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A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma

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ABSTRACT

Purpose: Survival rates for paediatric diffuse intrinsic brainstem glioma (DIBSG) are dismal. Metronomic dosing of temozolomide (TMZ) combined with standard radiotherapy may improve survival by increasing the therapeutic index and anti-angiogenic effect of TMZ. This study aimed to evaluate the safety and efficacy of this regimen in paediatric DIBSG patients.

Methods: Children aged 18 years or younger with newly diagnosed DIBSG were treated with standard radiotherapy and concomitant metronomic TMZ at 85 mg/m^2/day for 6 weeks, followed by metronomic TMZ monotherapy at the same dose. Treatment was continued until tumour progression or unacceptable toxicity occurred. Primary endpoints included overall survival and toxicities. For patients who consented, plasma and urine samples were collected at diagnosis, post-induction and prior to each course of maintenance therapy for the quantification of angiogenesis markers.

Results: Fifteen eligible patients were enrolled, with a median age of 6.4 years. The most common toxicities were myelosuppression, most notably prolonged lymphopaenia and thrombocytopaenia. The only dose-limiting toxicity was thrombocytopaenia. Intratumoural haemorrhage was confirmed in one patient. Median time to progression was 5.13 months (95% CI = 6.4, 10.8) and median overall survival (OS) was 9.8 months (95% CI = 6.4, 10.8). Six-months OS was 80% ± 10.3%, with a 1-year OS of 20% ± 10.3%. Serum levels of both VEGF and endoglin tended to decrease during the first two cycles of therapy.

Conclusion: Chemoradiotherapy with metronomic dosing of TMZ showed similar toxicity to previous TMZ regimens, and does not appear to improve survival in paediatric DIBSG.

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1. Introduction

Brain stem gliomas constitute 10–20% of childhood central nervous system tumours. The majority are diffuse gliomas, most commonly astrocytomas of the pons. Patients usually present with a short duration of symptoms, including long tract, cranial nerve and cerebellar deficits. Most patients have a rapidly progressive and fatal course and die within 18 months of diagnosis, with a median survival of only 8–11 months.[1]

The mainstay of therapy includes early use of corticosteroids and conventional fractionated radiotherapy, which usually provide transient clinical improvement, but are not curative. Radiotherapy allows steroid reduction or discontinuation in many patients.[1] Despite numerous collaborative studies aimed at improving the treatment for diffuse intrinsic brain stem gliomas (DIBSGs) in children, survival rates remain dismal. New approaches to treatment are needed. Studies evaluating enhanced delivery of radiotherapy utilising acceleration or hyperfractionation show no survival benefits over conventional fractionated radiotherapy.[1–3] Numerous phase I/II trials of neo-adjuvant, concomitant or adjuvant radiosensitising agents, such as topotecan,[4] etanidazole,[5] cisplatin[6] and carboplatin,[7] have failed to demonstrate reliable clinical efficacy.

Despite these disappointing results, radiosensitisation is still an area of considerable interest in paediatric DIBSGs. Temozolomide (TMZ) (Temodal®), an orally administered cytotoxic alkylating agent that readily crosses the blood–brain barrier,[8] is another potential radiosensitiser. Combining TMZ and radiotherapy causes 2- to 3-fold increase in cell kill *in vitro* when compared to radiotherapy alone, likely by synchronising the cell cycle in G2-M arrest—a radiosensitive phase.[9,10] With the Stupp regimen, TMZ has been used in combination with radiotherapy to successfully improve outcomes for adults with glioblastoma.[11,12]

TMZ has traditionally been administered in a standard 5-day schedule every 28 days at maximum tolerated dose: 200 mg/m^2 in paediatric studies.[13,14] An alternative is the metronomic dosing schedule. Although there is no consensus on the definition of 'metronomic', it broadly refers to frequent drug administration at a relatively low dose, without extended rest periods. For the purpose of this study, it refers to daily administration, with only short breaks between cycles. Metronomic TMZ has been tested in adult malignant gliomas[15,16] and paediatric brain tumours.[17,18] Response and survival rates were similar to the 5-day regimen.

