The use and effectiveness of temozolomide in children with central nervous system tumours: a survey from the Canadian Paediatric Brain Tumour Consortium

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ABSTRACT

Objective

To describe the use of temozolomide (TMZ) in Canadian children treated for brain tumours and to evaluate survival and predictors of survival for children treated with this agent.

Methods

A survey was conducted within the Canadian Paediatric Brain Tumour Consortium (CPBTC), a group of tertiary care centres in pediatric neuro-oncology (n = 16) in Canada that are involved in the treatment of children with central nervous system tumours.

Results

In 10 of the 16 participating pediatric oncology centres of the CPBTC, 137 children with brain tumours were treated with TMZ between January 2000 and March 2006. Although 33% of the children were enrolled into a clinical trial, 67% were treated outside open studies. Most patients (72%) received TMZ treatment on recurrence of their brain tumour (first or subsequent). The most commonly administered regimen was single-agent TMZ 150–200 mg/m^2 administered on 5 consecutive days every 28 days. The median duration of TMZ treatment was 141 days (range: 4–1102 days). Response data were provided for 127 of the 137 patients, of whom 6 showed a complete response. Sixteen patients experienced a minor or partial response, 53 had stable disease, and 52 had progressive disease. Of 32 patients alive at last follow-up, 19 had a diagnosis of low-grade glioma.

Conclusions

Temozolomide is used in a variety of pediatric brain tumours, often at the time of recurrence. The lack of insight into clear indications for this agent in pediatric brain tumours—used either alone or in combination therapy—may be a result of suboptimal design of phase I and II studies and a lack of phase III trials in the pediatric brain tumour population.

KEY WORDS

Temozolomide, children, pediatric, CNS, brain tumour

1. INTRODUCTION

Temozolomide (TMZ) is an oral alkylating agent that received accelerated approval from the U.S. Food and Drug Administration in 1999 because of its promising activity in high-grade glioma (HGG) in adults. A European Organisation for Research and Treatment of Cancer randomized trial eventually confirmed a significant survival benefit in adults with newly diagnosed glioblastoma multiforme when TMZ was added concomitant and adjuvant to standard radiation treatment [1–3].

In the late 1990s, TMZ was introduced into the management of pediatric brain tumours. In addition to anecdotal case reports and retrospective studies, several phase I and II pediatric studies have since been published [4–9], but no phase III study with this agent has ever been conducted. The low toxicity profile of TMZ, its oral administration, and the lack of effective treatment alternatives in certain malignant brain tumours or recurrent pediatric brain tumours have all contributed to widespread use of TMZ in pediatric clinical practice. However, evaluation of the effectiveness of TMZ has been limited, and its impact in current pediatric neuro-oncology practice is unknown.

In the present study, we set out to describe the use of TMZ among Canadian children treated for brain tumours and to evaluate survival and predictors of survival for children treated with this agent.

2. METHODS

The Canadian Paediatric Brain Tumour Consortium (CPBTC) is a network of 16 pediatric neuro-oncology programs in Canada. Since its inception in 2002, the CPBTC has regularly communicated by teleconference. These monthly conferences serve to review and re-evaluate current practice in neuro-oncology and to support or initiate research projects and collaborative studies. Discussions during one teleconference about indications for TMZ resulted in the decision to undertake a descriptive retrospective national study.

A questionnaire was sent to all participating centres to collect data on the use of TMZ, its indications, and its outcomes in all children treated with this agent between January 2000 and March 2006. Ten centres participated in the study, 2 smaller centres indicated that they had not treated any children with TMZ during the applicable time period, and 4 centres did not participate. The data collected included histologic diagnosis (when available), metastatic status at initial diagnosis, whether the child was treated with TMZ at initial diagnosis or at first or subsequent recurrence, and whether the child was enrolled into a clinical trial. In addition, data on TMZ dose, schedule, concomitant treatment, best response to treatment on imaging, and need for admissions and transfusions were collected. We requested information on best response to TMZ on magnetic resonance imaging. Response was categorized as complete resolution of tumour; minimal response, with 25%–50% reduction; partial response, with greater than 50% reduction; stable disease (SD), with less than 25% decrease; and progressive disease (PD), with more than 25% increase in tumour size or new lesions.

The primary outcome was overall survival. Variables examined that were potentially associated with survival were pathology diagnosis, location, metastasis (present or absent), age at treatment (≤3, >3 to <10, ≥10 years), dose and schedule of TMZ treatment, and administration of TMZ treatment alone or in combination with other drugs.

