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Bevacizumab for the Treatment of Patients with Glioblastoma Multiforme That Has Relapsed or Progressed Following Prior Therapy

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

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Bevacizumab for the Treatment of Patients with Glioblastoma Multiforme That Has Relapsed or Progressed Following Prior Therapy

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

Report Date: July 8, 2010

SUMMARY

QUESTION(S)

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

Outcomes of interest include: overall survival, progression-free survival, time-to-progression, response rate, duration of response, quality of life, and adverse effects.

TARGET POPULATION

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

RECOMMENDATIONS

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

- **Bevacizumab 10mg/kg given intravenously every 2 weeks is a reasonable treatment option in patients with recurrent GBM and should be offered to eligible patients with the following potential benefits in mind:**
  - **Partial or complete response in up to 30-40% with subsequent sparing of dexamethasone toxicity**
  - **Prolongation of progression-free survival at 6 months in approximately 40% of patients, resulting in stabilization or improvement in quality of life during that time.**
- **Bevacizumab toxicities should be considered both in the selection, and the monitoring of patients**
  - **Hypertension is common and should be frequently monitored**
  - **Bleeding, thrombosis, and bowel perforation appear not to be more frequent than in other cancer sites and should be clinically monitored.**

QUALIFYING STATEMENTS

- Repeat surgery and conventional chemotherapy agents such as lomustine or temozolomide (in either standard or alternative schedules) continue to be reasonable treatment options

for patients with recurrent GBM. The optimal timing and sequence of the various options for disease recurrence, including bevacizumab, has not been established.

- None of the currently used systemic therapies have been compared to bevacizumab monotherapy in controlled trials in the setting of recurrent GBM.
- Practitioners should use both clinical and radiological information to diagnose progression of GBM. Consideration must be given to changes due to treatment effects (pseudoprogression), especially during the first three months following completion of standard chemoradiation.
- Although progression-free survival is improved with bevacizumab compared to all other available agents, this may be at least in part due to its interaction with tumour vasculature and resulting 'pseudoresponse' on imaging. Overall survival has not been proven to change with the use of bevacizumab.
- As the majority of patients with recurrent GBM do not respond to the first treatment option used, patients must be closely monitored and therapy discontinued if no benefit is seen for the patient. For bevacizumab, early clinical and imaging improvement can be seen after just one treatment in some responders. Based on clinical experience and expert consensus, in order to detect non-responders it is recommended that patients are seen at least once per month and evaluated by brain imaging (CT or MRI) at least every two months while on treatment. MRI is the preferred imaging modality since both changes in contrast-enhancement and surrounding T2-weighted parameters are important in the determination of response, or failure, of the drug.

KEY EVIDENCE

Two trials investigating the use of bevacizumab in recurrent glioblastoma were identified. Friedman et al (1) reported the results of a randomized phase II trial comparing bevacizumab monotherapy (n=85) to therapy with bevacizumab in combination with irinotecan (n=82). The authors did not plan to compare the two treatment arms, instead the authors planned to compare each arm to estimated historical control rates for progression-free survival and response that pooled data from several publications. The authors assumed six-month PFS to be 15% for salvage therapy and for single-agent irinotecan based on reports of several trials of recurrent glioblastoma multiforme. Objective response rates were assumed to be 5.0% with salvage therapy and 10% with irinotecan. The authors reported six-month progression-free survival of 42.6% for bevacizumab monotherapy and median progression-free survival was 4.2 months (95% confidence interval [CI] 2.9 months to 5.8 months). The objective response rate was 28.2% (97.5% CI 18.5% too 40.3%) and the median duration of response was 5.6 months. Median overall survival was 9.2 months (95% CI 8.2 months to 10.7 months).

Kriesl et al (2) reported the results of a single-arm phase II trial investigating bevacizumab monotherapy in recurrent GBM. The authors reported six-month progression-free survival of 29% (95% CI 18% to 48%) and median progression-free survival of 16 weeks (95% CI 12 weeks to 16 weeks; approximately 3.7 months). Objective response rates were 71% by Levin criteria and 35% by Macdonald criteria. Median overall survival was 31 weeks (95% CI 21 weeks to 54 weeks; approximately 7.2 months). Both studies showed a reduction in corticosteroid use in association with bevacizumab therapy.

FUTURE RESEARCH

Randomized controlled clinical trials of various available agents in recurrent GBM are recommended.

