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Temozolomide Monotherapy for the Treatment of Patients with Glioblastoma That Has Relapsed or Progressed Following Prior Therapy

J. Perry, W. Mason, D. Macdonald, and A.E. Haynes

Report Date: March 1, 2011

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CED-CCO Special Advice Report 20

Temozolomide Monotherapy for the Treatment of Patients with Glioblastoma That Has Relapsed or Progressed Following Prior Therapy

J. Perry, W. Mason, D. Macdonald, and A.E. Haynes

Report Date: March 1, 2011

SUMMARY

QUESTION

Does the use of temozolomide monotherapy in patients with glioblastoma (GB) that has relapsed or progressed following prior therapy result in improved outcomes?

The outcomes of interest are overall survival (OS), progression-free survival (PFS), time-to-progression (TTP), objective response (OR), duration of response, quality of life (QOL), and adverse effects.

TARGET POPULATION

Adult patients with GB that has relapsed or progressed following prior therapy.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- **Temozolomide is a treatment option in patients with GB that has relapsed or progressed following prior therapy.**

QUALIFYING STATEMENTS

- There are several treatment options in patients with recurrent GB including, temozolomide, lomustine, and bevacizumab. All these agents have demonstrated activity in recurrent GB. In addition, several doses and schedules of temozolomide have been studied in this disease setting, and have shown activity. However, no comparative data exist that would support or refute the use of one agent over another, or the use of one dose and/or schedule over another. The choice of agent and the dose/schedule should be at the discretion of the treating physician.

KEY EVIDENCE

Three randomized controlled trials that enrolled patients with recurrent GB who did not receive temozolomide during first-line therapy were identified. The authors of one trial reported data for only 20 patients; no statistical differences were reported for OS and PFS (1). Yung et al (2) reported a significant difference in OS in favour of temozolomide (200 mg/m^2 per day, days 1-5, every 28 days [five-day schedule]) compared to procarbazine (60% at six months versus 44% at six months, respectively; HR, 1.44; p=0.019). The authors also reported a significant difference in PFS, in favour of temozolomide (21% at six months versus 8% at six months; HR, 1.54; p=0.008). Brada et al (3) reported no significant differences in OS or PFS for patients who received temozolomide (five-day schedule or temozolomide at 100 mg/m^2 per day, days 1-21, every 28 days [21-day schedule]) compared to combination chemotherapy with procarbazine, lomustine, and vincristine (OS HR, 0.91; p=0.35; PFS HR, 0.89; p=0.23). No randomized trials investigating the use of temozolomide in patients with recurrent GB who received temozolomide during first-line therapy were identified.

Several single-arm phase II trials have investigated the use of temozolomide in patients with recurrent GB who received temozolomide during first-line therapy. Six trials were identified in which all the enrolled patients received temozolomide during first-line therapy (4-9). The number of enrolled patients with GB ranged from 12 (6) to 91 patients (4). Three of the trials investigated a daily schedule of temozolomide (40-50 mg/m^2) (4-6). Perry et al (4) reported one-year OS of 27.3% of patients who progressed early (i.e., before completing six cycles of adjuvant temozolomide; early group), 14.8% of 28 patients who progressed during extended adjuvant therapy (i.e., while receiving extended adjuvant temozolomide; extended group), and 28.6% of 27 patients who progressed after completing adjuvant treatment (rechallenge group). Kong et al (5) reported a median OS of 9.4 months in 38 patients. In an earlier trial, Kong et al (6) reported a median OS of 11 months in 12 patients. The median PFS ranged from 1.8 months in the extended group of Perry et al (4) to 6.0 months in Kong et al (6). Berrocal et al (7) and Strik et al (8) investigated the use of temozolomide, using a 21-day schedule. Strik et al (8) reported a median OS of 17.9 months in 18 patients, whereas Berrocal et al (7) did not report on OS. PFS was reported only by Berrocal et al (7) and was 0% at six months. Yang et al (9) investigated the use of temozolomide using a five-day schedule at 150-200 mg/m^2. The authors reported that the median OS was 3.9 months for 16 patients and the median PFS was 1.8 months.

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FULL REPORT

QUESTION

Does the use of temozolomide monotherapy in patients with glioblastoma (GB) that has relapsed or progressed following prior therapy result in improved outcomes?

The outcomes of interest are overall survival (OS), progression-free survival (PFS), time-to-progression (TTP), objective response (OR), duration of response, quality of life (QOL), and adverse effects.

INTRODUCTION

GB is the most common primary malignant brain tumour, and the incidence of GB is increasing to as high as 20/100,000, especially in middle-aged to elderly individuals (1). Unfortunately GB is a genetically heterogeneous disease, and multiple mechanisms of treatment resistance are increasingly described. The treatment of recurrent GB is especially problematic as very few effective therapies are available, and none have been compared in head-to-head studies.

In 2005, Stupp et al (2) demonstrated in a randomized controlled trial that the addition of temozolomide, given orally for 42 consecutive days in combination with standard radiotherapy (RT) (60Gy/30 days), and followed by six months of adjuvant temozolomide, clearly increases both median survival and one- and two-year survival compared to standard radiotherapy alone in patients with newly diagnosed GB. This therapy is now considered standard of care in Canada (3), including Ontario where it is routinely used as part of front-line treatment. At present it is available to practitioners through third-party prescription plans or the exceptional access program.

Inevitably, virtually all GBs recur. Options at the time of recurrence depend upon the location of the recurrent disease (for example, local recurrence versus diffuse recurrence in the brain or neuroaxis). Re-operation is considered for individuals with larger recurrences that are accessible to surgical resection and who might benefit from the reduction in mass effect and steroid use. Re-irradiation is not commonly considered. For patients with reasonable neurological function and QOL, systemic therapy is often considered in practice. For patients who are unlikely to benefit from systemic therapy (e.g., patients with poor performance status, inability to tolerate therapy), palliative measures are considered.

Conventional systemic therapies were primarily evaluated prior to 2005 when patients did not receive temozolomide during first-line therapy. Prior to 2005, patients with recurrent GB were temozolomide-naïve at recurrence as they would have received radiation treatment alone or radiation with a nitrosourea chemotherapeutic agent (carmustine [BCNU] or lomustine [CCNU]) for their first-line therapy. These patients were routinely offered temozolomide at the time of recurrence (approved for both recurrent anaplastic astrocytoma and GB and, funded in Ontario under Limited Use Code 320). The majority of the other systemic therapies were also evaluated in the pre-2005 era, before the standard of care using upfront chemotherapy with temozolomide came into common practice.

Systemic therapy options now available in Ontario include nitrosoureas (BCNU or CCNU), procarbazine, etoposide, and carboplatin. Of these, only lomustine has been evaluated at the time of progression following first-line therapy with RT, temozolomide, and adjuvant temozolomide. In a randomized phase III trial in recurrent GB, lomustine was chosen as the comparator drug to evaluate the efficacy of the small molecule inhibitor enzastaurin (4). Enrolment was terminated at 266 patients (enzastaurin n=174, lomustine n=92) after a planned interim analysis for futility. The six-month PFS for enzastaurin of 11.1% and for lomustine of 19% was no higher than prior reports of efficacy in the pre-temozolomide era. These data point to the urgent unmet need for more effective therapies in recurrent GB.

Temozolomide is active in a variety of treatment schedules, including the standard 150-200mg/m^2, days 1-5/28 as described in the original temozolomide studies. Alterative schedules have been explored, given putative advantages such as dose density and metronomic dosing. The Committee to Evaluate Drugs (CED)-Cancer Care Ontario (CCO) subcommittee asked the Neuro-oncology Disease Site Group (DSG) of CCO's Program in Evidence-based Care (PEBC) to provide advice on the use of temozolomide in patients with GB that has relapsed or progressed following prior therapy.

METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC) of CCO, is a convenient and up-to-date source of the best available evidence on temozolomide monotherapy in patients with GB that has relapsed or progressed following prior therapy, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (1950 to December Week 4, 2010 [January 11, 2011]), EMBASE (Ovid) (1980 to Week 01, 2011 [January 11, 2011]), and the Cochrane Library (January, 2011) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO), 2005 to 2010, were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp), and the National Institute for Clinical Excellence (http://www.nice.org.uk/) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were:

1. Published full report articles or published meeting abstracts of randomized trials comparing temozolomide monotherapy to placebo, best supportive care, or another agent or combination of agents.
2. Published full report articles of non-comparative phase II trials investigating temozolomide monotherapy.
3. Published full report articles of systematic reviews, meta-analyses, or practice guidelines investigating or providing advice on the use of temozolomide monotherapy in patients with GB that has relapsed or progressed following prior therapy.

