Canadian recommendations for the treatment of recurrent or progressive glioblastoma multiforme

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ABSTRACT

Recommendation 1: Multidisciplinary Approach
To optimize treatment outcomes, the management of patients with recurrent glioblastoma should be individualized and should involve a multidisciplinary team approach, including neurosurgery, neuropathology, radiation oncology, neuro-oncology, and allied health professions.

Recommendation 2: Imaging
The standard imaging modality for assessment of recurrent glioblastoma is Gd-enhanced magnetic resonance imaging (MRI). Tumour recurrence should be assessed according to the criteria set out by the Response Assessment in Neuro-Oncology Working Group. The optimal timing and frequency of MRI after chemoradiation and adjunctive therapy have not been established.

Recommendation 3: Pseudo-progression
Progression observed by MRI after chemoradiation can be pseudo-progression. Accordingly, treated patients should not be classified as having progressive disease by Gd-enhancing MRI within the first 12 weeks after the end of radiotherapy unless new enhancement is observed outside the radiotherapy field or viable tumour is confirmed by pathology at the time of a required re-operation. Adjuvant temozolomide should be continued and follow-up imaging obtained.

Recommendation 4: Repeat Surgery
Surgery can play a role in providing symptom relief and confirming tumour recurrence, pseudo-progression, or radiation necrosis. However, before surgical intervention, it is essential to clearly define treatment goals and the expected impact on prognosis and the patient's quality of life. In the absence of level 1 evidence, the decision to re-operate should be made according to individual circumstances, in consultation with the multidisciplinary team and the patient.

Recommendation 5: Re-irradiation
Re-irradiation is seldom recommended, but can be considered in carefully selected cases of recurrent glioblastoma.

Recommendation 6: Systemic Therapy
Clinical trials, when available, should be offered to all eligible patients. In the absence of a trial, systemic therapy, including temozolomide rechallenge or anti-angiogenic therapy, may be considered. Combination therapy is still experimental; optimal drug combinations and sequencing have not been established.

KEY WORDS

Glioblastoma multiforme, guidelines, pseudo-progression, re-irradiation, re-operation, chemotherapy, recurrence, progression

1. INTRODUCTION

Glioblastoma multiforme (GBM) is a World Health Organization grade IV astrocytoma and the most common type of primary brain tumour in adults; its estimated age-adjusted incidence in North America is 3.0 per 100,000 population [1,2]. An aggressive malignancy, GBM has an estimated 2-year survival rate of 8.7% in the absence of therapy [1]. The median duration of survival with maximal treatment is 12–18 months [3].

Glioblastomas are characterized by high mitotic activity, microvascular proliferation, and necrosis [3]. *De novo* (primary) GBM is more common in older patients (mean age: 55 years) [4], and the tumours are typically characterized by loss of heterozygosity on chromosome 10, overexpression or mutation of the epidermal growth factor receptor (EGFR), and alteration or loss of the tumour-suppressor protein PTEN (phosphatase and tensin homolog) [5–9]. Secondary GBM develops more slowly from lower-grade tumours and typically occurs in younger patients. Genetic alterations may include *TP53* mutation or

overexpression of platelet-derived growth factor receptor (PDGFR) alpha [10].

In newly-diagnosed glioblastoma, methylation of the *O*6-methylguanine DNA methyltransferase (MGMT) promoter has been shown to predict response to alkylating agents such as temozolomide, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU, carmustine), and cyclophosphamide [11,12]. After phase III study of combined radiotherapy and temozolomide in GBM [13], an analysis of MGMT promoter methylation status found that median survival was longer with than without promoter methylation (18.2 months vs. 12.2 months respectively) [14].

Accordingly, current Canadian guidelines recommend that newly-diagnosed glioblastoma be treated with maximal tumour resection, postoperative external-beam radiotherapy (60 Gy in 2-Gy fractions) with concurrent temozolomide (75 mg/m^2), and adjuvant temozolomide (150–200 mg/m^2) for 6 cycles [15].