The results of two large ongoing phase III studies of bevacizumab combined with chemoradiation for newly diagnosed GBM may replace the use of bevacizumab at recurrence for many patients.

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES
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- #9-2: *Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma.*
  Available at:
  http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/neuro-ebs/.

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For further information about this special advice report, please contact:
Dr. James Perry; Co-Chair, Neuro-oncology Disease Site Group
Odette Cancer Centre, Toronto, ON
Phone: 416-480-4766 Fax: 416-480-5054 E-mail: james.perry@sunnybrook.ca
or
Dr. Normand Laperriere; Co-Chair, Neuro-oncology Disease Site Group
Princess Margaret Hospital, Toronto, ON
Phone: 416-946-2127 Fax: 416-946-2038 Email: norm_laperriere@rmp.uhn.on.ca

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REFERENCES—SUMMARY

1. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009 Oct 1;27(28):4733-40.
2. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009 Feb 10;27(5):740-5.

FULL REPORT

QUESTION

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

Outcomes of interest include: overall survival, progression-free survival, time-to-progression, response rate, duration of response, quality of life, and adverse effects..

INTRODUCTION

Historical background: Recurrent Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumour and the incidence of GBM is increasing to as high as 20/100,000, especially in middle-aged to elderly individuals (1). Unfortunately GBM is a genetically heterogenous disease and multiple mechanisms of treatment resistance are increasingly described. The treatment of recurrent GBM 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 (TMZ), given orally for 42 consecutive days in combination with standard radiotherapy (60Gy/30 days), and followed by six months of adjuvant TMZ clearly increases both median survival and one- and two-year survival compared to standard radiotherapy alone in patients with newly diagnosed glioblastoma. 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 GBMs recur. Options at the time of recurrence depend upon the location of recurrent disease (for example; local recurrence versus diffuse recurrence in the brain or neuraxis). Re-operation is considered for individuals with larger recurrences which are accessible to surgical resection, who might benefit from reduction in mass effect and steroid use. Re-irradiation is not commonly considered. For patients with reasonable neurological function and quality of life, systemic therapy is often considered in practice. For patients who are unlikely to benefit from systemic therapy (i.e. patients with poor performance status, inability to tolerate therapy, etc.), palliative measures are considered.

Conventional systemic therapies have largely been evaluated prior to 2005, when patients did not receive TMZ during first-line therapy. Prior to 2005, patients with recurrent GBM were TMZ-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 TMZ at time of recurrence (approved for both recurrent anaplastic astrocytoma and GBM, 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 TMZ came into common practice.

Systemic therapy options available in Ontario include nitrosoureas (lomustine [CCNU], carmustine [BCNU]), procarbazine, etoposide, and carboplatin. Of these listed, only lomustine has been evaluated at the time of progression following first-line therapy with RT/TMZ and adjuvant TMZ. In a randomized phase III trial in recurrent GBM, 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 = 92) after a planned interim analysis for futility. The six-month progression-free survival for enzastaurin was 11.1% and for lomustine was 19% and therefore no higher than prior reports of efficacy in the pre-TMZ era. These data point to the urgent unmet need for more effective therapies in recurrent GBM.

Temozolomide is active in a variety of treatment schedules, including the standard 150-200mg/m2, days 1-5/28 as described in the original TMZ studies. Interest in alterative schedules has been explored due to putative advantages such as dose-density, and metronomic dosing. In 2010, a 120 patient single-arm phase II trial testing a metronomic schedule of TMZ (50mg/m2 orally daily, continuously) was reported and detected six-month progression-free survival of 24% for recurrent GBM after failure on conventional TMZ treatment (5). Median overall survival from progression was 9.4 months and treatment was well tolerated (5). Continuous daily TMZ for recurrent GBM has become a commonly used regimen in Ontario and, along with lomustine, these are the only two standard chemotherapy regimens well-studied in the post-2005 era. The role of bevacizumab in recurrent GBM should be placed into context with lomustine and daily TMZ as the two most commonly prescribed treatment options.

There exists an urgent unmet need for more effective therapies for disease recurrence despite first-line use of radiation therapy combined with TMZ in patients with GBM. None of the currently available treatment options have been directly evaluated in controlled clinical trials. Thus practitioners are left to individualize treatment recommendations based upon the patient's clinical condition, the characteristics of the tumour, and the availability of treatment options.