2.1 Statistical Analysis

All statistical analyses were performed using the SAS software program (SAS-PC, version 9.1: SAS Institute, Cary, NC, U.S.A.). Categorical clinical data are expressed descriptively with numbers and percentages. Overall survival time was calculated as time from the start of TMZ treatment to death or to last follow-up in surviving patients, and was described using Kaplan–Meier curves. To determine whether survival was different in various subgroups, the log-rank test was used. Statistical significance was considered at a p value of less than 0.05.

3. RESULTS

In 10 pediatric oncology centres of the CPBTC, 137 children with brain tumours were treated with TMZ between January 2000 and March 2006. Of those 137 patients, 45 (33%) were enrolled in a clinical trial: 10 participated in ongoing Children's Oncology Group (COG) studies (search for ACNS0126, ACNS0423, and ADVL0011 at www.cancer.gov/clinicaltrials/search), and 35 were enrolled in either a Canadian phase I/II study [10] or a Canadian multicentre pilot study [11]. The remaining 92 patients (67%) were treated outside of an open study.

In 38 patients, TMZ was part of initial treatment (including 17 patients treated in an open study), but most patients (n = 99, 72%) were treated at either first or a subsequent relapse; 28 of those 99 patients were enrolled to a trial. Table I shows stage of disease, pathology at initial diagnosis, and age of patients at time of treatment with TMZ.

The diagnosis in 50% of patients was either HGG (n = 34) or brainstem glioma (n = 34). The remaining diagnoses were low-grade glioma [LGG (n = 28)], medulloblastoma (n = 19), ependymoma (n = 13), supratentorial primitive neuroectodemal tumour (n = 3), ependymoblastoma (n = 2), atypical teratoid rhabdoid tumour (n = 2), choroid plexus carcinoma (n = 1), and gliosarcoma (n = 1). Most patients (85%) did not have evidence of dissemination on imaging, and cerebrospinal fluid staging was not routinely performed at initial diagnosis.

TABLE I Characteristics of the patients receiving temozolomide (TMZ)

Characteristic	(n)	*(%)*
Patients	137	100
Age at TMZ treatment (years)		
≤3	7	5
>3 to <10	59	43
≥10	71	51
Diagnoses		
High-grade glioma	34	25
Brainstem glioma	34	25
Low-grade glioma	28	20
Medulloblastoma	19	14
Ependymoma	13	9
Other	9	7
Metastasis at diagnosis		
M0	116	85
M+	21	15

3.1 Evolution of Prescription Over the Study Period

Quantitatively, use of TMZ in the surveyed Canadian institutions increased steadily over the study period, particularly between 2000 and 2003 (Figure 1).

3.2 Temozolomide Dosing and Tolerability

The most common TMZ regimen was 150–200 mg/m^2 administered on 5 consecutive days every 28 days (n = 82). A smaller subset of children received TMZ in metronomic dosing: 50–100 mg/m^2 for 42 consecutive days, followed by a 1-week rest period (n = 36). The other patients received varying TMZ doses, mainly lower doses in varying schedules: that is, 3 weeks of treatment, with 1 week of rest, or an unspecified schedule. In 109 children, TMZ was given as a single agent (with or without irradiation). In 27 children, TMZ was given in combination with etoposide (n = 10), *cis*-retinoic acid (n = 9), lomustine (n = 4), tamoxifen (n = 41), tamoxifen plus celecoxib (n = 1), thalidomide plus celecoxib (n = 1), or topotecan (n = 1).

Table II illustrates TMZ tolerability, which was evaluated as either the need for admission or for transfusion. Platelet or red blood cell transfusions (or both) were required in 18 patients (13%), and 41 patients (33%) required admission during TMZ treatment. When the reasons for admission were provided, they included progressive symptoms (n = 6), fever and neutropenia (n = 5), and infection (n = 8).

3.3 Overall Response Data

Response data were provided for 127 patients (Table II). Most patients showed SD or PD. Only 6 patients showed complete response. One patient with LGG remains without evidence of progression at 5 years of follow-up. Another ependymoma patient was treated at recurrence and underwent surgical resection in the context of SD; he remains without evidence of disease at 5.5 years of follow-up. Of the remaining 4 patients, 3 with HGG received TMZ as an upfront treatment with radiation. They eventually experienced recurrence and died of progression at a median 26 months (range: 16–41 months) after initial diagnosis.