Metronomic dosing of TMZ has several benefits, including increasing plasma exposure levels to 1.5- to 2-fold higher than those seen in the 5-day regimen over a similar time period, with no increased toxicity.[15,18] In addition, frequent, low-dose administration of chemotherapy may exert anti-angiogenic effects in various brain tumours.[20] Despite the extent of vascularity in DIBSG being largely unknown, anti-angiogenic approaches are still an area of interest in these very treatment-resistant tumours. Potential serum markers of angiogenesis, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), vascular cell adhesion molecule-1 (VCAM-1), inter-cellular adhesion molecule-1 (ICAM-1) and endoglin, are elevated in patients with various malignancies, including brain tumours.[21]

In a preceding phase I study of metronomic TMZ monotherapy for recurrent paediatric brain tumours, Baruchel et al. report two complete and two partial responses to therapy.[18] These promising findings, combined with the need for new treatment strategies in DIBSG, provided rationale for the current study piloting a novel treatment regimen for these patients: administration of metronomic TMZ concomitantly with standard radiotherapy, followed by daily metronomic TMZ monotherapy.

2. Patients and methods

2.1. *Patient eligibility*

Patients aged 18 years or younger were eligible for inclusion, provided that they had a newly diagnosed diffuse intrinsic lesion centred in the brain stem, confirmed by MRI. Patients were required to have at least two of three typical brainstem symptoms (cranial nerve deficit, long tract signs or ataxia) and a clinical history no longer than 6 months.

Additional eligibility criteria included Karnofsky or Lansky Performance Status of >60% or >50%, respectively, and life expectancy >12 weeks. Participants required laboratory evidence of adequate bone marrow function within 14 days prior to beginning therapy, including: absolute neutrophil count (ANC) >1500/mm^3, platelet count >100,000/mm^3 and haemoglobin >100 g/L. Laboratory evidence of adequate renal and hepatic function was also required, including: urea, creatinine, total and direct bilirubin <1.5 times the upper limit of normal. Patients with a history of frequent vomiting or medical conditions that could interfere with oral medication intake (e.g. partial bowel obstruction) were excluded.

2.2. *Study conduct*

Patients started TMZ within a week of initiating radiotherapy. During treatment induction, TMZ was given daily for 6 weeks at a dose of 85 mg/m^2 in combination with standard radiotherapy treatments in daily fractions of 1.8 Gy over the same 6-week period (total dose: 54 Gy). Dose escalation was not permitted. Patients without evidence of clinical progression 3 weeks post-induction were eligible to commence maintenance therapy. Patients with evidence of clinical progression were removed from the study. Given that no study has identified a correlation between radiological tumour response and either progression-free or overall survival in children with brain stem glioma,[1] patients were not taken off study based solely on radiological progression.

Maintenance therapy consisted of TMZ at 85 mg/m^2 daily for 6 weeks. The 6-week courses could then be repeated, with 1-week (or longer, as required) breaks for haematological count recovery after each course. If counts did not recover within 4 weeks, patients were withdrawn from the study. Tumour response (or lack of progression) was evaluated both clinically and radiologically throughout the treatment period. Patients without clinical progression were eligible for a maximum of one year of total therapy.

All patients were treated prophylactically with trimethoprim–sulphamethoxazole. Concomitant therapy with steroids and anticonvulsants was allowed but was monitored for requirement of dose adjustments. No granulocyte stimulating growth factors or other investigational drugs were allowed.

Toxicity was monitored using the NCI Common Toxicity Criteria (CTC) version 3.0. Dose interruptions and reductions were made for patients with grades 3–4 neutropaenia (ANC <500/mm^3), grades 3–4 thrombocytopaenia (platelet count <50,000/mm^3) or grades 3–4 non-haematological toxicity, unless the toxicity was considered unrelated to TMZ.

Dose-limiting toxicity was established after induction therapy. Patients with continued toxicity after dose reduction to <50 mg/m^2 were withdrawn from the study.

The study was reviewed and approved by the individual institutional ethics committee at each participating centre.

2.3. Surrogate marker analysis

For patients who consented to participate in a biological study evaluating markers of angiogenesis, plasma and urine samples were collected at diagnosis, post-induction cycle and prior to each course of maintenance therapy. The markers endoglin, bFGF, VEGF, VCAM-1 and ICAM-1 were quantified using commercially available ELISA kits (R&D Systems, Minneapolis, MN) in accordance with the manufacturers' recommended methodology.