Despite optimal treatment, the estimated recurrence rate is in excess of 90%, with most patients recurring fewer than 4 cm from the site of the original tumour [16–18]. "Recurrent glioblastoma" has been variously defined and may be difficult to distinguish from progression. Because overall prognosis seems to depend little on the ability to make a distinction between recurrent and progressive disease, those two terms are used interchangeably for the purposes of the present recommendations.

Because of a paucity of clinical trials at the time of writing, the management of recurrent glioblastoma was not adequately addressed by the previously-published Canadian recommendations. In the intervening period, new data on the use of agents such as temozolomide and bevacizumab in recurrent glioblastoma have altered the treatment paradigm. The recommendations that follow were developed by a multidisciplinary panel of Canadian neuro-oncologists, neurosurgeons, and radiation oncologists in accordance with the levels of evidence set out by the American Society for Clinical Oncology (Table I) [19]. They are meant to guide the optimization of patient management in recurrent or progressive glioblastoma.

2. METHODS

The Canadian Glioblastoma Recommendations Committee, comprising medical oncologists, surgical oncologists, radiation oncologists, and medical imaging specialists met in March 2010 to develop recommendations for the management of recurrent or progressive glioblastoma. Draft guidelines were based on expert opinion and a literature review. For the systematic literature review, the MEDLINE database was searched for all published studies before June 2010, and that search was supplemented by a search of the American Society for Clinical Oncology annual meeting abstracts for 2005–2010. Search terms included "glioblastoma"; "GBM" (glioblastoma multiforme); "progressive"; "recurrent"; "surgery"; "radiotherapy"; "pseudoprogression"; "stereotactic radiosurgery" and its abbreviation "SRS"; "fractionated"; "IMRT" (intensity-modulated radiotherapy); and generic and brand names of agents for chemotherapy and biologic therapy. Because of the continuing paucity of randomized controlled trials, relevant articles necessarily included retrospective analyses and case series. Draft recommendations were prepared by JCE and further refined at a committee meeting in May 2010. Revisions by the contributing author were coordinated by JCE into a final manuscript for submission.

TABLE I Evidence levels and recommendation grades used in the consensus meeting[a]

Item		*Source or quality*
Evidence		
	I	Meta-analysis of well-designed controlled studies; high-quality randomized trial
	II	At least one well-designed study; lower-quality randomized trial
	III	Quasi-experimental study—for example, nonrandomized, uncontrolled, case–control
	IV	Non-experimental study—for example, comparative, case studies
	V	Case reports and clinical examples
Recommendation		
	A	Type I or consistent findings from multiple studies of types II, III, or IV
	B	Type II, III, or IV, findings generally consistent
	C	Type II, III, or IV, inconsistent findings
	D	Little or no empiric evidence

[a] Adapted from Somerfield *et al.,* 2000 [19].

3. RECOMMENDATIONS

3.1 Multidisciplinary Approach

To optimize treatment outcomes, the management of patients with recurrent glioblastoma should be individualized and should involve a multidisciplinary team approach, including neurosurgery, neuropathology, radiation oncology, neuro-oncology, and allied health professions.

The care path of patients with recurrent glioblastoma is complex, and cooperation and integration of services from multiple health care specialties and institutions are required. Factors that will influence the management approach include patient age, performance status, histology, extent of initial

resection, response to initial therapy, time since diagnosis, and whether the recurrence is local or diffuse. To better inform decision-making, patients should receive a brain tumour information package that will help them understand glioblastoma and their treatment options. We encourage tumour banking whenever possible.

3.2 Imaging

The standard imaging modality for assessment of recurrent glioblastoma is Gd-enhanced magnetic resonance imaging (MRI) (grade of recommendation: A). The optimal timing and frequency of MRI in the adjuvant setting have not been established, but scans are often performed every 2–3 months while the patient is on therapy.