In addition, the trials must have included patients with GB that has relapsed or progressed following prior therapy, and the published studies must have reported data on one or more of the following outcomes: OS, PFS, TTP, OR, duration of response, QOL, or adverse effects.

Exclusion Criteria

Studies were excluded if they were:

1. Abstracts of non-randomized phase II trials.
2. Practice guidelines that did not report whether a systematic literature search was conducted.
3. Letters, comments, books, notes, or editorial publication types.

Articles published in a language other than English, because of financial considerations for translation.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data were pooled using the Review Manager software (RevMan 5.0) provided by the Cochrane Collaboration (5). Since hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (6), those were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CI) using the methods described by Parmar et al (6). A random effects model was used for all pooling.

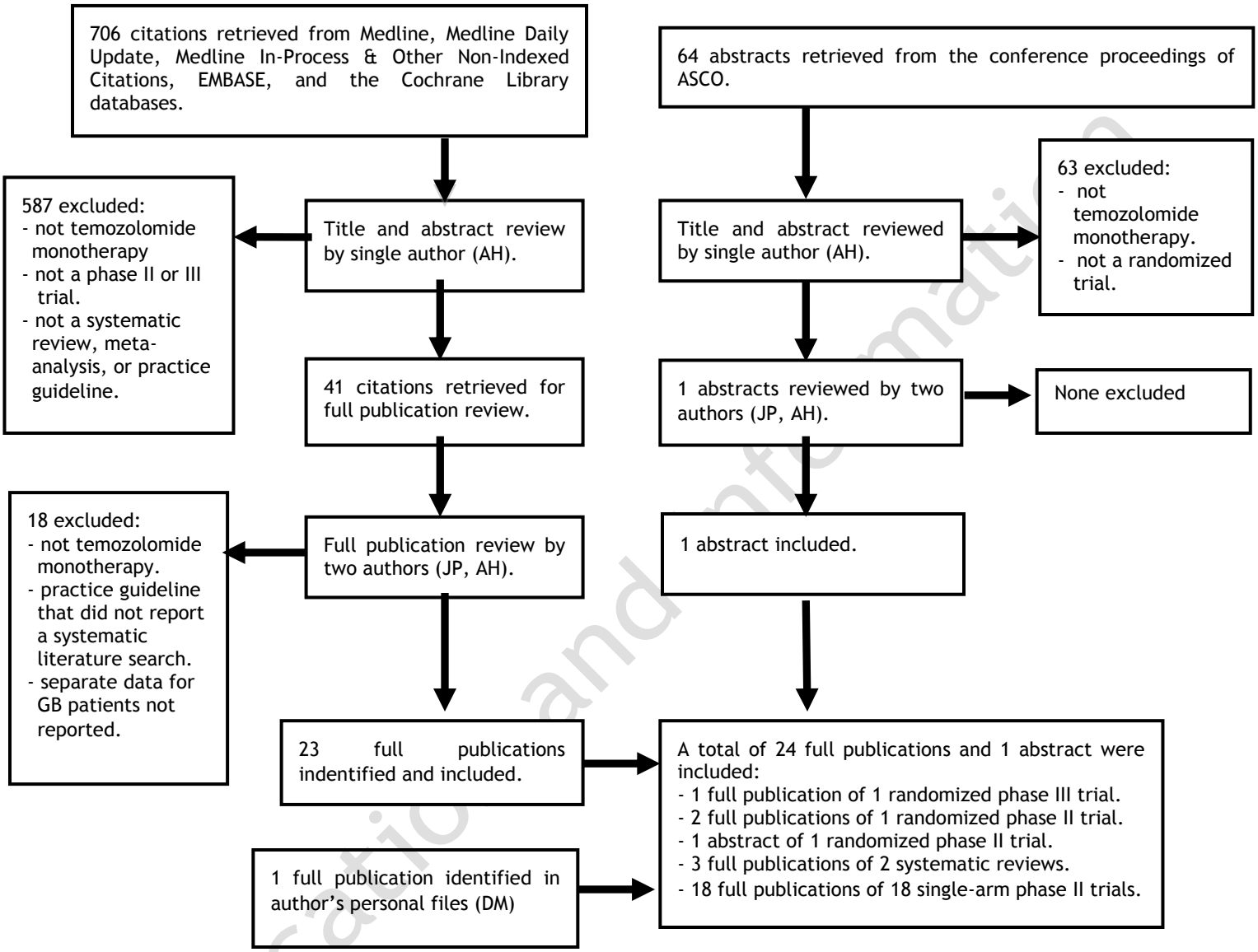
Statistical heterogeneity was calculated using the X^2 test for heterogeneity and the I^2 percentage. A probability level for the X^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% CI. An HR < 1.0 indicates that patients receiving the experimental treatment had a lower probability of experiencing an event; conversely, an HR > 1.0 suggests that patients in the control arm experienced a lower probability of an event.

RESULTS

Literature Search Results

A total of 706 citations were identified in the databases of MEDLINE, EMBASE, and the Cochrane Library (Figure 1), of which 23 full publications reporting on two systematic reviews, one randomized trial, and 18 non-comparative single-arm phase II trials were identified that investigated the use of temozolomide monotherapy in patients with recurrent or progressive GB. In addition, one abstract of a randomized trial was identified from the conference proceedings of ASCO. No clinical practice guidelines were identified that reported whether a systematic literature search was conducted as part of the development process. One additional full publication of a randomized trial was identified from the files of one of the authors (DM). That trial investigated the use of temozolomide compared to procarbazine, lomustine, and vincristine in patients with recurrent high-grade glioma, the article was not captured in our search of MEDLINE or EMBASE as the article was indexed as a glioma and not specifically as a glioblastoma. In our search, "glioblastoma" was included as a text word; however, the term "glioblastoma" was not used in the title, keywords, or abstract, therefore the citation was not captured in our search. In this case, the study population consisted of a large number of patients with glioblastoma (approximately 76% of 447 patients). It is rare that a study including so many patients with glioblastoma would not be indexed as such, or at least mention that patients with glioblastoma were included in the abstract. Therefore, we did not alter our literature search. The study was included as it met our eligibility criteria.

Figure 1. Selection of studies investigating temozolomide monotherapy, 50 mg/m^2 daily in patients with recurrent or progressive GB from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO.



Systematic Reviews

Dinnes et al reported a health technology assessment in 2001 (7) that investigated the use of temozolomide in patients with recurrent malignant glioma. In 2002, the authors published just the systematic review in the *British Journal of Cancer* (8). The authors searched several medical literature databases, including MEDLINE and EMBASE up to August 2000 and June 2000, respectively. Randomized controlled trials or non-randomized trials with over 45 patients were included. Only one trial was identified that investigated the use of temozolomide in patients with recurrent or progressive GB. As no other trials in recurrent or progressive GB were included, no pooling of data was conducted. Given that the authors identified only a single trial of temozolomide monotherapy in patients with recurrent or progressive GB, and as the literature search is 10 years out of date, that systematic review is not discussed further. Of note, the included randomized trial, reported by Yung et al (9), was also identified in our literature search.

Hart et al (10) published a Cochrane systematic review that investigated the use of temozolomide in primary or recurrent high-grade gliomas, including GB. The authors searched several medical literature databases, including MEDLINE and EMBASE, up to 2007 and included only randomized controlled trials. The authors identified the same randomized trial as Dinnes et al (8); however, Hart et al identified an abstract publication from ASCO 2000. The authors did not identify the full publication reported by Yung et al (9). The Cochrane systematic review shares the same limitations as the systematic review reported by Dinnes et al (8), in addition to the fact that Hart et al (10) did not identify the full publication of the randomized trial. Given these limitations, the Cochrane systematic review is not discussed further.

Randomized Trials

Patient Characteristics, Study Design, and Trial Quality

Three randomized trials of temozolomide monotherapy in patients with recurrent or progressive GB were identified. Details of each trial, including patient eligibility criteria and treatment arms, can be found in Table 1. Select aspects of trial quality can be found in Table 2.