2.4. Statistical analysis

The primary objective was to estimate the median survival time after study entry. These values were compared to reported historical controls with standard radiotherapy alone (median overall survival 9-months) using the one-sided triangular test as previously reported.[22] Secondary objectives included evaluating time to disease progression, rate of radiological response, rates and types of toxicity as well as reduction or discontinuation of steroid usage. Trends in surrogate markers of angiogenesis were evaluated with paired Student's *t*-tests.

3. Results

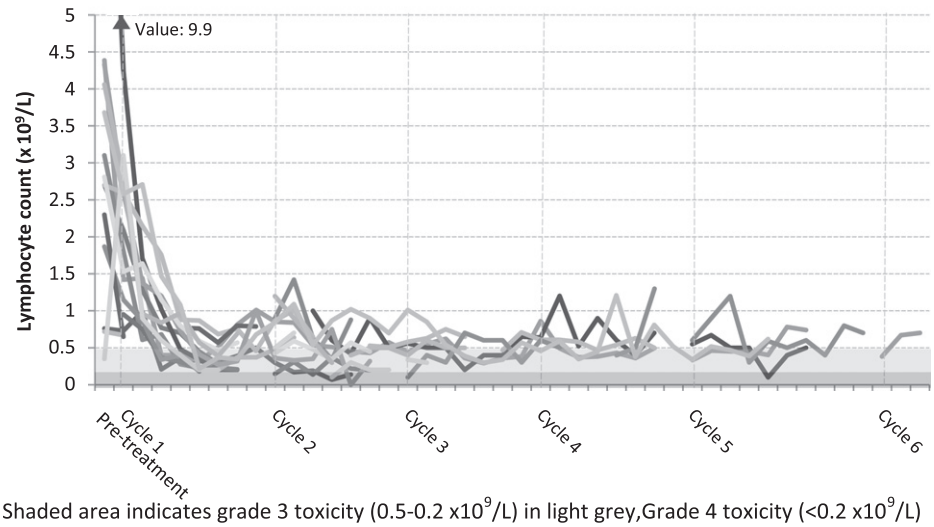
3.1. Patient characteristics

Between April 2005 and July 2007, 15 children with newly diagnosed DIBSGs were enrolled in five centres across Canada. The study group consisted of six males and nine females with a median age of 6.4 years (range 2.4–12.3). The median time to treatment after diagnosis was 7 days (range 2–47). All patients were being treated with corticosteroids at the start of the study. Patients completed a median of three 6-week courses of therapy (range 1–5), the first of which was the induction cycle with concurrent radiotherapy. The families of three patients withdrew consent to continue treatment with TMZ, two after completing cycle 1, and one after completing cycle 2.

3.2. Observed toxicities

Fifteen patients received a total of 40 full courses of TMZ. All patients completed induction cycles. The most common toxicities were haematological. During induction therapy, the only common grades 3–4 toxicity was grade 3 lymphopaenia in thirteen patients (87%), which continued into all subsequent courses as prolonged lymphopaenia (Fig. 1). The remaining two patients had grade 2 lymphopaenia.

Maintenance cycle haematological toxicities were similar to those during induction therapy. In total, grades 3–4 lymphopaenia were present during 28 (93%) of the evaluable maintenance TMZ cycles (Fig. 1). Other grades 3–4 haematological toxicities included leucopaenia, neutropaenia and thrombocytopaenia. Grades 3–4 non-haematological toxicities were



Shaded area indicates grade 3 toxicity (0.5-0.2 x10^9/L) in light grey,Grade 4 toxicity (<0.2 x10^9/L) in dark grey.

Note that some patients required longer than 1 week between treatment cycles for haematologic recovery; measured lymphocyte counts during those weeks are included in the graph, thus causing different lengths of cycles in the x-axis and resulting in gaps in remaining patients' lines.

Fig. 1 – Lymphocyte count throughout treatment cycles for individual patients (*n* = 15). C = cycle number, W = week number.

rare. Grade 3 headache, abdominal pain and shingles each only occurred in one (4%) of the patients. A summary of toxicities is presented in Tables 1 and 2.

Table 1 – Haematological toxicities during induction and maintenance cycles.