Glioblastoma multiforme is characterized by robust neoangiogenesis which is highly controlled by upregulation and overexpression of vascular endothelial growth factor (VEGF) and its receptor (VEGFR). Extensive pre-clinical and clinical evidence has shown that inhibition of VEGF activity, either directly at the ligand, or from suppression of downstream signalling events, can reduce the angiogenic process and improve tumour control. Bevacizumab was developed as the first prototypical anti-angiogenic drug and is a humanized monoclonal antibody against the VEGF ligand. Bevacizumab has been shown to have anti-tumour efficacy in other several solid cancers and is approved for use and funded in Ontario for indications other than brain. Investigation of the effectiveness of bevacizumab in GBM was delayed due to fear of toxicities, especially intracranial bleeding; however, GBM is amongst the most highly vascularised human cancers and is a target for this therapy. Development of bevacizumab in GBM offers a novel therapeutic target and potentially addresses an important unmet need for patients with recurrent disease.

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 bevacizumab monotherapy in patients with GBM 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) (2000 to May Week 4 [June 9] 2010), EMBASE (Ovid) (2000 to 2010 Week 22 [June 8]), and the Cochrane Library (June 2010) 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) 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 three 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 published full report articles or published meeting abstracts of:

1. Practice guidelines or systematic reviews of bevacizumab monotherapy in patients with GBM that has relapsed or progressed following prior therapy.
2. Randomized phase II or phase III clinical trials comparing the use of bevacizumab monotherapy to either therapy without bevacizumab or placebo.
3. Randomized phase II or phase III clinical trials that included bevacizumab monotherapy in one arm of the study or non-comparative phase II trials investigating the use of bevacizumab monotherapy.
4. Clinical trials must have included patients with GBM that relapsed or progressed following prior therapy.
5. Published studies must have reported data on one or more of the following outcomes: overall survival, progression-free survival, time-to-progression, response rate, duration of response, quality of life, and adverse effects.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Abstracts of non-comparative phase II trials.
3. Articles published in a language other than English, due to financial considerations for translation.

Synthesizing the Evidence

A meta-analysis of the trial results will not be conducted as no randomized trials comparing bevacizumab monotherapy to either placebo or therapy without bevacizumab are expected to be identified.

RESULTS

Literature Search Results

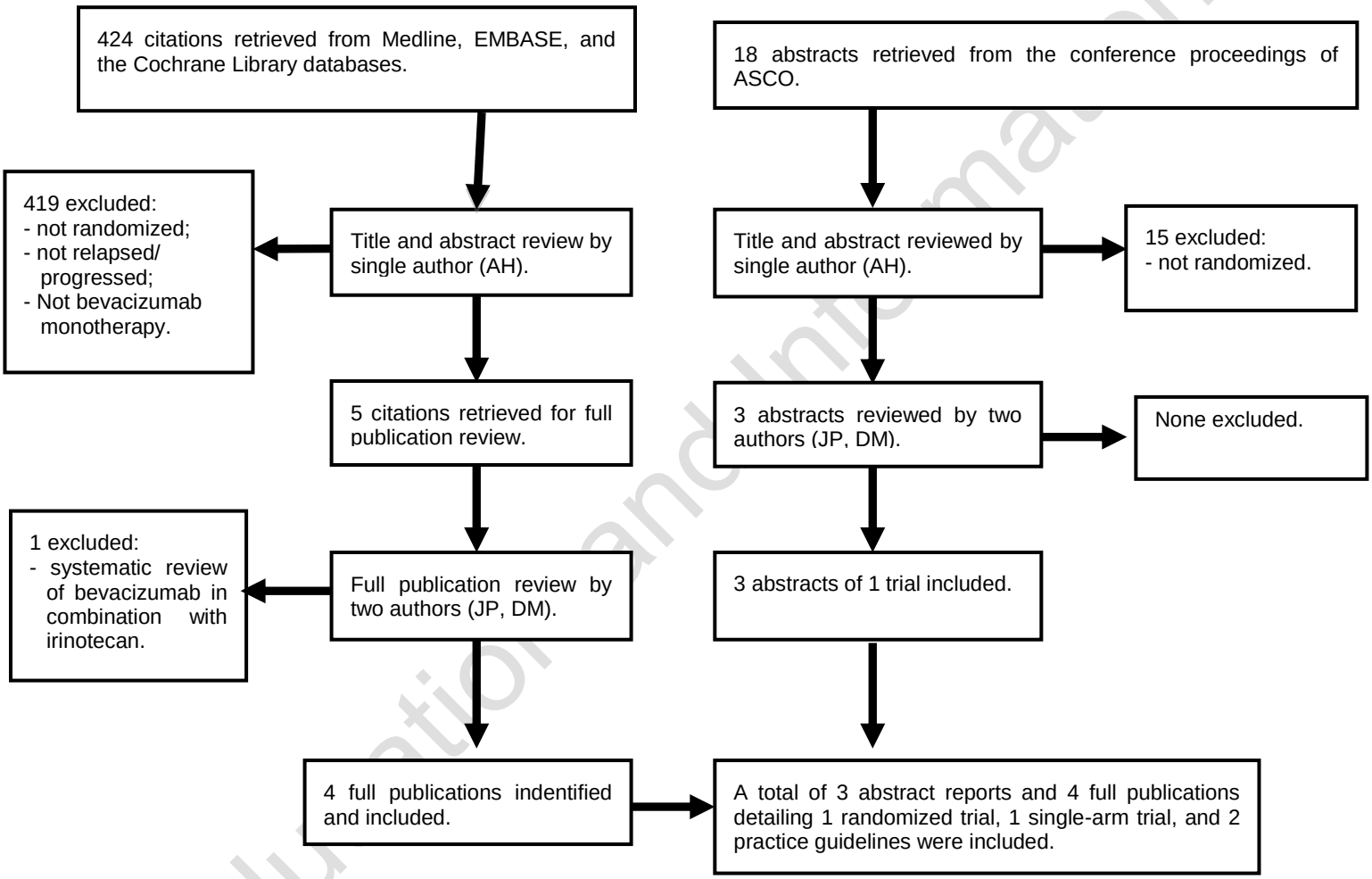
A total of 424 citations were identified in the databases of MEDLINE, EMBASE, and the Cochrane Library (Figure 1). Four full publications including one randomized phase II trial (6), one single-arm phase II trial (7), and two practice guidelines were identified (8,9). Eighteen abstracts were identified from ASCO. Of those, three abstracts were included that reported on the fully published randomized trial. Two of the abstracts were published prior to the full publication (10,11). The remaining abstract provided updated survival and safety data (12).