Yung et al (9) reported a trial in which patients with GB or gliosarcoma were randomized to receive temozolomide monotherapy (n=112) or procarbazine (n=113). Osoba et al (11) reported, in a separate full publication, QOL data for that trial. The authors assumed that if the true PFS at six months for temozolomide was 20%, the 95% confidence interval (CI) would range from 12.2% to 27.8% with 100 patients in each arm. This would ensure that the lower boundary of the 95% CI would remain higher than 10%, which was assumed by the authors to be the threshold of effectiveness. The authors used a retrospective log-rank test to determine whether meaningful differences between the treatment groups were detectable. Therefore, the authors did not calculate, a priori, a required sample size to detect meaningful differences between the treatment groups for any of the outcomes of interest. The trial was open label, and the analysis was both intent-to-treat and final. No information was reported on the method of randomization, allocation concealment, or losses to follow-up.

D'Amico et al (12) reported a randomized trial of two different dose and/or schedules of temozolomide in patients with GB (Table 1). In the first arm, 10 patients received temozolomide at a standard dose and/or schedule, i.e., 200 mg/m^2/day, days 1-5 every 28 days for 8 cycles. In the second arm, 10 patients received a one week on, one week off (1 week on/1 week off) schedule, i.e., temozolomide 50 mg/m^2/day days 1-7 every 14 days for 12 cycles. The dose in that arm was escalated by 25 mg/m^2/day in each subsequent cycle to a maximum of 150 mg/m^2/day in the fifth cycle. The authors reported that the primary outcomes were PFS and response. No sample-size calculation was reported, and only 20 patients were enrolled in the trial. No other details regarding trial quality were reported.

Brada et al (13) reported a randomized phase III trial of temozolomide versus procarbazine, lomustine, and vincristine (PCV) in patients with high-grade glioma. Patients were

randomized to receive either temozolomide or PCV. Patients receiving temozolomide were further randomized to receive either temozolomide at 200 mg/m^2 days 1-5 every 28 days for up to nine cycles (TMZ-5), or to receive 100 mg/m^2 days 1-21 every 28 days for up to nine cycles (TMZ-21). The authors planned two comparisons: PCV versus [vs.] temozolomide with the primary outcome being OS, and; TMZ-5 vs. TMZ-21 with the primary outcome being 12-week PFS. Details regarding the sample-size requirements can be found in Table 2. Patients were also stratified by centre, World Health Organization (WHO) tumour grade, and performance status. The authors reported the final analysis, which was intent-to-treat. The authors did not report on the randomization method, other than that it was stratified, nor was the number of patients lost to follow-up reported.

Table 1. Study and patient characteristics of identified randomized trials.

Author, year (ref)	Patient characteristics	Treatment	N
Yung, 2000 (9)	Patients aged ≥18 years with GB or gliosarcoma that is recurrent of progressive at first relapse after RT for initial disease.	TMZ 150 mg/m^2/d d1-5 (received prior CT) or 200 mg/m^2/d d1-5 (no prior CT), q28d	112
		Procarbazine 125 mg/m^2/d d1-28, q56d	113
D'Amico, 2006 (12) [abs]	Adult patients with GB in progression after surgery and adjuvant RT.	TMZ 200 mg/m^2/d d1-5, q28d; up to 8 cycles Note: first cycle at 150 mg/m^2/d	10
		TMZ 50 mg/m^2/d d1-7, q14d; up to 12 cycles. Note: dose escalations in each cycle of 25 mg/m^2/d until 150 mg/m^2/d in 5th cycle	10
Brada, 2010 (13)	Adult patients with recurrent AA, GB, gemistocytic astrocytoma, oligoastrocytomas, or gliosarcoma. Patients underwent primary treatment including radiotherapy more than 2 months prior.	TMZ-5: 200 mg/m^2 d1-5, q28d; up to 9 cycles	112
		TMZ-21: 100 mg/m^2 d1-21, q28d; up to 9 cycles	111
		PCV: procarbazine 100 mg/m^2 d1-10 + lomustine 100 mg/m^2 d1 + vincristine 1.5 mg/m^2 d1, q28d; up to 6 cycles	224

Notes: AA=anaplastic astrocytoma; abs=abstract; CT=chemotherapy; d=day(s); GB=glioblastoma; PCV=procarbazine, lomustine, vincristine; q=every; ref=reference; RT=radiotherapy; TMZ=temozolomide.

Table 2. Quality characteristics of identified randomized trials.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
Yung, 2000 (9)	PFS	Not calculated a priori	OS, response, QOL	NR	NR	No	Yes	Yes	No	NR	Yes
D'Amico, 2006 (12) [abs]	PFS/ response	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brada, 2010 (13)	OS	500 pts req'd to observe 380 deaths to detect a 2 month increase in mdn OS (HR=0.75) with power of 80%, α=0.05. Also 333 pts with GB req'd to detect same difference in OS with power of 80%, α=0.05.	PFS, adverse events, QOL	Centralized telephone system with stratification[A]	Yes	No	Yes	Yes	No	NR	Yes

Notes: GB=glioblastoma; HR=hazard ratio; ITT=intent-to-treat; mdn=median; NR=not reported; OS=overall survival; PFS=progression-free survival; pts=patients; QOL=quality of life; ref=reference; req'd=required.
[A]Patients stratified by center, tumour grade (World Health Organization), and performance status.

Meta-Analysis

A meta-analysis of the studies was not conducted due to heterogeneity between the study designs and lack of sufficient data.

Efficacy Outcomes

Efficacy outcomes can be found in Table 3.

Overall Survival

Yung et al (9) reported that OS was significantly higher for patients who received temozolomide compared to those who received procarbazine (60% at six months vs. 44% at six months, respectively; HR, 1.44; p=0.019). D'Amico et al (12) reported a higher rate of overall survival at two years for patients who received temozolomide on the 1 week on/1week off dose and/or schedule compared to those who received the standard dose and/or schedule (40% vs. 10%, respectively); however, the authors did not report whether any statistical comparison was made. Brada et al (13) reported no significant differences in OS for patients who received temozolomide compared to PCV chemotherapy or for patients who received five-day temozolomide compared to 21-day temozolomide (Table 3).

Table 3. Outcomes in the randomized trials of temozolomide monotherapy in patients with recurrent or progressive GB following prior therapy..

Author, year (ref)	Treatment	N	OS (%)	PFS (%)	OR (%)	PR (%)	SD (%)	Follow-up (mdn, mos)
Yung, 2000 (9)	TMZ 200 mg 5-day q28d	112	**6-mos** 60	**6-mos** 21	45.6	5.4	40.2	NR
	PCB	113	44 HR 1.44; p=0.019	8 HR 1.54; p=0.008	32.7 p=0.049	5.3	27.4	
D'Amico, 2006 (12) [abs]	TMZ 200 mg 5-day q28d	10	**2-yr** 10	**2-yr** 0	NR	NR	NR	NR
	TMZ 50 mg 1wk-on/1wk-off	10	40	20	NR	NR	NR	
Brada, 2010 (13)	TMZ-5 and TMZ-21	223	**Mdn** 7.2 mos	**Mdn** 4.7 mos	NR	NR	NR	14.0
	PCV	224	6.7 mos HR 0.91; p=0.35	3.6 mos HR 0.89; p=0.23	NR	NR	NR	10.5
	TMZ-5	112	8.5 mos	5.0 mos	NR	NR	NR	14.0
	TMZ-21	111	6.6 mos HR 1.32; p=0.056	4.2 mos HR 1.38 p=0.023	NR	NR	NR	

Notes: abs=abstract; d=day; HR=hazard ratio; mdn=median; mos=months; N=number of patients randomized; NR=not reported; OR=objective response; OS=overall survival; PCB=procarbazine; PCV=procarbazine, lomustine, vincristine; PFS=progression-free survival; PR=partial response; q=every; ref=reference; SD=stable disease; TMZ=temozolomide; TMZ-5=temozolomide received on 5 days in a 28-day cycle; TMZ-21=temozolomide received on 21 days in a 28-day cycle; wk=week; yr=year.

Disease Control

Yung et al (9) reported that PFS was significantly improved for patients who received temozolomide compared to procarbazine (21% at six months vs. 8% at six months, respectively; HR, 1.54; p=0.008). Brada et al (13) reported no significant difference in PFS for patients who received temozolomide compared to PCV chemotherapy (Table 3); however, the authors did note a significant difference in PFS in favour of patients who received five-day temozolomide compared to 21-day temozolomide (median PFS for TMZ-5 was 5.0 months vs. 4.2 months for TMZ-21; HR, 1.38; 95% CI, 1.04 to 1.82; p=0.023).