During the follow-up period, 105 of 137 patients succumbed to their disease. Of the 32 patients alive at last follow-up, 19 have a diagnosis of LGG. Overall survival remains poor for brainstem glioma and unsatisfactory for HGG and for recurrent medulloblastoma and ependymoma (Table III).

The median duration of TMZ treatment was 141 days (range: 4–1102 days), with 30 children treated for more than 1 year. A patient with 1102 days of TMZ treatment had been diagnosed with leptomeningeal dissemination of a ganglioglioma. Treatment, consisting of TMZ with *cis*-retinoic acid, was stopped because of SD and concerns about cumulative toxicity. The child succumbed to his disease 33 months after discontinuation of TMZ.

Table IV shows that location was the only significant predictor of overall survival, the prognosis for supratentorial tumours being better than that for posterior fossa and brainstem tumours. This difference is likely related to the histologic diagnosis of LGG; tumour location is considered a confounder.

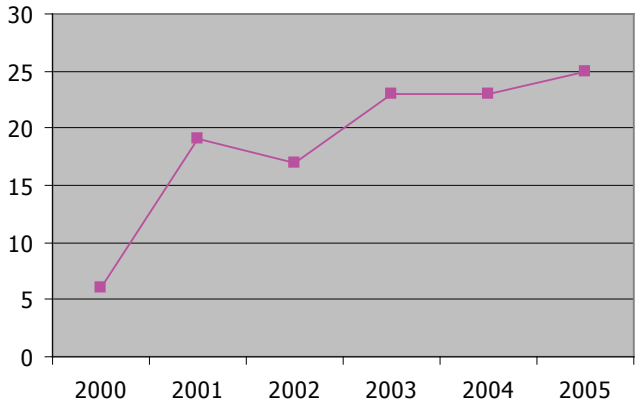

FIGURE 1 *Evolution of temozolomide prescription over time, patients per year.*

TABLE II Temozolomide (TMZ) side effects and response

Parameter	(n)	*(%)*
Admissions for TMZ toxicity	41	33
Required transfusion		
No	113	86
Platelet (PLT) transfusions	8	6
Red blood cell (RBC) transfusions	8	6
PLT and RBC transfusions	2	1.5
Best response to TMZ		
CR/NED	6	5
MR/PR	16	13
Stable disease	53	42
Progressive disease	52	41

CR = complete resolution; NED = no evidence of disease; MR = minimal response; PR = partial response.

TABLE III Survival from initiation of temozolomide treatment, mean ± standard error

Tumour type	*Overall survival (%)*	
	At 1 year	*At 2 years*
High-grade glioma	62.0±0.9	25.7±0.8
Brainstem glioma	6.5±0.4	3.2±0.3
Low-grade glioma	75.0±0.8	71.1±0.9
Medulloblastoma	40.5±1.2	29.0±1.1
Ependymoma	38.5±1.3	28.9±1.3

TABLE IV Predictors of survival from initiation of temozolomide (TMZ) treatment, mean ± standard error

Variable	Patients *[n (%)]*	*1-Year survival*	p *Value*
Location			
Brainstem	42 (31)	26.3±0.4	0.003
Post fossa	35 (26)	42.9±0.9	
Supratentorial	54 (41)	68.4±0.7	
Other	6 (2)		
Metastasis at diagnosis			
M0	116 (85)	46.3±0.5	0.5
M+	21 (15)	31.2±1.0	
TMZ treatment			
As part of a study	45 (33)	43.3±0.8	0.9
Outside of a study	92 (68)	44.5±0.5	
TMZ treatment			
At initial diagnosis	38 (28)	49.3±0.8	1.0
At first or later recurrence	87 (63)	39.3±0.5	
Other/unknown	12 (9)		
Age at TMZ treatment (years)			
≤3	7 (5)	83.3±1.5	0.1
>3 to <10	59 (43)	33.9±0.6	
≥10	71 (52)	49.2±0.6	
TMZ dose and schedule			
150–200 mg/m^2×5 days	82 (60)	48.2±0.6	0.3
50–100 mg/m^2×42 days	36 (26)	39.8±0.8	
Other	19 (14)	33.3±1.1	
TMZ ± radiation			
Single agent	110	44.5±0.6	0.3
With additional agent	27	50.8±1.0	

4. DISCUSSION

Our study shows that use of TMZ in pediatric neuro-oncology has been increasing steadily. This change in practice was certainly triggered by the enthusiasm of the neuro-oncology community after promising results with TMZ in the adult population [1,2].