We recommend that a radiology evaluation be conducted using the recently published Response Assessment in Neuro-Oncology (RANO) criteria [20]. While incorporating many of the elements from the previously used Macdonald criteria [21], the RANO criteria

- modify the definition of measurable disease, addressing subcentimetre lesions, tumour cysts, and surgical cavities;
- include evaluation of non-enhancing MRI (T2-weighted or fluid attenuation inversion recovery tumour volume) changes; and
- operationalize the definition of pseudo-progression (see the pseudo-progression recommendation, next subsection).

As previously described in the Macdonald criteria, treatment response is defined as a minimum decrease of 50% in tumour area (defined as the product of the maximal cross-sectional enhancing diameters). Progression is defined as a 25% increase.

3.3 Pseudo-progression

After chemoradiation, the diagnosis by MRI of radiologic tumour progression can be challenging. Tumour recurrence should be assessed according to the RANO criteria [19] (grade of recommendation: A). Progression observed by MRI after chemoradiation can be pseudo-progression in 20%–50% of cases, particularly in patients treated with concurrent radiation and temozolomide [22–24].

Pseudo-progression is diagnosed retrospectively when the post-radiotherapy MRI shows increased tumour enhancement that stabilizes or improves with the same or no further therapy. This phenomenon was first described by Hoffman *et al.,* who reported clinical deterioration suggestive of progression in 49% of patients treated with radiotherapy and carmustine, among whom 28% subsequently improved with the same or no further therapy [25]. It has been suggested that radiation-related vascular effects result in increased capillary permeability, which in turn is associated with increased enhancement and fluid leakage into the interstitial space and brain edema [26,27].

A recent Canadian study examined pseudo-progression in 104 evaluable glioblastoma patients [24]. Pseudo-progression was defined as early progression, with disease stabilization in the absence of salvage therapy for at least 6 months after completion of chemoradiotherapy with temozolomide. Early progression was observed in 26% of the patients, 32% of whom had pseudo-progression. Median survival was significantly prolonged for patients with pseudo-progression as compared with those showing true progression (124.9 weeks vs. 36.0 weeks). Pseudo-progression appears to be more common in patients with MGMT promoter methylation. Brandes *et al.* reported lesion enlargement at first MRI in 50 of 103 patients who had received a regimen of radiotherapy with temozolomide and subsequent maintenance temozolomide; 32 of the 50 were subsequently classified as having pseudo-progression [28]. Of 23 patients with MGMT promoter methylation, 21 (91%) showed pseudo-progression; among patients lacking such methylation ($n = 27$), 11 (41%) showed pseudo-progression.

If improperly characterized, pseudo-progression may lead to either premature termination of therapy or unnecessary debulking surgeries. Accordingly, adjuvant temozolomide 150 mg/m^2 on a 5-days-in-28-days schedule (200 mg/m^2 at the second cycle if well tolerated) should be continued for a minimum of 3 cycles, after which Gd-enhancing MRI should be used to ascertain progression. In the presence of new enhancement outside the radiotherapy field in the first 3 months of adjuvant temozolomide (which is suggestive of true progression), alternative adjuvant regimens should be considered.

Other imaging techniques—such as proton magnetic resonance spectroscopy as it becomes more widely available—may assist in differentiating pseudo-progression from true progression. High choline levels generally indicate tumour cell proliferation and disease progression; low choline levels have been reported in radiation necrosis [29]. Weybright *et al.* observed that the ratios of choline/creatine and choline/*N*-acetylaspartate are higher in tumour than in radiation injury [30]. Assessment by diffusion tensor imaging of the mean apparent diffusion coefficient may also help to differentiate tumour from radiation-induced changes [31].