Response

Yung et al (9) reported that the objective response rate was significantly improved for temozolomide compared to procarbazine (45.6% vs. 32.7%, respectively; p=0.049). D'Amico et al (12) reported a higher objective response rate and improved PFS in favour of the 1-week on/1-week off dose schedule (Table 3); however, the authors did not report whether a statistical comparison was made. Brada et al did not report response data (13).

Quality of Life

D'Amico et al (12) did not report data on QOL. Osoba et al reported QOL data for the randomized trial reported by Yung et al (9). QOL was assessed using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Questionnaire (QLQ) Core 30+3 (C30+3) (14) and the Brain Cancer Module 20 (BCM20) (15). The authors decided a priori to limit the number of QOL domains that would be statistically compared. The authors chose seven domains from the EORTC QLQ-C30+3: role functioning, social functioning, global QOL, visual disorder, motor dysfunction, communication deficit, and drowsiness. The authors expected that those domains were likely to be most affected in GB. A clinically significant change in scores was defined as a change of 10 or more (on a scale from 0 to 100) lasting for at least two QOL

assessments four weeks apart. For the functioning domains, a higher score indicated better functioning, whereas for the symptom items, a higher score indicated more of the symptom or difficulty. Patients were given the EORTC QLQ-C30 (+3) and BCM20 questionnaires prior to their first cycle of chemotherapy as a baseline assessment, and prior to each subsequent cycle of chemotherapy (or before non-chemotherapy visits for patients taking procarbazine). The authors examined the change in scores from baseline to specified time points for each individual patient to determine whether there was an improvement over the baseline score in each group. Of 225 patients enrolled in the trial, 179 provided baseline data and at least one assessment while on treatment (89 patients in the temozolomide group and 90 patients in the procarbazine group). After six months, only 28 patients in the temozolomide group and 10 in the procarbazine group remained on the QOL study. Due to high attrition rates, the authors did not make comparisons between the treatment arms for QOL data. Although the authors concluded that treatment with temozolomide was associated with improvements in QOL scores compared to procarbazine, no statistical comparisons of the treatment arms were made.

Brada et al (13) assessed QOL using the EORTC QLQ C30 Version 3 and the Brain Cancer Module questionnaires. Patients were asked to complete the questionnaires at baseline and at 12 and 24 weeks. The authors defined a moderate improvement in QOL as a 10-point change from baseline to 12 weeks or from baseline to 24 weeks. Of the 447 patients enrolled in the trial, 415 or 92.8% of patients completed a questionnaire at baseline. In the PCV chemotherapy arm, 211 of 224 patients completed a baseline questionnaire. At 12 weeks, 27% of 101 patients reported an improvement in QOL and at 24 weeks, 23% of 54 patients reported an improvement. In the temozolomide five-day arm, 103 of 112 patients completed a baseline questionnaire. At 12 weeks, 32% of 77 patients reported an improvement in QOL and at 24 weeks, 49% of 46 patients reported an improvement. In the temozolomide 21-day arm, 101 of 111 patients completed a baseline questionnaire. At 12 weeks, 27% of 60 patients reported an improvement in QOL and at 24 weeks, 19% of 38 patients reported an improvement. The authors did not make statistical comparisons between the treatment arms for QOL data.

Adverse Events

Data on grade 3 or 4 adverse events can be found in Table 4. D'Amico et al (12) did not report data on adverse events. Yung et al (9) reported that the most common grade 3 or 4 adverse events in both arms were nausea, vomiting, fatigue, thrombocytopenia, and neutropenia (Table 4). Brada et al (13) reported similarly that the most common grade 3 or 4 adverse events in any arm were nausea, vomiting, neutropenia, anemia, thrombocytopenia, and leukopenia. Unfortunately, the authors of both trials did not report whether statistical comparisons were made between the treatment arms.

Table 4. Grade 3 or 4 adverse events in randomized trials of temozolomide monotherapy in patients with recurrent or progressive GB following prior therapy.

Author, year (ref)	Treatment	N	Nausea (%)	Vomiting (%)	Anorexia (%)	Constipation (%)	Diarrhea (%)	Headache (%)	Fatigue (%)	Neutropenia (%)	Anemia (%)	Thrombo-cytopenia (%)	Leukopenia (%)
Yung, 2000 (9)	TMZ 200 mg 5-day q28d	112	2.7	2.7	0	0.9	0	1.8	2.7	3.6	0.9	6.2	0.9
	PCB	113	2.7	4.4	1.8	0.9	0.9	1.8	1.8	2.7	1.8	3.5	0
D'Amico, 2006 (12) [abs]	TMZ 200 mg 5-day q28d	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TMZ 50 mg 1wk-on/1wk-off	10	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Brada, 2010 (13)	TMZ-5	110	1.8	5.4	NR	NR	NR	NR	NR	10.0	0.9	15.5	8.2
	TMZ-21	110	6.4	6.4	NR	NR	NR	NR	NR	6.4	0.9	10.0	8.2
	PCV	221	4.1	3.7	NR	NR	NR	NR	NR	8.1	1.9	7.2	8.6

Notes: abs=abstract; d=day; N=number of patients evaluable; NR=not reported; PCB=procarbazine; PCV=procarbazine, lomustine, vincristine; q=every; ref=reference; TMZ=temozolomide; wk=week.

Non-Comparative Phase II Trials

Patient Characteristics, Study Design, and Trial Quality

Eighteen single-arm phase II trials were identified that investigated the use of temozolomide monotherapy in patients with recurrent or progressive GB. Information on the study designs and patient characteristics of the identified trials can be found in Appendix 2-1. Nine trials (16-24) investigated a standard dose and schedule (i.e., temozolomide 150-200 mg/m^2 per day on days 1-5, repeated every 28 days). An additional nine trials (25-33) investigated other doses and/or schedules of temozolomide monotherapy (Appendix 2-1). The two largest trials of standard dose and/or schedule temozolomide were reported by Chang et al (20) and Brada et al (23); those trials enrolled 142 and 138 patients with GB, respectively. The enrolment in the remaining trials ranged from 12 patients to 68 patients. Perry et al (26) reported the largest trial of an alternative dose and/or schedule of temozolomide, with a total of 91 patients with GB. The authors administered temozolomide at 50 mg/m^2 every day for 12 months or until disease progression. Wick et al (29) reported the next largest trial with a total of 64 patients. Temozolomide was administered at 150 mg/m^2 per day on days 1-7 and days 15-21 of a 28-day cycle, for a total of 12 cycles. Enrolment in the remaining trials ranged from 10 patients to 33 patients. A majority of the trials enrolled patients with malignant gliomas other than GB (Appendix 2-1). Only the results from patients with GB are discussed in this special advice report.

Efficacy Outcomes

Efficacy outcomes for the identified phase II trials can be found in Appendix 2-2.

Survival

Among the nine trials that investigated TMZ at a standard dose and schedule, median OS ranged from 3.9 months to 18.5 months (Appendix 2-2). It should be noted that seven of the nine trials reported median OS data that ranged from 3.9 months for 16 patients to nine months for 68 patients. Only two trials reported longer median OS: Teraskai et al (16) reported a median OS of

17 months for 12 patients, and Hassler et al (18) reported a median OS of 18.5 months for 30 patients. The two largest trials reported median OS of 7.36 months for 142 patients (20) and 5.4 months for 138 patients (23).

The nine trials that investigated other doses and/or schedules of temozolomide reported median OS that ranged from 7.7 months in 28 patients to 17.9 months in 18 patients (Appendix 2-2). Perry et al (26), one of the two largest trials investigating alternative doses and/or schedules, reported a one-year OS of 27.3% in 33 patients who progressed early (i.e., before completing six cycles of adjuvant temozolomide; early group), 14.8% in 28 patients who progressed during extended adjuvant therapy (i.e., while receiving extended adjuvant temozolomide; extended group), and 28.6% in 27 patients who progressed after completing adjuvant treatment (rechallenge group); all patients received daily temozolomide at 50 mg/m^2 for 12 months or until progression. Kong et al (27) reported a similar dose/schedule as Perry et al (26) and found that for 38 patients who progressed following prior therapy, the six-month OS was 56.0% and the median OS was 9.4 months (Appendix 2-2). Wick et al (29), the second of the largest trials, investigated temozolomide at 150 mg/m^2 in a 1-week-on/1-week-off schedule. The authors reported a median OS of 8.7 months for 64 patients and a one-year OS of 23%. Of note, a 2004 trial published by Wick et al (32) used the same dose and schedule of temozolomide and reported a one-year OS of 81% for 21 patients.