Practice Guidelines

The National Comprehensive Cancer Network (NCCN) published an updated practice guideline on central nervous system cancers in 2010 (8). The authors did not report the methods used to develop the guideline, nor did they report if a systematic search of the evidence was conducted. Given these limitations, the guideline was not considered further.

The European Society for Medical Oncology (ESMO) published clinical recommendations in 2009 on the diagnosis, treatment and follow-up of malignant glioma (9). The authors did not report the methods used to develop the guidelines, nor did they report if a systematic literature search was conducted. Given these limitations, the report was not considered further.

Figure 1. Selection of studies investigating bevacizumab monotherapy in patients with relapsed or progressed glioblastoma multiforme from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO.



Clinical Trials

Patient Characteristics, Study Design, and Trial Quality

One randomized phase II trial was identified (6) that enrolled patients with histologically confirmed glioblastoma in first or second relapse and who had disease progression confirmed by magnetic resonance imaging (MRI) within 14 days of study treatment (BRAIN study). Patients had received standard radiotherapy and temozolomide. Patients had Karnofsky performance status ≥70% and a life expectancy of at least 12 weeks. One hundred sixty-seven patients were randomized to receive bevacizumab (n=85) or bevacizumab plus irinotecan (n=82) (Table 1). Although the authors randomized patients to receive bevacizumab monotherapy or to bevacizumab plus irinotecan, the trial was not designed to make statistical comparisons between the two treatment arms. Instead the trial was designed to make comparisons of each treatment arm to historical data. The authors assumed six-month PFS of 15% with salvage therapy or single-agent irinotecan, based on data from four full publications (13-16) of five single-arm phase II trials of irinotecan in progressive or recurrent GBM, as well as data from two full publications (17,18) that pooled data from 16 and eight single-arm trials, respectively. The authors also assumed an objective response rate of 5.0% with salvage therapy and 10.0% with single-agent irinotecan. The authors therefore designed the study so that 80 patients in each treatment arm would provide 80% power to detect at least a 13.0% improvement in six-month progression-free survival and at least 90% power to detect at least a 13.0% improvement in objective response rate, with a two sided alpha of 0.025. As the data in that study were compared with aggregate historical data obtained from publications of prospective single arm phase II trials, it is difficult to generalize any findings from the comparison.

