56%), and nausea (52%). Although fatigue was common, it was generally limited and did not interfere significantly with patients' daily activities. With regards to constipation, in all affected patients, symptoms were effectively treated with the use of stool softeners. While nausea was effectively treated in most patients with antiemetic medications, intolerable nausea (grade 2) required changes in TMZ dosing in two patients. In one patient, the daily dose of TMZ was reduced to 50 mg/m^2/day for 3 cycles before changing to a standard TMZ regimen after 3 additional cycles due to persistent nausea. In the other case, the patient, who had a history of nausea, was immediately changed to a standard TMZ regimen after experiencing intolerable nausea during the first cycle of chemotherapy. In both cases, the patients tolerated standard dose TMZ without significant or disabling nausea and vomiting.

Delay in chemotherapy was not required in this series of patients for adverse events. Dose reductions and regimen changes however were implemented in the setting of some adverse events as described above.

Outcomes

Although the primary purpose of this study was to report the toxicity and tolerability of protracted low dose TMZ for the treatment of LGG, we evaluated tumor responses as a secondary measure. The overall response rate (ORR, including CR, PR, and MR) was 52% (95% CI, 33–70%) and disease control rate (DCR, including CR, PR, MR, and SD) was 84% (95% CI, 65–94%). Tumor responses were detected between the completion of 2nd and 10th cycle of chemotherapy, with a median time to radiographic response of 4 cycles. There were no significant differences in ORR and DCR when patients were stratified according to indication for chemotherapy (i.e., initial therapy versus progressive disease), histology, 1p/19q deletion status, or the presence or absence or pretreatment imaging enhancement ($P > 0.05$ for each comparison, Kruskal–Wallis nonparametric test, Table 3). This study was not however designed or powered to detect such differences. Steroid use during chemotherapy was also assessed independently of other response rates. Out of eight patients that were on steroids at the initiation of treatment, four patients (50%) discontinued and 2 patients (25%) significantly decreased use of steroids after starting treatment with protracted low dose TMZ. The two remaining patients (both of whom were considered to have progressive disease) required increasing steroids during treatment.

Progression free survival (PFS) was also evaluated. For the entire series, six month PFS was 92% and 12 month PFS was 74% (Table 4). Median PFS was not reached for the entire series despite a median follow-up of 19.8 months (range 5.3–26.2 months). There was no difference in PFS when patients were stratified according to indication, histology, deletion status, the presence or absence of imaging enhancement, or by age ($P > 0.05$ for each comparison). As explained before, this study was not designed or powered to necessarily detect such differences.

Four patients did not complete their originally prescribed course of protracted low dose TMZ due to disease progression while on therapy (during cycles 4 [$n = 2$], 7, and 10). Patients noted to have progression were all referred for radiation therapy since none had had such therapy prior to initiation of chemotherapy.

Table 3 Tumor response to protracted low dose temozolomide

No. of patients (%)	Total	Complete response	Partial response	Minimal response	Stable disease	Progressive disease
All patients	25	0 (0%)	6 (24%)	7 (28%)	8 (32%)	4 (16%)
By indication						
Initial treatment	15	0 (0%)	3 (20%)	6 (40%)	3 (20%)	3 (20%)
Progression	10	0 (0%)	3 (30%)	1 (10%)	5 (50%)	1 (10%)
By histology						
Oligodendroglioma	15	0 (0%)	3 (20%)	5 (33%)	6 (40%)	1 (7%)
Oligoastrocytoma	6	0 (0%)	2 (33%)	2 (33%)	0 (17%)	2 (33%)
Astrocytoma	1	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
LGG, NOS	3	0 (0%)	1 (33%)	0 (0%)	1 (33%)	1 (33%)
By deletion status						
1p/19q deleted	11	0 (0%)	2 (18%)	4 (36%)	4 (36%)	1 (9%)
1p/19q intact	11	0 (0%)	4 (36%)	2 (18%)	2 (27%)	3 (18%)
By enhancement pattern						
No enhancement	19	0 (0%)	3 (16%)	6 (32%)	7 (37%)	3 (16%)
Enhancement	6	0 (0%)	3 (50%)	1 (17%)	1 (17%)	1 (17%)