3.4 Repeat Surgery

Repeat surgery may play a role in debulking tumour, providing symptom relief, and differentiating tumour recurrence from pseudo-progression or radiation necrosis (grade of recommendation: B). However, before surgical intervention, it is essential to clearly define treatment goals and the effect on prognosis and quality of life for the patient. In the absence of level 1 evidence, the decision to re-operate should be made according to individual circumstances and in consultation with the multidisciplinary team and the patient.

A number of case series have reported modest benefits after re-operation in selected patients, with the caveat that patient selection bias may have influenced the results. In general, patients with a high Karnofsky performance status (KPS) score (>70) and those with a tumour in a favourable location appear to be candidates for repeat surgery.

In an early review of 55 consecutive patients with glioblastoma or anaplastic astrocytoma (AA) undergoing repeat surgery, Ammirati *et al.* reported a median survival of 36 weeks with a mortality rate of 1.6% and a morbidity rate of 16%[32]. The patient's KPS score before surgery and the extent of surgical resection were independent factors for survival post surgery. Other groups have reported survival times of 36–76 weeks[33–36]. However, Guyotat and co-authors noted that, even in carefully selected glioblastoma patients, the improvement in survival was only 3 months (5 months with repeat surgery vs. 2 months without)[36]. Other authors have suggested that repeat surgery should be considered only in patients who are candidates for salvage chemotherapy or SRS[37].

Compared with surgery alone, implantation of biodegradable chemotherapy wafers (for example, wafers with carmustine) at the time of repeat surgery may prolong survival; however, this practice remains highly controversial[38]. Preliminary evidence suggests that survival may be improved in patients with MGMT promoter hypermethylation at recurrence[39]. Survival in those cases is reported to be in the range of 25–35 weeks[40], but may be adversely affected by postoperative complications such as bone marrow suppression, infection, and poor wound healing[41,42].

3.5 Re-irradiation

Radiation therapy is seldom recommended, but may be considered in carefully selected cases of recurrent glioblastoma (grade of recommendation: C).

Radiosurgery [Gamma Knife (Elekta, Stockholm, Sweden), CyberKnife (Accuray, Sunnyvale, CA, U.S.A.), linear accelerator) delivers a radiation dose in one or several fractions ("fractionated SRS"). Although studies have been conducted, the data do not support the use of re-irradiation as a standard treatment for recurrent GBM. The choice to re-irradiate depends on several factors, including the size and location of the tumour, prior radiotherapy dose, time since last radiation, and target volume. As a general rule, an increase in the fraction size is associated with an increased risk of adverse effects[43].

Stereotactic radiosurgery has the advantages of sparing normal tissue, of shortening recovery time, and potentially of being delivered on an outpatient basis in selected patients. Median survival after SRS is in the range of 8–16 months[44–48]. Potential adverse effects include radiation necrosis, edema, hydrocephalus, and worsening of previous symptoms. Hypofractionated SRS has similar survival outcomes, in the range of 9–12 months[49–51].

Newer approaches include IMRT and three-dimensional conformal radiation therapy. Intensity-modulated radiotherapy is able to deliver highly conformal radiation doses with a reduced dose to areas adjacent to critical tissues, such as the brainstem and optic chiasm[52,53]. The IMRT technique may minimize adverse effects, but compared with SRS, it is more costly and has not been shown to improve outcomes[54–56].

3.6 Systemic Therapy

Clinical trials, when available, should be offered to all eligible patients. In the absence of a trial, systemic therapy may be considered, including temozolomide rechallenge (grade of recommendation: B) and anti-angiogenic therapy such as bevacizumab (grade of recommendation: B).

In the pre-temozolomide era, Wong *et al.*[57] reported the pooled results of eight phase II chemotherapy trials in recurrent glioblastoma or AA ($n = 375$). The chemotherapeutic regimens assessed were interferon-β (IFNβ), IFN-β with 13-*cis*-retinoic acid, menogaril, carboplatin, and carboplatin–fluorouracil/procarbazine. The overall 6-month progression-free survival (PFS) rate was 15% in GBM. The 1-year overall survival (OS) rate was 32%, and median OS was 30 weeks.