Table 1. Trial and patient characteristics of trials investigating the use of bevacizumab monotherapy in patients with recurrent GBM following prior therapy.

Author, year (ref)	Patient characteristics	Treatment	N	Differences between treatment groups at baseline
Friedman, 2009 (6)	Patients with GBM in first or second relapse with disease progression confirmed by MRI; had received standard radiotherapy and TMZ; Karnosfky PS ≥70%; life expectancy ≥12 weeks.	Bevacizumab 10 mg/kg iv every other week.	85	Similar; however, groups were not directly compared
		Bevacizumab 10 mg/kg iv every other week + irinotecan 340 mg/m^2 (125 mg/m^2 if not taking EIAEDs) iv over 90 minutes every other week.	82	
Kreisl, 2009 (7)	Patients with recurrent GBM after standard external-beam fractionated radiotherapy and TMZ; Karnofsky PS ≥60%; life expectancy ≥2 months.	Bevacizumab 10 mg/kg every 14 days on a 28 day cycle.	48	NA

Notes: EIAEDs=enzyme-inducing antiepileptic drugs; GM=glioblastoma multiforme; iv=intravenous; N=number enrolled or randomized; PS=performance status; ref=reference; TMZ=temozolomide.

One single-arm phase II trial was identified (7) that enrolled patients with recurrent GBM who had received standard external-beam radiotherapy and temozolomide (Table 1).

Forty-eight patients received bevacizumab monotherapy at 10 mg/kg every 14 days over a 28-day cycle. Kreisl et al (7) enrolled 48 patients with recurrent GBM in a single-arm, non-comparative phase II trial of bevacizumab monotherapy.

Efficacy Outcomes

Efficacy outcomes for the two identified phase II trials can be found in Table 2.

Table 2. Efficacy outcomes in trials of bevacizumab monotherapy in patients with recurrent GBM.

Author, year (ref)	Treatment	N	OR (%)	Duration of response (median)	6-month PFS (%)	Median PFS	OS (median)	Follow-up
Friedman, 2009 (6)	Bev monotherapy	85	28.2 (97.5% CI: 18.5%-40.3%)	5.6 mos (95% CI: 3.0-5.8)	42.6	4.2 mos (95% CI: 2.9-5.8)	9.2 mos (95% CI: 8.2-10.7)	All pts had at least 8 months follow-up
	Bev + irinotecan	82	37.8 (97.5% CI: 26.5%-50.8%)	4.3 mos (95% CI: 4.2-NYR)	50.3	5.6 mos (95% CI: 4.4-6.2)	8.7 mos (95% CI: 7.8-10.9)	
Kreisl, 2009 (7)	Bev monotherapy	48	Levin: 71% (all PR) Macdonald: 35% (1 CR, 16 PR)	NR	29% (95% CI: 18%-48%)	16 wks (95% CI: 12-16)	31 wks (95% CI: 21-54) ***6-mos:*** 57% (95% CI: 44%-75%)	NR

Notes: Bev=bevacizumab; CI=confidence interval; mos=months; N=number enrolled or randomized; NR=not reported; NYR=not yet reached; OR=objective response; OS=overall survival; PFS=progression-free survival; ref=reference; wks=weeks.

Survival

Friedman et al (6) reported that for 85 patients who received bevacizumab monotherapy, the median overall survival was 9.2 months (95% confidence interval [CI] 8.2 months to 10.7 months). Kreisl et al (7) reported that for 48 patients who received bevacizumab monotherapy, the median overall survival was 31 weeks (95% CI 21 weeks to 54 weeks). At six months, the authors reported overall survival of 57% (95% CI 44% to 75%).

Disease control

Six-month progression-free survivals of 42.6% and 29% were reported by Friedman et al (6) and Kreisl et al (7), respectively. The authors of those trials also reported median progression-free survivals of 4.2 months and 16 weeks (approximately 3.7 months).

Response

Friedman et al (6) reported an objective response rate of 28.2% of 85 patients (97.5% CI 18.5% to 40.3%) by World Health Organization (WHO) response evaluation criteria. The duration of response was 5.6 months (95% CI 3.0 months to 5.8 months). Kreisl et al (7) reported an objective response rate of 71% by Levin criteria (all were partial responses), and 35% by Macdonald criteria (one complete and 16 partial responses). The authors did not report on duration of response.