LGG, NOS = low grade glioma, not otherwise specified

Discussion

TMZ induces a substantial rate of clinical and radiographic response and can be used as a first-line, single-agent treatment in patients with recurrent LGG when administered in a standard dosing regimen (Table 5) [4, 5, 7–10]. Several factors may alter the success of treatment. Specifically, the expression of AGATis inversely related to tumoral chemosensitivity [8, 20, 22, 28]. Because of the apparent importance of AGAT levels in regulating chemosensitivity, means of depleting intra-tumoral AGAT levels have been sought, including co-administering O^6-benzylguanine (an AGAT substrate that irreversibly inactivates AGAT) with TMZ and using extended, or protracted, TMZ dose schedules [13, 14, 29, 30]. Protracted low dose TMZ is also potentially advantageous because it provides increased cumulative drug exposure [13–16]. While the modified dosing schedule may result in greater chemotherapeutic efficacy, it also changes the toxicity profile of treatment [15, 16, 24–26]. This study represents the first report of the toxicity and efficacy of protracted low dose TMZ for the treatment of LGG.

Toxicity of protracted low dose TMZ

A limited number of studies have reported on the toxicity of protracted low dose TMZ for the treatment of various tumors including gliomas, soft tissue sarcomas, melanomas, and renal cell carcinomas [15, 16, 24–26, 31]. Similar to prior studies, we found the most common and severe toxicities to be hematologic, especially lymphopenia (Table 6). Two opportunistic infections were identified in our series (both Herpes Zoster) and, like the report of Tosoni and colleagues, were associated with lymphopenia rather than neutropenia [25]. Despite the high rate of high grade lymphopenia, there were few clinically significant consequences. Lymphopenia seems to be a unique toxicity of protracted low dose TMZ administration, never having been reported with standard TMZ schedules [4, 5, 7]. Although corticosteroid use (in eight patients) may have contributed in part to the observed lymphopenias, high grade lymphopenias (total incidence = 12) occurred in patients both

Table 4 Progression free survival in patients treated with protracted low dose TMZ

	N	6 month PFS (%)	12 month PFS (%)	P Log-Rank
All	25	92	74	-
By indication				
Initial treatment	15	93	71	0.50
Progression	10	90	80	
By histology				
Oligodendroglioma	15	93	93	0.07
Oligoastrocytoma	6	83	50	
Astrocytoma	1	100	100	
LGG, NOS	3	100	33	
By deletion status				
1p/19q deleted	11	91	91	0.33
1p/19q intact	11	91	58	
MRI enhancement				
No	19	95	77	0.22
Yes	6	83	67	
By Age				
<=45 years	11	82	72	0.32
>45 years	14	100	77	

LGG, NOS = low grade glioma, not otherwise specified

PFS = progression free survival

Table 5 Temozolomide chemotherapy for low-grade gliomas

Author	N	TMZ dosing	Pathology	Enhancing (%)	Indications for chemo.	Response, CR + PR + MR	Median PFS	6 month PFS	12 month PFS	Toxicity, grade 3/4 (% of pts)
Quinn et al.[10]	46	Standard	O, OA, A	70	Progression	61%	22	98%	76%	13%
Hoang-Xuan et al. [7]	60	Standard	O, OA	11	Progression	31%	N/A	N/A	73%	8%
Pace et al. [9]	43	Standard	O, OA, A	60	Progression	47%	10	76%	39%	23%
Brada et al. [5]	30	Standard	O, OA, A	0	Initial and progression	58%	N/A	>90%	>90%	38%
Van den Bent et al. [4]	38	Standard	O, OA	100	Progression	53%	10	71%	40%	33%
Levin et al. [8]	28	Standard	O	N/A	Progression	61%	31	N/A	89%	0%
Current study	25	Protracted low dose	O, OA, A	24	Initial and progression	52%	NR	92%	74%	72%

O = oligodendroglioma, OA = oligoastrocytoma, A = astrocytoma

CR = complete response, PR = partial response, MR = minor response

PFS = progression free survival

N/A = not available, NR = not reached

receiving (*n* = 5) and not receiving corticosteroids (*n* = 7). Other high grade hematological toxicities that are commonly reported with standard TMZ regimens, including neutropenias and thrombocytopenias (at a combined rate of between 8 and 25%) are rare with protracted low dose TMZ (Table 2) [25].