3.6.1 Temozolomide

Since the emergence of reports showing a survival benefit with the addition of temozolomide to radiotherapy in the first-line setting[13], temozolomide has been the most studied agent in recurrent glioblastoma, either as monotherapy or as the backbone of a combination regimen. Many trials evaluating temozolomide in the recurrent setting have also included anaplastic glioma, which appears to be highly responsive to repeat temozolomide therapy[58]. Table II summarizes data from trials that evaluated temozolomide in recurrent GBM only or that separated out the effect on a GBM subgroup. Several dosing regimens have been tested, including the standard temozolomide dosing regimen of 150–200 mg/m^2 for the first 5 days of a 28-day cycle[59–61,63,66] and novel schedules such as 150 mg/m^2 daily, 1 week on, 1 week off[67,70]; 75 mg/m^2 daily, 3 weeks on, 1 week off[64]; and 75 mg/m^2 daily for 42 of 70 days[62]. An alternative approach has been to administer continuous low-dose temozolomide at 40–50 mg/m^2 daily[65,66,69] or to start with a 200 mg/m^2 loading dose followed by a lower-dose regimen (for example, 90 mg/m^2 every 12 hours[68]). With these various approaches, the estimated 6-month PFS rate has been reported to be 24%–44%.

The rationale for using metronomic chemotherapy (that is, a continuous low-dose regimen) is that this approach may deplete MGMT. The prognostic value of MGMT promoter methylation at progression is unclear. Some of the available data suggest that MGMT status influences the pattern of recurrence[71], but a retrospective analysis by Brandes *et al.*[72] found

TABLE II Temozolomide (TMZ) monotherapy trials in recurrent or progressive glioblastoma multiforme (GBM)[a]

Study	*TMZ regimen*	*Pts (n)*	*6-Month PFS (%)*
Yung *et al.,* 2000 [59]	150–200 mg/m^2 daily × 5 days every 28 days	112	21
Brandes *et al.,* 2001 [60]	150 mg/m^2 daily × 5 days every 28 days	22	31.8
Brandes *et al.,* 2002 [61]	150 mg/m^2 daily × 5 days every 28 days	42	24
Khan *et al.,* 2002 [62]	75 mg/m^2 daily × 42 days every 70 days	28	19
Chan *et al.,* 2005 [63]	200 mg/m^2 daily × 5 days every 28 days	13	21.0
Brandes *et al.,* 2006 [64]	75 mg/m^2 daily × 21 days every 28 days	33	30.3
Kong *et al.,* 2006 [65]	40 mg/m^2 daily (3 months)	12	58.3
Nagane *et al.,* 2007 [66]	150–200 mg/m^2 daily × 5 days every 28 days	30	22.2
Wick *et al.,* 2007 [67]	150 mg/m^2 on days 1–7 and days 15–21 every 28 days (1 week on, 1 week off)	64	43.8
Balmaceda *et al.,* 2008 [68]	200 mg/m^2 initial dose, then 9 × 90–100 mg/m^2 every 12 hours every 28 days	68	35
Perry *et al.,* 2010 [58]	50 mg/m^2 daily, continuous	91	23.9
Kong *et al.,* 2010 [69]	40–50 mg/m^2 daily	38	32.5
Wick *et al.,* 2009 [70,b]	75 mg/m^2 daily (days 1–42 during RT), plus 150–200 mg/m^2 daily × 5 days every 28 days; OR 150–200 mg/m^2 daily × 5 days every 28 days; OR 150 mg/m^2 daily × 1 week on, 1 week off; OR 75 mg/m^2 daily × 21 days every 28 days; OR 40 mg/m^2 daily, continuous[c]	47	27.7

[a] Data presented for GBM patients only.
[b] Retrospective review.
[c] Eleven patients also received 13-*cis*-retinoic acid or pegylated liposomal doxorubicin.
Pts = patients; RT = radiotherapy.