Disease control

Among the nine trials that reported a standard dose and schedule of temozolomide, median PFS ranged from 1.8 months in 16 patients to 6.8 months in 40 patients (Appendix 2-2). Six-month PFS ranged from 13% of 68 patients to 50% of 12 patients (Appendix 2-2). Chang et al (20) reported a six-month PFS of 18% in 142 patients, and Brada et al (23) reported a six-month PFS of 19% and median PFS of 2.1 months in 138 patients.

The median PFS ranged from 1.8 months in 28 patients to 5.5 months in 64 patients among the nine trials that investigated other doses and/or schedules of temozolomide (Appendix 2-2), and the six-month PFS ranged from 0% in 27 patients to 47.6% in 21 patients. In patients who received daily temozolomide at 50 mg/m^2, Perry et al (26) reported a six-month PFS of 27.3% in 33 patients in the early group, 7.4% in 28 patients in the extended group, and 35.7% in 27 patients in the rechallenge group. The median PFS was 3.6 months, 1.8 months, and 3.7 months, respectively. Kong et al (27) reported a six-month PFS of 32.5% for 38 patients and median PFS of 17 weeks. In patients who received temozolomide at 150 mg/m^2 in a 1-week-on/1-week-off schedule, Wick et al (29) reported the median PFS was 5.5 months in 64 patients and the six-month PFS was 43.8%. The earlier 2004 study by Wick et al (32) reported similar data: a median PFS of 4.8 months and a six-month PFS of 47.6% in 21 patients.

Response

Complete response data for each trial can be found in Appendix 2-2. Among the nine trials of standard dose and/or schedule temozolomide, the OR rates ranged from 8.0% in 138 patients to 37.5% in 16 patients (Appendix 2-2). Stable disease rates ranged from 13.3% in 30 patients to 83.3% in 12 patients (Appendix 2-2). Chang et al (20) reported an OR rate of 15.5% and a stable disease rate of 30.3% in 142 patients. Brada et al (23) reported an OR rate of 8.0% and a stable disease rate of 43.5% in 138 patients.

Among the trials of alternative dose and/or schedules of temozolomide, the OR rates ranged from 0% of 28 patients to 22.2% of 18 patients (Appendix 2-2). Stable disease rates ranged from 7.7% of 28 patients to 81.0% of 21 patients (Appendix 2-2). Two trials did not report stable disease rates (25,29). In patients who received daily temozolomide at 50 mg/m^2, Perry et al (26) reported an OR and stable disease rates of 3% and 24.2%, respectively, of 33 patients in the early group, 0% and 7.7% of 28 patients in the extended group, and 11.1% and 25.9% of 27 patients in

the rechallenge group. Kong et al (27) reported an OR rate of 5.3% of 38 patients and a stable disease rate of 55.3%. In patients who received temozolomide at 150 mg/m^2 in a 1-week-on/1-week-off schedule, Wick et al (29) reported an OR rate of 10.9% of 64 patients; the authors did not report on stable disease. In the similar trial, Wick et al (32) reported objective response and stable disease rates of 9.5% and 81.0% in 21 patients.

Quality of life

A total of three single-arm phase II trials investigated the effect of temozolomide treatment on patient QOL.

Two trials that investigated a standard temozolomide dose/schedule reported QOL data. Hassler et al (18) reported data on all 40 enrolled patients (30 had GB and 10 had anaplastic glioma); however, the authors did not provide separate data for those patients who had GB. The authors measured QOL using the EORTC QLQ-C30 (version unknown) and the BCM-20 (15) (described in 'Randomized Trials' section above). Data for 19 of 40 patients were available to assess changes in QOL. The authors concluded that QOL was stable throughout temozolomide treatment. Brada et al (23) used the EORTC QLQ-C30+3 (14) and the BCM-20 (15) to assess QOL. Data were available for 105 of 138 enrolled patients. The authors reported that an improvement in QOL occurred in at least one domain for 62 patients (59.0%). Of those patients, QOL was improved in 43 (41.0%) patients in at least two domains, 26 (24.8%) improved in at least three domains, and 16 (15.2%) improved in at least four domains. The remaining 43 patients (41.0%) showed no improvement in any domain of QOL.

Kong et al (27) administered daily temozolomide at 40 to 50 mg/m^2 in 38 patients with GB. The authors measured QOL through the mental and physical components of the short form-36 (SF-36) QOL measure. The SF-36 is a validated general health QOL measure (34). Higher scores are indicative of a better health status for each measure. The questionnaire was administered at baseline, three months, and six months from the beginning of treatment. The authors reported that for all 38 patients at three-months follow-up, there was a significant decrease in QOL score for the physical health component but no significant difference for the mental health component (for baseline score compared to three-month score; no p-values were reported). The authors noted that for 23 patients who showed a response to treatment (including stable disease), there was no significant difference in either the mental or physical health components of the SF-36 for the baseline score compared to the three-month score.

Adverse Events

Data on grade 3 or 4 adverse events for each trial can be found in Appendix 2-3. Reporting of adverse events was variable. Trials that enrolled histologies other than GB, reported pooled data that included all enrolled patients. As a result, the data in Appendix 2-3 is not just of patients with GB. The most commonly reported grade 3 or 4 adverse events were nausea, vomiting, fatigue, leucopenia, lymphopenia, neutropenia, and thrombocytopenia. Balmaceda et al reported that two patients of 120 enrolled died of treatment-related causes.

DISCUSSION

Three randomized trials investigating temozolomide in patients with relapsed or progressive GB have been conducted to date. One trial, reported in abstract form only, included only 10 patients in each arm (12). That trial is of low quality, and no conclusions can be drawn from the results. Yung et al (9) published a trial in 2000 that compared a standard temozolomide dose and schedule to procarbazine. The authors did not calculate the required sample size a priori, the trial was open label, and the randomization method was not reported. With a total of 225 patients enrolled in the trial, the authors reported a significant difference in favour of temozolomide for OS (HR, 1.44; p=0.019), PFS (HR, 1.54; p=0.008), and the OR rate (45.6% vs.

32.7%; p=0.049). Brada et al (13) compared temozolomide to a regimen including procarbazine, lomustine, and vincristine (PCV). The authors reported no significant differences in OS or PFS for temozolomide compared to PCV. The authors did report a significant difference in favour of temozolomide five-day compared to 21-day (median 5.0 months vs. 4.2 months, respectively; HR, 1.38; 95% CI, 1.04 to 1.82; p=0.023).

It is important to note that all the above randomized trials enrolled patients who did not receive temozolomide during first-line therapy of GB. Prior to 2005, patients with recurrent GB were temozolomide-naïve at recurrence as they would have received RT alone or RT in combination with a nitrosurea chemotherapeutic agent (e.g., lomustine or carmustine) during first-line therapy. The current practice in Ontario for the first-line treatment of GB includes temozolomide. Therefore, it is difficult to generalize the results of the above randomized trials to the current population of GB patients in Ontario.

An urgent, unmet need exists for more effective therapies for disease recurrence despite the first-line use of RT combined with temozolomide in patients with GB. Only one of the currently available systemic treatment options available in Ontario has been directly evaluated in a randomized controlled trial. In that trial, patients with recurrent GB who received temozolomide during first-line therapy were enrolled and randomized to receive lomustine or enzastaurin (4). The trial was terminated early for futility after a planned interim analysis demonstrated that the six-month PFS of 19% for lomustine and 11.1% for enzastaurin was no higher than in prior reports of efficacy in the pre-temozolomide era. Based on the single-arm phase II data identified in this report, temozolomide has an activity in patients with recurrent GB who have received temozolomide during first-line therapy; however, definitive conclusions regarding the choice of one agent over another cannot be made given the lack of randomized controlled trial data.