Toxicity	Number of cycles (%[a])
Induction cycle (TMZ + radiotherapy)	
Number of evaluable patients/cycles[b]	15
Haematological toxicities	
Lymphopaenia (*n* = 15)	
Grades 1–2	2 (13%)
Grade 3	13[c] (87%)
Leucopaenia (*n* = 15)	
None	7 (47%)
Grades 1–2	7 (47%)
Grade 3	1[c] (7%)
Neutropaenia (*n* = 14)	
None	11 (79%)
Grades 1–2	2[c] (14%)
Grade 3	1 (7%)
Thrombocytopaenia (*n* = 15)	
None	14 (93%)
Grade 3	1[c] (7%)
Maintenance cycle (adjuvant TMZ)	
Number of evaluable patients	15
Number of cycles[b]	31
Haematological toxicities	
Lymphopaenia (*n* = 30)	
Grades 1–2	2 (7%)
Grade 3	22 (73%)
Grade 4	6 (20%)
Leukopaenia (*n* = 29)	
None	1 (2%)
Grades 1–2	24 (83%)
Grade 3	3 (10%)
Grade 4	1 (2%)
Neutropaenia (*n* = 27)	
None	12 (44%)
Grades 1–2	8 (30%)
Grade 3	5 (19%)
Grade 4	2 (7%)
Thrombocytopaenia (*n* = 29)	
None	23 (79%)
Grades 1–2	5 (17%)
Grade 4	1 (3%)
Anaemia (*n* = 29)	
None	11 (38%)
Grades 1–2	18 (62%)

TMZ = Temozolomide.

[a] Totals may not add due to rounding.

[b] Note that data of specific laboratory values were incomplete for various cycles, which led to varying decreased numbers of evaluable cycles for each toxicity category.

[c] In one patient, results taken during time of accidental overdose by parent administering the medication.

Table 2 – Non-haematological toxicities reported by patients during all cycles.

Toxicity	Number of patients (%)
Number of evaluable patients	15
Number of evaluable completed cycles	40
Number of evaluable partially completed cycles	6
Non-Haematological toxicities	
Vomiting	
Grades 1–2	2 (13%)
Headache	
Grades 1–2	2 (13%)
Grades 3–4	1 (7%)
Abdominal pain	
Grades 1–2	1 (7%)
Grades 3–4	1 (7%)
Insomnia	
Grades 1–2	1 (7%)
Anorexia	
Grades 1–2	1 (7%)
Lethargy	
Grades 1–2	1 (7%)
Constipation	
Grades 1–2	1 (7%)
Shingles	
Grades 3–4	1 (7%)
Pruritus (hands and legs)	
Grades 1–2	1 (7%)
Upper respiratory tract symptoms	
Grades 1–2	1 (7%)
Intratumoural haemorrhage	1 (7%)
Intracranial haemorrhage	1 (7%)[a]

[a] Note that this intracranial haemorrhage was suspected to be an intratumoural haemorrhage, but the imaging reports were not clear enough to be certain.

Thirteen serious adverse events were reported, of which seven were considered possibly or probably related to TMZ: during the induction cycle, there was one hospital admission with intratumoural haemorrhage in the absence of thrombocytopaenia, and one admission for unintentional drug overdose resulting in prolonged thrombocytopaenia; during the maintenance cycles, there was one admission for coagulopathy with headache and shunt infection, one for an intracerebral bleed in the absence of thrombocytopaenia and three for thrombocytopaenia (and neutropaenia in two cases). Dose reduction was made for the patient with overdose-associated grade 3 thrombocytopaenia in the induction cycle. The patient completed three additional cycles at reduced dose. No other dose reductions were made. Therapy was delayed for the three patients with prolonged thrombocytopaenia (and neutropaenia). Given that this lasted for more than 4 weeks, all the three required study discontinuation: two during cycle 2 and one during cycle 5. Five patients died within 30 days of the last dose of TMZ. All were related to progressive disease, and not to TMZ.