Quality of life

Neither of the trials reported data on quality of life in the parent publication. Wefel et al (11) reported in abstract form on neurocognitive functions in the 85 patients in the bevacizumab-alone arm of the BRAIN trial using a standard neuro-oncology test battery. The majority of patients completed the test instruments and were found to have stable or improved neurocognitive function during the first 6 weeks of treatment. Full analysis and publication is pending.

Adverse Events

Grade 3 or 4 adverse events can be found in Table 3. Friedman et al (6) reported that 98.8% of 84 patients who received bevacizumab monotherapy experienced an adverse event and that 46.4% experienced a grade 3 or higher adverse event. The most common adverse events of any grade reported by Friedman et al (6) in the bevacizumab monotherapy arm were fatigue (45.2%), and headache (36.9%) and hypertension (29.8%). Two patients experienced an adverse event that led to death. Both trials reported grade 3 or 4 thromboembolic events and grade 3 or 4 hypertension (Table 3). Kreisl et al (7) reported 2.1% of patients receiving bevacizumab monotherapy had a bowel perforation. Friedman et al (6) reported that 2.5% of patients who received bevacizumab and irinotecan had a bowel perforation; however, no patients who received bevacizumab monotherapy experienced a bowel perforation.

Table 3. Grade 3 or 4 adverse events in trials of bevacizumab monotherapy in patients with recurrent GBM.

Author, year (ref)	Treatment	N	Thromboembolic (%)	Hypertension (%)	Bowel perforation (%)
Friedman, 2009 (6)	Bev monotherapy	85	VTE: 3.6 ATE: 2.4 DVT: 2.4	8.3	0
	Bev + irinotecan	82	VTE: 8.9 ATE: 2.5 DVT: 6.3	1.3	2.5
Kreisl, 2009 (7)	Bev monotherapy	48	12.5	4.2	2.1

Notes: Bev=bevacizumab; N=number enrolled or randomized; ref=reference.

DISCUSSION

Evaluating efficacy of treatment for recurrent GBM: focus upon bevacizumab

Judging response to therapy in neuro-oncology is controversial. In the setting of recurrent GBM, the most commonly used parameters are tumour response and progression-free survival. Overall survival has some pitfalls as therapies used beyond first recurrence may influence overall survival, especially since this period of time is generally short. Historically, six-month progression-free survival on the order of 15-20% has been accepted as the minimum 'bar' by which to judge new therapies in the pre-TMZ era. The publication of the enzastaruin versus CCNU data (4) demonstrated that this modest improvement in progression-free survival has not substantially changed since the introduction of upfront TMZ in the treatment regimen. However, the use of TMZ in first-line disease creates a dilemma for practitioners since the most effective (and previously standard) therapy for recurrence has already been included in the initial treatment.

The use of imaging to judge therapeutic response is also problematic, and highly relevant to the topic of bevacizumab. Since the widespread adoption of RT/TMZ for newly diagnosed GBM, many centres noticed that MRI scans obtained in the first few months after completion of chemoradiation demonstrated increased contrast enhancement and edema; a picture of disease progression. Over time however, the imaging in up to 50% of such patients will improve: this has been termed 'pseudoprogression' and has been well documented in standard practice in Ontario (19). Canadian recommendations for the management of GBM encourage practitioners to recognize pseudoprogression and not to abandon standard adjuvant TMZ therapy based upon imaging results alone, especially during the first three

months following completion of radiotherapy (3). These recommendations are echoed by the newly developed Response Assessment in Neuro-Oncology (RANO) criteria (20).

In addition to pseudoprogression, the introduction of therapies targeted to tumour vasculature, such as bevacizumab, has created awareness of 'pseudoresponse'. Pseudoresponse is a term referring to the effects of therapies targeted to tumour vasculature in which a robust effect upon endothelial integrity (termed vascular normalization) leads to minimization of contrast leakage, and therefore apparent decrease in tumour size on imaging studies. Thus, traditional response measurements reliant on tumour size (Macdonald criteria, RANO criteria) may be somewhat misleading, especially if the effects of therapy are transient.

Bevacizumab in recurrent GBM: the data in context

Compared to currently used treatments, bevacizumab has the advantage of an unprecedentedly high response rate and six-month progression free survival. Whether this reduction in tumour-associated contrast enhancement and mass effect upon imaging is due to a direct effect on tumour vessels, or anti-tumour effect, or both, it appears to be clinically meaningful. Disease control is conferred for an average of four to six months and during that period of time most responders experience stable or improved neurocognition and a reduction in dexamethasone requirement. Dexamethasone-induced toxicities include muscle weakness resulting in immobility (leading to increased risk of secondary morbidities such as venous thromboembolism, infection), glucose intolerance, opportunistic infections, skin fragility, leg edema, change in body habitus ("Cushingoid" appearance) osteopenia, personality changes, and insomnia. These toxicities are highly clinically relevant and may lead to increased hospital visits and admissions.