Recently another CED-CCO Special Advice Report was completed on the use of bevacizumab in this same patient population. The authors recommended that bevacizumab is a reasonable treatment option in patients with recurrent GB and should be offered to eligible patients, with the following potential benefits in mind: partial or complete response in up to 30-40% of patients, subsequent sparing of dexamethasone toxicity, and prolongation of PFS at six months in approximately 40% of patients, with a stabilization or improvement in QOL during that time. The authors also stated that the potential toxicity of bevacizumab treatment would be considered in the selection and monitoring of patients.

Although comparing across multiple trials is problematic, the potential benefits of temozolomide therapy are similar with respect to six-month PFS and OR. Temozolomide therapy might also offer less risk of toxicity than does bevacizumab. Therefore, temozolomide is, at the least, a treatment option for patients with recurrent GB. Several different regimens have been studied and/or used in practice, including temozolomide at 150-200 mg/m^2 per day for the first five days out of 28 days (five-day schedule); temozolomide at 100 mg/m^2 per day for the first 21 days out of 28 days (21-day schedule); temozolomide at 100-150 mg/m^2 per day for seven days on then seven days off (7-days on/7-days off schedule), or temozolomide at 40-50 mg/m^2 per day (daily schedule). No comparative data exist that compare these different temozolomide dose/schedules; however, the most studied and widely used include the five-day schedule and the daily schedule.

There is a distinct lack of randomized controlled trial evidence in this disease setting. Thus, practitioners must individualize treatment recommendations based upon the patient's clinical condition, the characteristics of the tumour, and the availability and characteristics of the various treatment options.

CONCLUSIONS

Temozolomide is a treatment option in patients with GB that has relapsed or progressed following prior therapy. There are several treatment options for patients with recurrent GB, including temozolomide, lomustine, and bevacizumab. All of these have demonstrated activity in recurrent GB. In addition, several doses and schedules of temozolomide have been studied in this disease setting and have shown activity. However, no comparative data exist that would support or refute the use of one agent over another, or the use of one dose and/or schedule over another. The choice of agent and the dose and/or schedule should be at the discretion of the treating physician.

ONGOING TRIALS

The National Cancer Institute clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (http://clinicaltrials.gov/) were searched for reports of new or ongoing randomized trials investigating the use of temozolomide monotherapy in patients with recurrent GB. Details of the identified trials can be found in Appendix 3. One additional trial was identified from the files of the authors. Although the trial does not investigate the use of temozolomide, it is of interest as it utilizes two of the other chemotherapeutic agents available in Ontario: bevacizumab compared to bevacizumab plus lomustine in recurrent GB (Appendix 3).

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. Authors reported having acted as a consultant and/or having received honoraria exceeding $5000 annually (from Schering-Plough [Merck & Co., Inc.]—JP,WM,DM), or having received research support (from Schering-Plough [Merck & Co., Inc.]—WM,DM; from Hoffman-La Roche Canada—DM; from EMD Serono [Merck & Co KGaA) or other financial or material support exceeding $5000 annually (from Schering-Plough [Merck & Co., Inc]—JP). The remaining author (AH) reported no conflicts of interest.

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34. Ware JE, Jr. SF-36 health survey update. Spine. 2000 Dec 15;25(24):3130-9.

Appendix 1. Literature search strategies.

Ovid MEDLINE

1. temozolomide:.mp.
2. temodal:.mp.
3. temodar:.mp.
4. or/1-3
5. glioblastoma/
6. glioblastoma:.mp.
7. 5 or 6
8. relapse:.mp.
9. progress:.mp.
10. recur:.mp.
11. refractory:.mp.
12. or/8-11
13. 4 and 7 and 12
14. meta-analysis as topic/
15. meta analysis.pt.
16. meta analy$.tw.
17. metaanaly$.tw.
18. (systematic adj (review$1 or overview$1)).tw.
19. or/14-18
20. Cochrane.ab.
21. embase.ab.
22. (cinahl or cinhal).ab.
23. science citation index.ab.
24. bids.ab.
25. cancerlit.ab.
26. or/20-25
27. reference list$.ab.
28. bibliography$.ab.
29. hand-search$.ab.
30. relevant journals.ab.
31. manual search$.ab.
32. or/27-31
33. selection criteria.ab.
34. data extraction.ab.
35. 33 or 34
36. review.pt.
37. review literature as topic/
38. 36 or 37
39. 35 and 38
40. comment.pt.
41. letter.pt.
42. editorial.pt.
43. or/40-42
44. 19 or 26 or 32 or 39
45. 44 not 43
46. randomized controlled trials as topic/
47. randomized controlled trial.pt.
48. random allocation/

49. double blind method/
50. single blind method/
51. exp Clinical Trials as Topic/
52. exp clinical trial/
53. (clinic$ adj trial$).tw.
54. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
55. placebos/
56. placebo$.tw.
57. (allocated adj2 random$).tw.
58. random allocation.tw.
59. randomly allocated.tw.
60. or/46-59
61. case report.tw.
62. letter.pt.
63. historical article.pt.
64. or/61-63
65. 60 not 64
66. 45 or 65
67. practice guideline/
68. practice guideline$.mp.
69. 67 or 68
70. 66 or 69
71. 13 and 70
72. limit 71 to (English language and humans)

EMBASE

1. exp temozolomide/
2. temozolomide:.mp.
3. temodal:.mp.
4. temodar:.mp.
5. or/1-4
6. exp glioblastoma/
7. glioblastoma:.mp.
8. 6 or 7
9. relapse:.mp.
10. progress:.mp.
11. recur:.mp.
12. refractory:.mp.
13. or/9-12
14. 5 and 8 and 13
15. exp meta-analysis/
16. ((meta adj analy$) or metaanaly$).tw.
17. (systematic adj (review$1 or overview$1)).tw.
18. or/15-17
19. cancerlit.ab.
20. Cochrane.ab.
21. embase.ab.
22. (cinahl or cinhal).ab.
23. science citation index.ab.

24. bids.ab.
25. or/19-24.
26. reference list$.ab.
27. bibliograph$.ab.
28. hand-search$.ab.
29. manual search$.ab.
30. relevant journals.ab.
31. or/26-30
32. data extraction.ab.
33. selection criteria.ab.
34. 32 or 33
35. review.pt.
36. 34 and 35
37. letter.pt.
38. editorial.pt.
39. 37 or 38
40. 18 or 25 or 31 or 36
41. 40 not 39
42. clinical trial/
43. randomized controlled trial/
44. randomization/
45. single blind procedure/
46. double blind procedure/
47. crossover procedure/
48. placebo/
49. random?ed control$ trial$.tw.
50. rct.tw.
51. random allocation.tw.
52. randomly allocated.tw.
53. allocated randomly.tw.
54. (allocated adj2 random$).tw.
55. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
56. placebo$.tw.
57. prospective study/
58. or/42-57
59. case study/
60. case report.tw.
61. abstract report/
62. letter/
63. or/59-62
64. 58 not 63
65. 41 or 64
66. exp practice guideline/
67. practice guideline$.tw.
68. 66 or 67
69. 65 or 68
70. 14 and 69
71. limit 70 to (human and English language)

Appendix 2-1. Trial and patient characteristics of non-comparative phase II trials of temozolomide monotherapy in patients with recurrent or progressive GB following prior therapy.