Data on the efficacy of TMZ were indeed sparse in early 2000—and mostly anecdotal. The results of the phase I North American and European pediatric studies were reported in 1998 and suggested activity in HGG, brainstem glioma, medulloblastoma, and supratentorial primitive neuroectodermal tumour. Subsequent pediatric reports were mostly anecdotal until the results of a larger phase II study conducted in the United Kingdom and France became available, reporting no convincing evidence of activity in either supratentorial and cerebellar HGG or intrinsic brainstem tumours. Recent pediatric studies of radiotherapy with concomitant TMZ have since confirmed the lack of significant impact on outcomes in children with diffuse pontine glioma or HGG [12–15]. Some studies have reported a more positive contribution of TMZ in LGG and an interesting response rate in recurrent medulloblastoma [9,16–19]. The trend in TMZ use in pediatric neuro-oncology practice is therefore not supported by clinical results observed in early studies. Multiple reasons may account for these findings, and the trend is not surprising in the context of poor-prognosis diseases in which treatment options are lacking. The good toxicity profile of temozolomide may also account for its success.

The results of our survey suggest that some children treated with TMZ for recurrent tumours of the central nervous system (CNS) achieve a response. However, the overall survival rate of 32/137 is disappointing, particularly considering that 19/32 surviving children had LGG—a tumour with high survival expectancy [17].

Our results accord with recent reports of TMZ use in the pediatric CNS tumour population. Two phase II studies, one at a single institution (n = 24), and one from COG (n = 122) revealed only limited overall objective response to TMZ in children and adolescents with recurrent CNS tumours [5,6]. When compared with historical controls, patients treated with TMZ for newly diagnosed diffuse intrinsic pontine glioma showed no significant difference in outcome [13,20]. And a multi-institutional study that included 31 pediatric patients with newly diagnosed HGG did not find any significant difference in outcome when TMZ was added to radiation [16]. Along those lines, the COG phase II study in children with newly diagnosed HGG reported 71 treatment failures within 100 eligible patients at a median follow-up of 11 months [12]. These publications demonstrate that the prognosis for children with deep-seated lesions and HGG remains generally poor despite TMZ.

Our survey showed a wide difference between physicians in prescribed schedules and dosing. The benefit of the metronomic schedule as compared with other schedules is still uncertain [21]. A study evaluating the pharmacokinetic parameters of TMZ did not find a statistically significant difference between adults and children [22]. A phase I study evaluating the role of metronomic dosing compared with the 5-day TMZ schedule in recurrent pediatric brain tumours reported an increase by a factor of 1.5 in cumulative exposure to the drug, which was well tolerated and suggested potentially higher efficacy [10]. The present survey could not find a significant difference in overall outcome between children treated with TMZ 150–200 mg/m^2 for 5 days every 28 days and those treated with 50–100 mg/m^2 for 42 days with a 7-day rest.

Phase I studies supported synergistic efficacy for TMZ in combination with other anti-neoplastic drugs [8,23–26], but our survey could not identify a significant difference in overall survival with combination therapy. A prolongation of survival in some patients may be possible, but data on progression-free survival were insufficient in the present study.

Despite unsatisfactory results with TMZ in pediatric brain tumours, use of TMZ has been increasing, a situation that may be partly attributable to specific aspects of this agent. As an oral agent, TMZ is nearly 100% bioavailable and easy to administer, and it does not cause alopecia. Moreover, tolerability with TMZ is excellent, and the drug has a low toxicity profile [5,10]. It therefore has excellent properties for children, particularly in the context of supportive care and palliation. Although TMZ may not affect ultimate outcome, it does not appear to impair quality of life or to cause significant toxicities, at least in the short term, and it may prevent families from looking for more toxic options. However, TMZ may not be without danger in children with LGG. Reports on TMZ-related myelodysplastic syndromes [27] should caution against prolonged administration of TMZ in LGG patients who have excellent overall survival, but are facing significant LGG-associated morbidities.

5. CONCLUSIONS

Overall, the role of TMZ in pediatric brain tumours remains uncertain. The lack of clear indications for this agent in pediatric brain tumours, used either alone or in combination therapy, may be the result of suboptimal design of phase I and II studies and a lack of phase III trials in the pediatric brain tumour population.

6. CONFLICT OF INTEREST DISCLOSURES

The authors declare that no financial conflict of interest exists.

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