In the two published clinical trials the median overall survival from the time of first recurrence was 7.2 months and 9.2 months in patients treated with bevacizumab (6,7). Although requiring comparison across clinical trials, these data are very similar to the median overall survival reported with the use of daily TMZ from first relapse in the RESCUE trial (2). While TMZ may have fewer serious adverse effects than bevacizumab, clinicians do not often observe the high response rate, comparatively prolonged progression-free survival, and reduction in steroid requirement seen with bevacizumab.

Monitoring of patients with recurrent GBM

The majority of patients with recurrent GBM do not respond to the first treatment option used. Thus, patients must be closely monitored and therapy discontinued if no benefit is seen for the patient. In the case of daily TMZ, it is usual practice to clinically monitor patients monthly and to evaluate with brain imaging (CT or MRI) every two cycles (i.e. every two months). For lomustine, many practitioners offer every sixth-week treatment and re-image every 12 weeks if the patient is clinically stable. For bevacizumab, early clinical and imaging improvement can be seen after just one treatment in responders. Based on clinical experience and expert consensus, in order to detect non-responders it is recommended that patients are seen at least once per month and evaluated by MRI at least every two months while on treatment. Particular attention needs to be paid to unique bevacizumab toxicities including hypertension, proteinuria, thrombosis, and bleeding. Generally, no more than two to four cycles of bevacizumab monotherapy would be required to determine if a patient is deriving clinical and/or imaging benefit from therapy (i.e. clinical and radiologic disease stability, or response).

CONCLUSIONS

Glioblastoma recurring after the use of standard first line radiotherapy/TMZ is a therapeutic challenge. Current options for treatment available to practitioners in Ontario include systemic cytotoxic chemotherapy agents such as lomustine, TMZ, procarbazine, and carboplatin. Of these, only lomustine and daily TMZ have been evaluated in prospective studies in the modern setting of recurrence following the use of upfront TMZ treatment. Bevacizumab, a humanized monoclonal antibody against VEGF, is associated with the highest response rate and six-month progression free survival yet reported in patients with GBM who experience progression after standard RT/TMZ. While there are limitations to uncontrolled open-label phase II data, the results with bevacizumab strongly suggest clinical benefit for patients, including reduced dexamethasone requirements, improved or stable neurocognitive status, and enhanced disease control resulting in slower neurological progression.

GBM is a rare disease, and is managed almost entirely in Canada in specialized centres of excellence. Controlled trials testing new therapies in recurrent GBM are rarely performed due to the heterogeneity and rarity of the disease. Thus clinicians are left with recommending treatment to patients based upon individualized needs. For many patients, bevacizumab may provide clinical advantages that can be determined within several cycles of therapy. These advantages include prolonged progression-free survival and increased response rate which may confer an improvement or stabilization of neurocognitive status, improved neurological symptoms, slower neurological progression, and may reduce the patient's dexamethasone requirements. Bevacizumab must be closely monitored and should only be used by clinicians with specialized experience in the management of patients with GBM and the interpretation of the neuro-imaging effects of anti-tumour therapy.

ONGOING TRIALS

Many ongoing open-label single-arm phase II trials are in progress and aim to evaluate the addition of other targeted therapies or conventional cytotoxic treatments to bevacizumab for recurrent GBM. Two randomized phase II trials were identified and can be found in Appendix 2. No phase III trials incorporating bevacizumab in patients with recurrent GBM were identified.

There are two ongoing randomized phase III trials testing the effectiveness of bevacizumab when added to standard first line RT/TMZ for newly diagnosed GBM. The AVAglio trial is an industry-sponsored registration trial testing conventional RT/TMZ + bevacizumab versus RT/TMZ + placebo for newly diagnosed GBM with the dual primary endpoint of PFS and OS. RTOG 0825 is a similar phase III trial but uses bevacizumab somewhat later in upfront therapy. Both trials evaluate bevacizumab toxicities. AVAglio is designed to robustly test QOL and neurocognitive function, especially during any progression-free intervals gained by therapy. If bevacizumab is accepted as a part of standard front-line care, the use of bevacizumab at recurrence will likely be significantly reduced.