Author, year (ref)	Patient characteristics	Prior TMZ (%)	Treatment	Patient groups	N
Standard Dose/Schedule (150-200 mg/m^2/d d1-5; q28d)					
Terasaki, 2009 (16)	Recurrent or progressive high-grade glioma (AA or GB) after failed nitrosurea-based chemo. All patients received surgery and chemoradiotherapy.	0	TMZ 150-200 mg/m^2/d d1-5; q28d up to 24 cycles.	GB	12
				AA	13
Balmaceda, 2008 (17)	Recurrent of progressive malignant glioma (GB, AA, or AOD) with last RT at least 12 weeks prior and last chemo at least 6 weeks prior. Age ≥18 years, KPS >60.	0	TMZ 200 mg/m^2 d1 morning followed 12 hours later by 9 doses each of 90 mg/m^2 every 12 hours; q28d.	GB	68
				AA or AOD	52
Hassler, 2006 (18)	Recurrent or progressive grade III/IV malignant glioma with no previous RT or chemo within the last month. Age 18-70 years, KPS ≥70.	5.0	TMZ 150 mg/m^2/d (previous chemo) or 200 mg/m^2/d (chemo-naïve) d1-5; q28d, up to 6 cycles.	GB	30
				AA or other	10
Yang, 2006 (19)	Recurrent or progressive malignant glioma (GB, AA, or AOD). Age >17 years, KPS ≥60.	100	TMZ 150 mg/m^2/d (previous chemo) or 200 mg/m^2/d (chemo-naïve) d1-5; q28d, until progression.	GB	16
				Other	9
Chang, 2004 (20)	Recurrent high-grade glioma (GB, AA, AOD, or anaplastic mixed glioma). Age >18 years, KPS ≥70.	0	TMZ 150 mg/m^2/d (previous chemo) or 200 mg/m^2/d (chemo-naïve) d1-5; q28d, up to 1 year.	GB or GS[A]	142
				Grade III malignant glioma	71
Sipos, 2004 (21)	Recurrent malignant glioma. KPS >70.	NR	TMZ 200 mg/m^2/d d1-5; q28d, up to 16 cycles.	GB	40
				Astrocytoma	35
Brandes, 2002 (22)	Recurrent or progressive GB after surgery and RT followed by chemo with nitrosurea, procarbazine, and vincristine. Age ≥18 years, KPS ≥60.	0	TMZ 150 mg/m^2/d d1-5; q28d, until progression.	GB	42
Brada, 2001 (23)	GB at first relapse or recurrence or progression more than 12 week after completion of RT. KPS ≥70.	NR	TMZ 150 mg/m^2/d (previous chemo) or 200 mg/m^2/d (chemo-naïve) d1-5; q28d, up to 1 year.	GB	138
Brandes, 2001 (24)	Recurrent or progressive high-grade glioma after surgery and RT	0	TMZ 150 mg/m^2/d d1-5; q28d, up to 18	GB	22

Author, year (ref)	Patient characteristics	Prior TMZ (%)	Treatment	Patient groups	N
	followed by chemo with nitrosurea, procarbazine, and vincristine.		months.	AA or AOD	19
Other Doses and Schedules					
Berrocal, 2010 (25)	Age ≥18 years, TMZ-refractory, WHO-grade III/IV glioma with progressive disease during TMZ treatment or less than 3 months after finishing last TMZ treatment; KPS ≥60.	100	TMZ 85 mg/m^2/d d1-21; q28d.	GB	27
				AA, AOD, or other	20
Perry, 2010 (26)	Adult patients with malignant glioma with recurrence or progression while receiving standard TMZ on a 5 days out of 28 days dosing schedule. All patients must have completed radiotherapy, had chemoradiotherapy at least 3 months prior to enrolment, and have radiologic evidence of progression.	100	TMZ 50 mg/m^2/d for 12 months or until disease progression.	GB with progression while receiving adjuvant TMZ before completion of 6 cycles of adjuvant TMZ. ***(early)***	33
				GB with progression while receiving extended adjuvant TMZ beyond the standard 6 cycles but before completion of adjuvant treatment. ***(extended)***	29
				GB with progression after completion of adjuvant treatment and a treatment-free interval of greater than 2 months. ***(rechallenge)***	29
				AA, AO, AOA	29
Kong, 2010 (27)	Adult patients with KPS ≥60 with histologically proven GB. Patients must have received chemotherapy using TMZ following radiation therapy or concomitant chemoradiotherapy.	100	Cohort 1: TMZ 40 mg/m^2/d	GB	10
			Cohort 2: TMZ 50 mg/m^2/d		28
Strik, 2008 (28)	Recurrent or progressive glioma with KPS ≥50.	100	TMZ 100 mg/m^2/d d1-21; q28d.	GB	18
				AA or AOD	3
Wick, 2007 (29)	Recurrent or progressive glioma, age >17 years, KPS ≥60, with prior RT ± chemo.	10	TMZ 150 mg/m^2/d d1-7, d15-21; q28d, up to 12 cycles.	GB	64
				AA, AOA, low-grade glioma, or other	26
Brandes, 2006 (30)	Recurrent or progressive GB after previous surgery and RT. Age ≥18 years, KPS ≥60.	0	TMZ 75 mg/m^2/d d1-21; q28d.	GB	33
Kong, 2006 (31)	Recurrent GB after previous RT, standard TMZ after surgery, or gamma knife surgery. Age 18-70 years.	100	TMZ 40 mg/m^2/d	GB	12
Wick, 2004 (32)	Recurrent or progressive GB with previous RT ± non-TMZ chemo. KPS ≥60.	0	TMZ 150 mg/m^2/d d1-7, d15-21; q28d.	GB	21

Author, year (ref)	Patient characteristics	Prior TMZ (%)	Treatment	Patient groups	N
Khan, 2002 (33)	Recurrent WHO grade III or IV malignant glioma without previous TMZ or procarbazine. Age ≥18 years, KPS ≥60.	0	TMZ 75 mg/m^2/d for 42d then 28d rest.	GB	28
				AA, AOD, AOA	7

Notes: AA=anaplastic astrocytoma; AOA=anaplastic oligoastrocytoma; AOD=anaplastic oligodendroglioma; chemo=chemotherapy; GB=glioblastoma; KPS=Karnofsky performance status; N=number enrolled or randomized; ref=reference; RT=radiotherapy; TMZ=temozolomide WHO=World Health Organization.

[A]Four patients had gliosarcoma.

Appendix 2-2. Efficacy outcomes in non-comparative phase II trials of temozolomide monotherapy in patients with recurrent GB following prior therapy.

Author, year (ref)	Treatment	N	OS	PFS	OR (%)	CR (%)	PR (%)	SD (%)	Response criteria	Follow-up, mdn
Standard Dose/Schedule (150-200 mg/m^2/d d1-5; q28d)										
Terasaki, 2009 (16)	TMZ 150-200	12	Mdn: 17 mos	6-mos: 50%	8.3	0	8.3	83.3	WHO	49 mos
Balmaceda, 2008 (17)	TMZ 200	68	Mdn: 9 mos 1-yr: 35%	Mdn: 4 mos 1-yr: 13%	30.9	4.4	26.5	32.4	Macdonald	21 mos
Hassler, 2006 (18)	TMZ 150-200	30	Mdn: 18.5 mos 1-yr: 62.5%	NR	23.3	6.7	16.7	13.3	Macdonald	NR
Yang, 2006 (19)	TMZ 150-200	16	Mdn: 3.9 mos	Mdn: 1.8 mos	37.5	12.5	25	18.8	Macdonald	15 mos
Chang, 2004 (20)	TMZ 150-200	142	Mdn: 7.4 mos 6-mos: 60%	6-mos: 18%	15.5	0.7	14.8	30.3	Similar[A] to Macdonald	NR
Sipos, 2004 (21)	TMZ 200	40	Mdn: 8.75 mos	Mdn: 6.8 mos	22.5	7.5	15.0	42.5	Macdonald	NR
Brandes, 2002 (22)	TMZ 150	42	Mdn: 7.0 mos 1-yr: 28%	Mdn: 2.7 mos 6-mos: 24%	19.0	4.7	14.3	21.4	Macdonald	NR
Brada, 2001 (23)	TMZ 150-200	138	Mdn: 5.4 mos 6-mos: 46%	Mdn: 2.1 mos 6-mos: 19%	8.0	1.4	6.5	43.5	Macdonald	NR
Brandes, 2001 (24)	TMZ 150	22	Mdn: 7.5 mos 1-yr: 27.3%	Mdn: 2.8 mos 6-mos: 31.8%	22.7	9.1	13.6	18.2	Macdonald	12 mos
Other Doses and Schedules										
Berrocal, 2010 (25)	TMZ 85/d d1-21, q28d	27	NR	6-mos: 0%	7.4	0	7.4	NR	Macdonald	3.6 mos
Perry, 2010 (26)	TMZ 50/d-early	33	1-yr: 27.3%	6-mos: 27.3% Mdn: 3.6 mos	3	NR	NR	24.2	RECIST	19.1 mos
	TMZ 50/d-extended	28[B]	1-yr: 14.8%	6-mos: 7.4% Mdn: 1.8 mos	0	NR	NR	7.7		
	TMZ 50/d-rechallenge	27[C]	1-yr: 28.6%	6-mos: 35.7% Mdn: 3.7 mos	11.1	NR	NR	25.9		
Kong, 2010 (27)	TMZ 40-50/d	38	Mdn: 9.4 mos 6-mos: 56.0%	Mdn: 3.9 mos 6-mos: 32.5%	5.3	0	5.3	55.3	Macdonald	NR
Strik, 2008 (28)	TMZ 100/d d1-21, q28d	18	Mdn: 17.9 mos	NR	22.2	16.7	5.6	38.9	Macdonald	NR
Wick, 2007 (29)	TMZ 150/d d1-7+d15-21, q28d	64	Mdn: 8.7 mos 1-yr: 23%	Mdn: 5.5 mos 6-mos: 43.8%	10.9	1.6	9.4	NR	Macdonald	NR
Brandes, 2006 (30)	TMZ 75/d d1-21, q28d	33	Mdn: 9.2 mos 1-yr: 38%	Mdn: 3.7 mos 6-mos: 30.3%	9.1	3.0	6.1	51.5	Macdonald	NR
Kong, 2006 (31)	TMZ 40/d	12	Mdn: 11 mos	Mdn: 6.0 mos	16.7	0	16.7	41.7	Macdonald	NR
Wick, 2004 (32)	TMZ 150/d d1-7+d15-21, q28d	21	1-yr: 81%	Mdn: 4.8 mos 6-mos: 47.6%	9.5	0	9.5	81.0	Macdonald	NR
Khan, 2002 (33)	TMZ 75/d, for 42d then 28d rest	28	Mdn: 7.7 mos 6-mos: 60%	Mdn: 2.3 mos 6-mos: 19%	0	0	0	39.3	Macdonald	NR