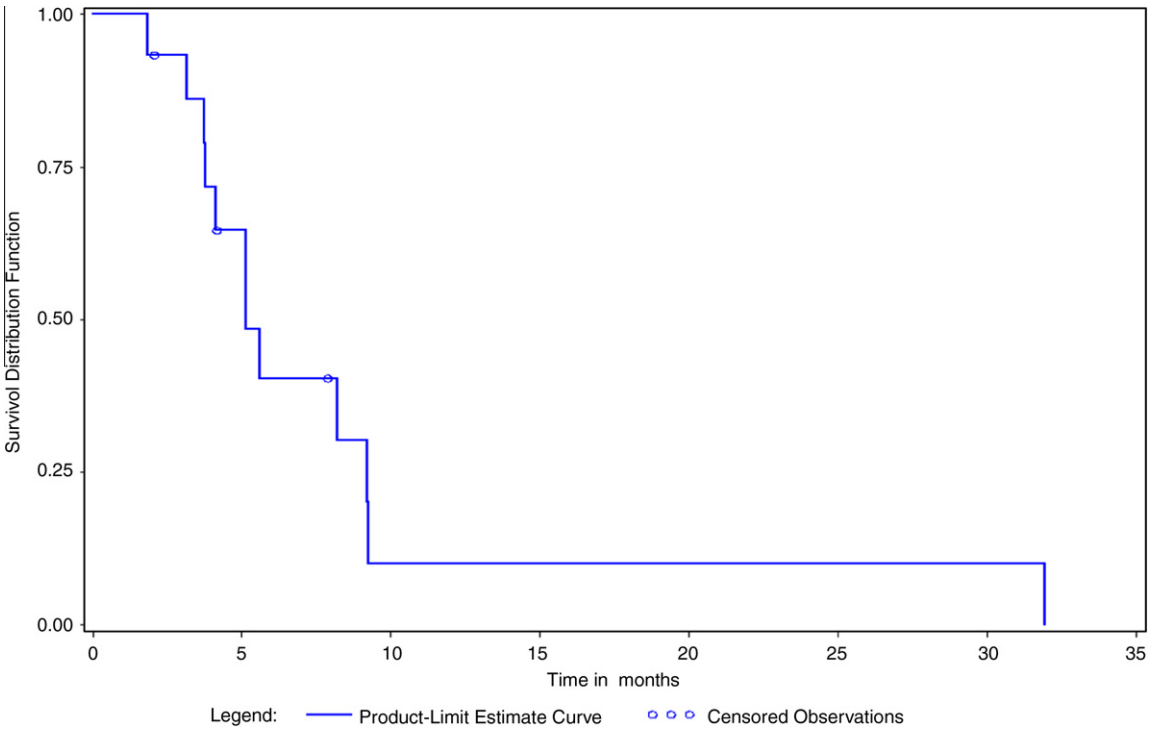


Fig. 2 – Kaplan-Meier analysis for progression-free survival.