In addition to the hematological toxicities, fatigue, nausea, and constipation are noted at high rates, although never greater than grade 2. Garcia del Muro and colleagues reported fatigue in 58% of patients and nausea and vomiting in 56% of patients [26]. Fatigue was well managed with appropriate rest and occasional stimulant medication (methylphenidate, *n* = 1) and never interfered with daily activities. Likewise, although nausea and constipation were common, these were almost always well managed with antiemetics (as needed or scheduled) and stool softeners, respectively. As in previous reports, in two patients, protracted low dose TMZ could not be tolerated due to intractable nausea, necessitating conversion to standard dose TMZ (which relieved the nausea) [26]. Like Tosoni and colleagues who found a low grade transaminitis in 35% of patients and rise in creatinine in 6% of patients, we found similar toxicities in our patient

population, at a rate of 28% and 8%, respectively [25]. The similarity across studies suggests these observed toxicities are treatment related and may be due to increased cumulative drug exposure to end organs. Like them, however, all our patients received Bactrim prophylaxis, which may in part have contributed to renal dysfunction.

Overall, treatment was well tolerated with few clinical sequelae resulting from the reported adverse effects. No delays in treatment were required due to chemotherapeutic toxicities in this series of patients. Three patients (12%) who started protracted low dose TMZ for the treatment of LGG did not complete therapy due to adverse effects of treatment, similar to the report of Tosoni and colleagues, which is greater than that reported for standard TMZ dosing [25]. Nonetheless, there were no permanent sequelae of treatment in those patients who had to convert to standard dosing due to the toxicities of protracted low dose TMZ. This suggests that if protracted low dose TMZ is in fact more efficacious than standard dose TMZ, it is safe to initiate protracted low dose treatment in all patients and convert to standard dosing if the protracted dosing is not tolerated. A secondary

Table 6 Grade 3/4 lymphopenia rates of protracted low dose temozolomide

Author	No. of patients	Dose (mg/m^2/day)	No. of cycles	Grade 3/4 lymphopenia
Tosoni et al. [25]	51	75	295	27%
Bex et al. [24]	12	100	35	NR
Garcia del Muro et al. [26]	61	75–100	106	79%
Khan et al. [15]	35	75	55	17%
Current study	25	75	243	43%

malignancy (large B-cell lymphoma) was identified in one patient after 12 cycles of protracted low dose TMZ, presumably due to treatment. This has not been previously reported in any series of patients treated with protracted low dose TMZ. We must be cognizant of the potential complications of prolonged use of an alkylating agent, such as secondary malignancies and aplastic anemia, especially in young patients who have a relatively good prognosis [32]. While concerning, the true rate of secondary malignancy induction will have to be verified in larger Phase 2/3 trials, such as that planned by the EORTC and NCIC-CTG [23].

Efficacy of protracted low dose TMZ

Reports of the clinical efficacy of protracted low dose TMZ are limited. Garcia del Muro and colleagues found that protracted low dose TMZ was effective in a significant proportion of patients (15.5%) with advanced soft tissue sarcomas in whom second-line chemotherapy and standard TMZ was not effective [26]. Conversely, its efficacy in patients with malignant gliomas and metastatic renal cell carcinoma has been questioned [15, 24]. Establishing efficacy is particularly important in light of the pharmacoeconomic impact of this schedule change: low dose protracted TMZ roughly doubles the cost of chemotherapy compared to standard regimens, corresponding to approximately $6,000 greater cost per cycle.

Because this study was primarily intended to assess chemotherapy-related toxicity, follow-up is relatively short (median 19.8 months). Nevertheless, we provide a preliminary assessment of efficacy based on short term follow-up. The overall 6 and 12 month PFS reported in this study suggest improved or equivalent tumor control rates relative to those reported in studies of LGG using standard TMZ dosing (Table 5). Moreover, we found that tumor response rate to chemotherapy (CR+PR+MR, 52%) was similar to that reported in other studies (between 31 and 61%) (Table 5). While prior studies identified differences in treatment efficacy based on chromosome 1p deletion status, no significant effect was seen in this series of patients [7, 8]. Moreover, no differences were seen between groups of patients stratified by indication for chemotherapy, histology, age, or imaging enhancement pattern. While outcomes with protracted low dose TMZ are at least equivalent to other studies of TMZ therapy for LGG, the 12 month PFS appears inferior to that reported for XRT (>90%) and not significantly different than that reported for patients with LGG who

have only undergone surgery (biopsy or resection) and never received XRT or chemotherapy (between 70 and 80%) [33]. This study however was not designed to make such comparisons or to compare the relative risks and benefits of various therapies or observation. Larger scale, prospectively designed studies such as the ongoing EORTC trial are needed to adequately answer such questions [23]. Nonetheless, relative to other studies of TMZ for LGG, these preliminary outcomes are encouraging and suggest further characterization of the efficacy of protracted low dose TMZ for the treatment of LGG is warranted.

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