Notes: CR=complete response; d=days(s); mdn=median; mos=months; N=number included in analysis; NR=not reported; NYR=not yet reached; OR=objective response; OS=overall survival; PFS=progression-free survival; PR=partial response; q=every; RECIST=Response Evaluation in Solid Tumours; ref=reference; SD=stable disease; TMZ=temozolomide; WHO=World Health Organization; wks=weeks; yr=year.

[A]Gadolinium-enhanced MRI scans were performed at the end of every two cycles (approximately once every two months).

[B]One of the 29 enrolled patients was excluded from the efficacy analysis.

[C]Two of the 29 enrolled patients were excluded from the efficacy analysis.

Appendix 2-3. Grade 3 or 4 adverse events non-comparative phase II trials of temozolomide monotherapy in patients with recurrent GB following prior therapy.

Author, year (ref)	Treatment	N	Nausea/ Vomiting (%)	Fatigue (%)	Leukopenia (%)	Lympho-penia (%)	Neutropenia (%)	Thrombo-cytpenia (%)	Hematologic (%)	Elevated liver enzymes (%)	Headache (%)	Treatment-related deaths (%)
Standard Dose/Schedule (150-200 mg/m^2/d d1-5; q28d)												
Terasaki, 2009 (16)	TMZ150-200	25[A]	-	-	-	-	8	8	-	-	-	-
Balmaceda, 2008 (17)	TMZ 200	120[A]	-	-	-	0	-	-	-	-	-	1.7
Hassler, 2006 (18)	TMZ 150-200	40[A]	5.0	-	-	-	-	7.5	-	-	5.0	-
Yang, 2006 (19)	TMZ 150-200	25[A]	0	-	0	-	-	0	-	-	-	-
Chang, 2004 (20)	TMZ 150-200	213[A]	2.3[B]	4.7	-	-	-	-	29.1	-	-	-
Sipos, 2004 (21)	TMZ 200	75[A]	-	-	-	-	-	-	-	-	-	-
Brandes, 2002 (22)	TMZ 150	42	-	-	2.4	-	-	-	-	-	-	-
Brada, 2001 (23)	TMZ 150-200	138	3.6/3.6	2.2	6.5	-	4.3	9.4	-	-	1.4	-
Brandes, 2001 (24)	TMZ 150	41[A]	-	-	-	-	-	-	-	-	-	-
Other Doses and Schedules												
Berrocal, 2010 (25)	TMZ 85/d d1-21, q28d	47[A]	2.1	-	2.1	27.7	2.1	10.6	-	-	-	-
Perry, 2010 (26)	TMZ 50/d	120	6.7	5.8	-	15.8	-	-	-	0.8	-	-
Kong, 2010 (27)	TMZ 40-50/d	38	0	-	-	7.9	2.6	0	-	0	-	-
Strik, 2008 (28)	TMZ 100/d d1-21, q28d	21[A]	0	0	14.3	0	-	4.8	14.3	4.8	-	0
Wick, 2007 (29)	TMZ 150/d d1-7+d15-21, q28d	90[A]	-	-	-	-	-	-	14.4[C]	-	-	-
Brandes, 2006 (30)	TMZ 75/d d1-21, q28d	33	3.0/-	-	-	24.2	12.1	3.0	-	-	-	-
Kong, 2006 (31)	TMZ 40/d	12	0	0	0	0	0	0	0	0	0	0
Wick, 2004 (32)	TMZ 150/d d1-7+d15-21, q28d	21	9.5	19.0	9.5	-	-	28.6	-	-	-	-
Khan, 2002 (33)	TMZ 75/d, for 42d then 28d rest	35[A]	-	0	-	17.1	2.9	2.9	-	0	-	-

Notes: "-"=not reported; d=day(s); N=number enrolled; q=every; ref=reference; TMZ=temozolomide.
[A]All enrolled patients were included in safety analysis, including non-GB histologies.
[B]Nausea, vomiting, or diarrhea.
[C]All patients had grade 4 toxicity; grade 3 was not reported.

Appendix 3. Ongoing trials.

BIBW 2992 with or without daily temozolomide in the treatment of patients with recurrent malignant glioma.

Protocol ID:	NCT00727506
Last date modified:	November 15, 2010
Trial type:	Randomized, open-label, phase I/II
Accrual:	150
Primary outcome:	Phase I: dose-limiting toxicity; Phase II: progression-free survival
Sponsorship:	Boehringer Ingelheim Pharmaceuticals
Status:	Ongoing, not recruiting

Intensive dose temozolomide treatment or temozolomide with thalidomide treatment in recurrent glioblastoma after standard therapy: a randomized phase II trial

Protocol ID:	NCT00521482
Last date modified:	August 27, 2007
Trial type:	Randomized, open-label
Accrual:	40
Primary outcome:	Progression-free survival
Sponsorship:	University of Zurich
Status:	Not yet recruiting

A multi-centre, open-label, randomized, active-controlled parallel groups study comparing the efficacy and safety of Temodal vs. Semustine in the treatment of subjects with recurrent glioblastoma or anaplastic astrocytoma.

Protocol ID:	NCT00335075
Last date modified:	September 9, 2008
Trial type:	Randomized, open-label
Accrual:	151
Primary outcome:	Progression-free survival
Sponsorship:	Schering-Plough
Status:	Completed

Randomized trial assessing the significance of bevacizumab in recurrent grade II and III gliomas – the TAVAREC trial.

Protocol ID:	NCT01164189
Last date modified:	February 5, 2011
Trial type:	Randomized, open-label
Accrual:	144
Primary outcome:	Overall survival
Sponsorship:	European Organization for the Research and Treatment of Cancer
Status:	Ongoing, accruing

Appendix 3 (Continued). Ongoing trials

Randomized multicentric phase II study of prolonged adjuvant temozolomide or "stop and go" in glioblastoma patients: the PATSGO study.

Protocol ID:	NCT00643825
Last date modified:	July 22, 2010
Trial type:	Randomized, open-label
Accrual:	64
Primary outcome:	Progression-free survival and overall survival
Sponsorship:	Cliniques universitaires Saint-Luc Université Catholique de Louvain
Status:	Ongoing, accruing

Dose-intensified rechallenge with temozolomide, one week on one week off versus three weeks on one week off in patients with progressive or recurrent glioblastoma.

Protocol ID:	NCT00941460
Last date modified:	January 4, 2010
Trial type:	Randomized, open-label
Accrual:	166
Primary outcome:	Time to treatment failure
Sponsorship:	University of Heidelberg
Status:	Ongoing, accruing

Randomized phase II trial of standard dose bevacizumab versus low dose bevacizumab plus lomustine (CCNU) in adults with recurrent glioblastoma multiforme.

Protocol ID:	NCT01067469, EORTC 26101
Last date modified:	February 2, 2011
Trial type:	Randomized, open-label
Accrual:	102
Primary outcome:	Progression-free survival
Sponsorship:	M.D. Anderson Cancer Center
Status:	Ongoing, accruing