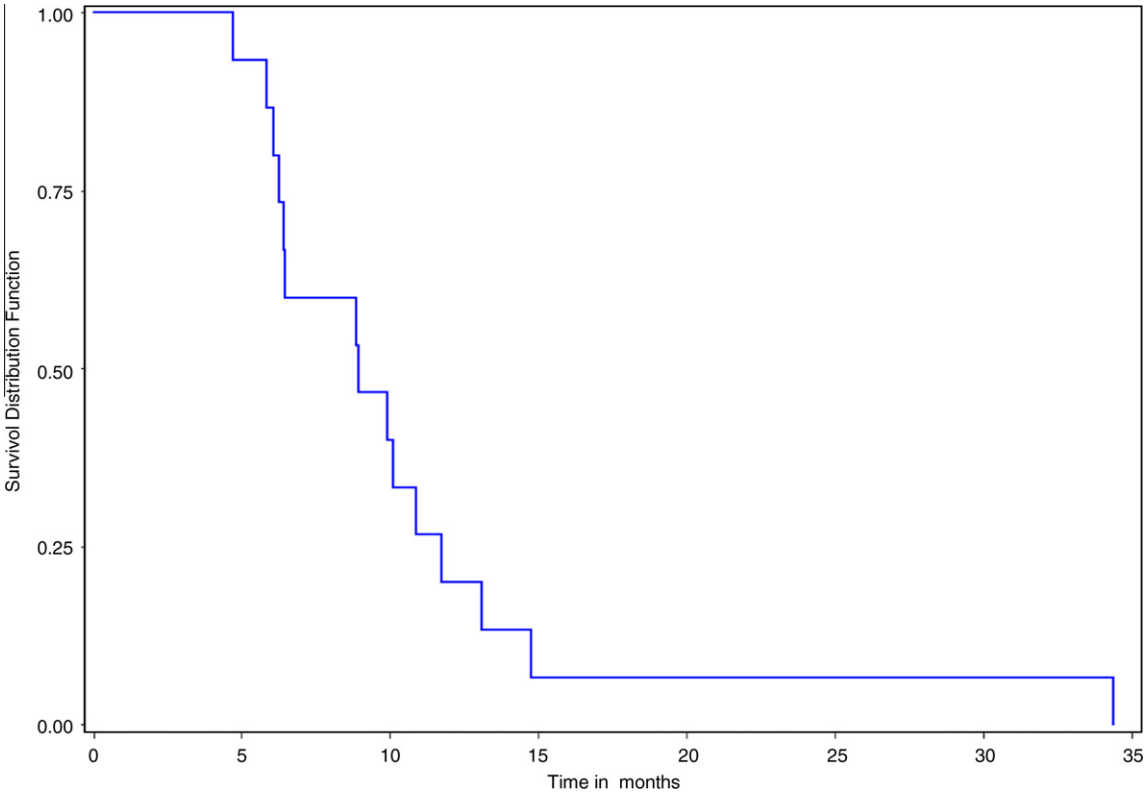


Fig. 3 – Kaplan–Meier analysis for overall survival.

3.3. *Outcome analysis*

Clinical response was evaluated in all 15 patients. Two of the three patients whose families withdrew consent to participate had no evidence of clinical progression at the time of study withdrawal. All patients were treated with curative intent. Median time to progression was 5.13 months (95% CI = 3.8, 7.9). The 6-month progression-free survival (PFS) rate was

33% ± 12% and 1-year PFS was 7% ± 6% (Fig. 2). Overall survival (OS) was similarly poor with a median OS of 9.8 months (95% CI = 6.4, 10.8). By Kaplan-Meier analysis, the 6-month OS was 80% ± 10.3%, with a 1-year OS of 20% ± 10.3% (Fig. 3). An interim analysis was performed for the 15 patients enrolled in the study. By one-sided triangular analysis, OS rates were similar to those of historical controls, indicating that the regimen had no survival benefit. Based on this analysis, the investigators terminated the trial. At the time of this report, all 15 of the patients had died due to progressive disease.

Complete data on corticosteroid requirements were available for seven patients. All of these patients became asymptomatic during the induction cycle, allowing tapering corticosteroids. Six of these patients (86%) were able to discontinue corticosteroids completely during induction therapy, with three remaining off steroids for the duration of their time on study (range 1–5 cycles), while the others required reintroduction of corticosteroids within the first maintenance cycle.

3.4. *Surrogate marker analysis*

Of the potential surrogate markers evaluated, plasma bFGF, VCAM-1 and ICAM-1 did not demonstrate any trends over time. Both plasma VEGF and endoglin tended to decrease during the first two cycles of therapy, after which VEGF tended to rise in those patients who remained on therapy while endoglin appeared to plateau (Figs. 4 and 5). For VEGF, paired *t*-test shows a statistically significant difference between baseline and post-cycle 2 ($p = 0.0377$), but the difference between baseline and

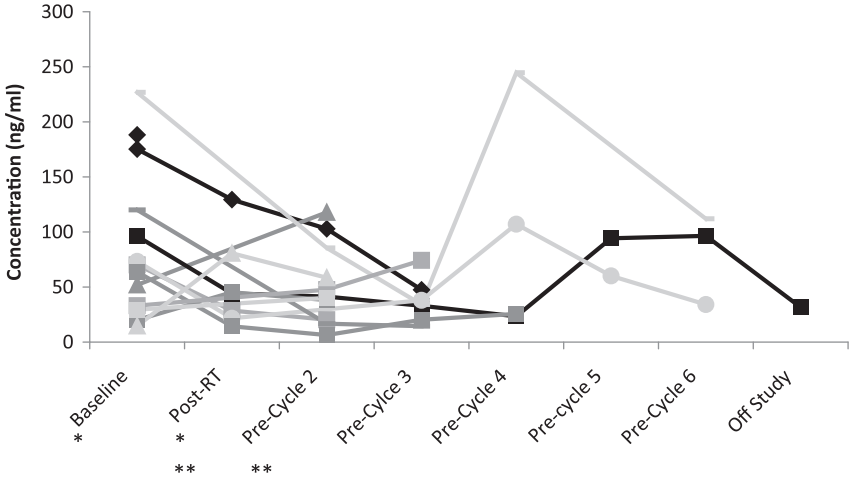


Fig. 4 – Variation in plasma levels of VEGF throughout treatment cycles for individual patients ($n = 13$). RT = radiotherapy. *N = 12; difference is not statistically significant ($p = 0.1065$). **N = 7; difference is statistically significant ($p = 0.0377$).