Many other anti-VEGF strategies are being tested both at recurrence and in the upfront setting. Cederanib is an oral VEGF-2 inhibitor and has been compared to lomustine in a randomized trial for recurrent GBM (the Regal trial). The preliminary results from this study are expected within the next 12 months. Trials to evaluate the addition of cediranib to standard RT/TMZ for newly diagnosed GBM are planned.

CONFLICT OF INTEREST

Dr. Perry has served on advisory boards for Hoffman-LaRoche (Basel, Switzerland), has received honoraria as a speaker for Roche Canada, and has provided preceptorships for employees of Roche Canada (non-remunerated). Dr. Macdonald is a local investigator for the Hoffman-La Roche Canada funded AVAglio phase III trial and has served on advisory boards for Hoffman-La Roche. Mr. Haynes declared no conflicts of interest.

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For further information about this special advice report, please contact:
Dr. James Perry; Co-Chair, Neuro-oncology Disease Site Group
Odette Cancer Centre, Toronto, ON
Phone: 416-480-4766 Fax: 416-480-5054 E-mail: james.perry@sunnybrook.ca
or
Dr. Normand Laperriere; Co-Chair, Neuro-oncology Disease Site Group
Princess Margaret Hospital, Toronto, ON
Phone: 416-946-2127 Fax: 416-946-2038 Email: norm_laperriere@rmp.uhn.on.ca

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

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Appendix 1. Literature search strategies.

Ovid MEDLINE

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

49. placebos/
50. placebo$.tw.
51. (allocated adj2 random$).tw.
52. random allocation.tw.
53. randomly allocated.tw.
54. or/40-53
55. case report.tw.
56. letter.pt.
57. historical article.pt.
58. or/55-57
59. 54 not 58
60. 39 or 59
61. practice guideline/
62. practice guideline$.mp.
63. 61 or 62
64. 60 or 63
65. 7 and 64

EMBASE

1. bevacizumab/
2. bevacizumab:.mp.
3. avastin:.mp.
4. or/1-3
5. exp glioblastoma/
6. glioblastoma:.mp.
7. 5 or 6
8. 4 and 7
9. meta-analysis/
10. ((meta adj analy$) or metaanaly$).tw.
11. (systematic adj (review$1 or overview$1)).tw.
12. or/9-11
13. cancerlit.ab.
14. Cochrane.ab.
15. embase.ab.
16. (cinahl or cinhal).ab.
17. science citation index.ab.
18. bids.ab.
19. or/13-18
20. reference list$.ab.
21. bibliograph$.ab.
22. hand-search$.ab.
23. manual search$.ab.
24. relevant journals.ab.
25. or/20-24
26. data extraction.ab.
27. selection criteria.ab.
28. 26 or 27
29. review.pt.
30. 28 or 29
31. letter.pt.

32. comment.pt.
33. 31 or 32
34. 12 or 19 or 25 or 30
35. 34 not 33
36. clinical trial/
37. randomized controlled trial/
38. randomization/
39. single blind procedure/
40. double blind procedure/
41. crossover procedure/
42. placebo/
43. randomi?ed control$ trial$.tw.
44. rct.tw.
45. random allocation.tw.
46. randomly allocated.tw.
47. allocated randomly.tw.
48. (allocated adj2 random$).tw.
49. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
50. placebo$.tw.
51. prospective study/
52. or/36-51
53. case study/
54. case report.tw.
55. abstract report/
56. letter/
57. or/53-56
58. 52 not 57
59. 35 or 58
60. exp practice guideline/
61. practice guideline$.tw.
62. 60 or 61
63. 59 or 62
64. 8 and 63

Appendix 2. Ongoing trials.

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

Protocol ID:	NCT01067469
Last date modified:	February 10, 2010
Trial type:	Randomized, open-label
Accrual:	102
Primary outcome:	Progression-free survival
Sponsorship:	M.D. Anderson Cancer Center
Status:	Recruiting

A randomized phase II trial of bevacizumab with irinotecan or bevacizumab with temozolomide in recurrent glioblastoma

Protocol ID:	NCT00433381
Last date modified:	June 13, 2009
Accrual:	121
Trial type:	Randomized, open-label
Primary outcome:	Progression-free survival, adverse events
Sponsorship:	Radiation Therapy Oncology Group
Status:	Ongoing, not recruiting