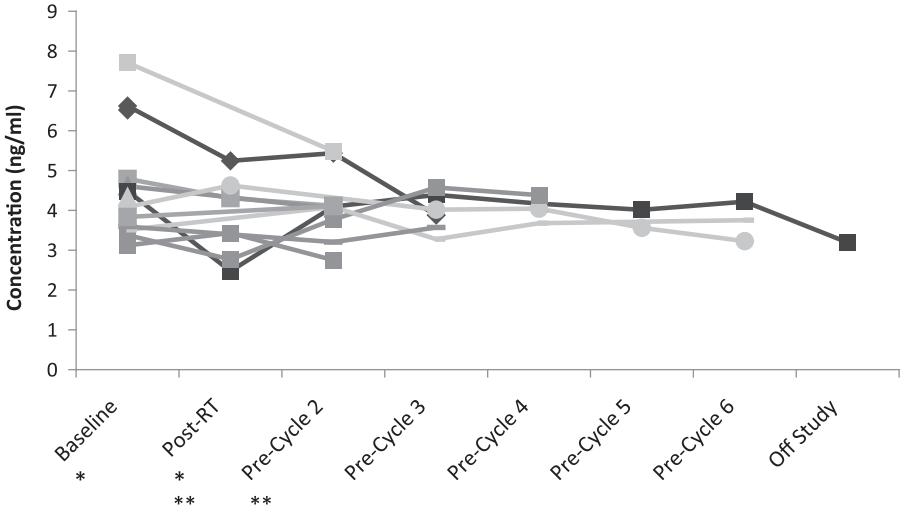


Fig. 5 – Variation in plasma levels of endoglin throughout treatment cycles for individual patients ($n = 13$). RT = radiotherapy. *N = 11; difference is not statistically significant ($p = 0.1763$). **N = 6; difference is not statistically significant ($p = 0.5629$).

post-cycle 1 is not significant ($p = 0.1065$). For endoglin, neither of these differences was significant. No correlations between VEGF or endoglin concentrations and PFS or OS were observed.

4. Discussion

Metronomic low-dose TMZ with concurrent radiotherapy was assessed in 15 paediatric patients with DIBSGs. Myelosuppression was the predominant toxicity. Lymphopaenia was most common, occurring in all induction and maintenance cycles. Previous studies of metronomic TMZ monotherapy have also demonstrated high rates of prolonged lymphopaenia,[18,19] suggesting that this is an effect of the TMZ itself, rather than its combination with radiotherapy. Infections associated with immune suppression have been previously reported with metronomic TMZ including herpes simplex, herpes zoster, mucocutaneous candidiasis and *Pneumocystis carinii* pneumonia.[18,19] Two infections occurred during the course of the current study; one patient had grade 3 herpes zoster and another had grade 3 shunt infection of unknown aetiology. Both had grade 3 lymphopaenia at the time. There were no cases of *Pneumocystis carinii* pneumonia, however all patients were on trimethoprim–sulphamethoxazole.

Non-haematological toxicities were uncommon. In studies assessing TMZ chemoradiotherapy followed by standard 5-day dosing of TMZ, vomiting was the most common non-haematological toxicity,[23,24] and was often grades 3–4. In this study and a previous study of metronomic TMZ,[18] vomiting was reported for few patients and was grades 1–2.

Seven TMZ-related serious adverse events were reported. Prolonged grade 4 thrombocytopaenia requiring study discontinuation occurred in three patients. Prolonged thrombocytopaenias leading to dose reductions and treatment delays have also been reported in paediatric studies assessing TMZ monotherapy given in the metronomic[18] or 5-day regimen.[13,14] In the current study, intratumoural haemorrhage was confirmed in one patient and suspected in another. Broniscer et al.[25] concluded that children with DIBSG have a definite risk of developing intratumoural haemorrhage, with an 8.9% 6-month cumulative incidence. In this retrospective study, the risk of haemorrhage was not related to treatment characteristics, and there is no suggestion that TMZ or chemotherapy concomitant with radiation increased the risk.

Overall, it is clear that the assumption of lower toxicity with low-dose TMZ is flawed, as this study demonstrated that metronomic TMZ has significant haematological toxicities, most notably prolonged lymphopaenia, putting patients at risk of opportunistic infections.

The phenomenon of pseudo-progression has been widely described in relation to concomitant TMZ and radiotherapy in glioblastoma multiforme (GBM). A review of clinical manifestations of disease and post-radiation scans does not support the existence of pseudo-progression with this regimen in this sample of paediatric DIBSG patients. However, the sample is too small to conclude this definitively.

With respect to the surrogate marker analysis, the initial decrease in both VEGF and endoglin during induction suggests that radiotherapy, or its combination with TMZ, may exert some activity on the expression of these markers. However, the small sample size and substantial interpatient variability preclude generalisation of the trends observed. Published data reporting serum VEGF or endoglin levels in patients treated solely with radiotherapy are not available. In a study by Merchant et al.,[27] patients with ependymoma treated with radiotherapy had decreased serum VEGF both during and at 12 months following radiation, but these patients had also undergone surgical tumour resection and many had been on alternate treatment regimens previously. Thus, while the trend for reduction of these markers induction phase is interesting, the absence of a control group makes it impossible to link this trend to the addition of metronomic TMZ to radiotherapy. In addition, although serum VEGF seems to be a reliable marker of angiogenic activity in multiple tumour types,[28] there is evidence that it does not correlate well with VEGF expression within brain tumours.[29,30]

This regimen of TMZ with radiotherapy does not improve DIBSG patient prognosis when compared to historical controls. These results are disappointing, given the success of the Stupp regimen[11,12] in newly diagnosed adult GBM, which was reported as safe and well tolerated, with survival benefits compared to radiation alone and to historical controls. There are several possible reasons for the failure of TMZ chemoradiotherapy to result in clinical responses in DIBSG, despite the successful treatment of GBM. Firstly, although DIBSG, like GBM, is considered a high-grade tumour based on its rapid clinical course, in cases when DIBSG tumours are biopsied, they sometimes show low-grade histology. This may respond differently to TMZ. Secondly, while GBM are known to be highly vascular tumours, evidence for vascularity of DIBSG is lacking. These tumours tend to be non-enhancing on imaging implying low vascularity, which would decrease drug delivery to the tumour, despite the fact that TMZ readily crosses the blood–brain barrier.[9] Although paediatric astrocytomas, GBM and medulloblastoma/PNET are considered highly vascular,[20] there are no studies on the extent of vascularity in paediatric DIBSG, likely because there are no DIBSG animal models, biopsies are rarely performed and sample sizes are usually limited.

In phases I and II studies of single-agent TMZ in standard 5-day dosing for relapsed or progressive paediatric brain tumours by the United Kingdom Children's Cancer Study Group,[13,14] there were no reported objective responses in DIBSG. However, TMZ did result in durable disease stabilisation in these patients, which was felt deserving of further study in this very challenging tumour group.

Disappointingly, the treatment regimen assessed in the current study showed no survival benefit for DIBSG patients. In a recent double-arm study of 85 adult GBM patients, Clarke et al.[26] compared TMZ chemoradiotherapy followed by either metronomic or dose-dense TMZ maintenance therapy. Dose-dense TMZ (given on days 1–7 and 15–21 of a 28-day cycle) was more clinically effective than metronomic dosing, with 80% versus 69% 1-year OS rates, respectively. Although not assessed for statistical significance, the findings suggest that the anti-tumour effects of the regimen used in the current study may be improved using standard dose-dense TMZ as maintenance therapy; this was not the case, however, in several recent trials in paediatric DIBSG patients. Both Jalali et al.[23] and Chiang et al.[31] assessed TMZ chemoradiotherapy

followed by adjuvant TMZ in a 5-day high-dose regimen, and found a 1-year survival of 35% and 51% and median OS of only 9.2 and 12.3 months, respectively. Sirachainan et al.[24] used a similar regimen combined with cis-retinoic acid. Survival rates were poor but slightly improved, with a 1-year OS of 58%, and median survival time of 13.5 months. This was not assessed for significance and requires further investigation in a larger series of patients.

In conclusion, the treatment of children with DIBSG using TMZ chemoradiotherapy followed by metronomic TMZ has moderate toxicity, but there is no added benefit for patients compared to radiotherapy alone, despite promising results of previously published studies of metronomic dosing.[15,18,20] Even with extensive multi-centre efforts, patient survival rates have remained stable over the past few decades. Investigators should continue to assess new approaches in an effort to improve the dismal prognosis of these tumours.

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Conflict of interest statement

None declared.

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