that MGMT methylation status changed from first to second surgery in 37% of patients and was no longer predictive of outcome after the second surgery. In an analysis of patients treated with radiotherapy alone or radiotherapy and temozolomide in the joint studies by the European Organisation for Research and Treatment of Cancer (26981, 22981) and the National Cancer Institute of Canada (CE.3), recurrence patterns were found to be independent of MGMT promoter methylation [73]. In the phase II RESCUE trial, 6-month PFS results were also independent of the MGMT status of patients [58]. A phase II trial of temozolomide in combination with the MGMT pseudo-substrate O_6-benzylguanine did not produce superior efficacy in recurrent glioblastoma [74].

A further hypothesis is that metronomic temozolomide may limit endothelial cell recovery and upregulate thrombospondin 1, leading to an anti-angiogenic effect [75–78]. *In vitro* studies have indicated that low-dose temozolomide, at a concentration equivalent to 20 mg/m^2 every 8 hours, inhibits angiogenesis [79]. Preliminary studies have reported that continuous low-dose temozolomide plus a cyclooxygenase 2 inhibitor has anti-angiogenic effects and is well tolerated [80,81]. Additional research in this area is required.

The RESCUE trial examined response to continuous temozolomide at a low dose (50 mg/m^2 daily, 28 of 28 days) in patients previously treated with the standard temozolomide adjuvant regimen [58]. The best responses were seen in patients with early progression (before completion of 6 cycles of adjuvant therapy—6-month PFS: 27.3%) and in previous responders who progressed more than 2 months after completing adjuvant therapy (6-month PFS: 35.7%). Patients who progressed while receiving extended adjuvant temozolomide had a poor response (6-month

PFS: 7.4%) and would therefore be candidates for alternative salvage chemotherapy.

Accordingly, treatment with temozolomide (for example, 50 mg/m^2 daily) is an option for patients who have completed a 6-month course of adjuvant temozolomide and have experienced a drug-free period of at least 2 months, or for those who progress 3–6 months after completing adjuvant temozolomide therapy. Other agents should be considered in patients who progress after receiving prolonged (>1 year) adjuvant temozolomide.

An alternative dosing schedule used in one phase II trial was temozolomide 150 mg/m^2 on days 1–7 and 15–21 in a 28-day cycle (1 week on, 1 week off) [67]. The 6-month PFS with that regimen was 43.8%, but it is important to note that only 9 of 64 subjects had received prior temozolomide. At entry, 22 patients were chemotherapy-naïve, 30 had received prior nimustine–teniposide, 3 had received procarbazine–lomustine–vincristine (PCV), and 9 had received lomustine–temozolomide. A retrospective review by the same authors reported a 6-month PFS of 27.7% for GBM patients rechallenged with temozolomide [70], results that are comparable to those seen with the continuous low-dose temozolomide regimen.

New trials will undoubtedly evaluate new cytotoxic regimens in recurrent GBM. One of the key lessons from the RESCUE study is that recurrent patients cannot be considered a homogeneous group. Patients who recur with GBM typically do so during the first 6 months of conventional temozolomide adjuvant therapy, after a break from conventional therapy, or immediately after prolonged adjuvant treatment. The RESCUE study demonstrated that survival rates were different in these 3 patient populations. Failure to recognize the different subgroups of recurrent patients may underestimate the potential benefits of cytotoxic agents that may have activity confined to discrete patient cohorts.

3.6.2 Anti-angiogenic Therapies

Glioblastomas are highly vascularized tumours, which express vascular endothelial growth factor (VEGF) and VEGF receptor, providing a rationale for the use of anti-angiogenic agents such as bevacizumab [82]. A phase II trial comparing bevacizumab 10 mg/kg alone or in combination with irinotecan 340 mg/m^2 or 125 mg/m^2 every 2 weeks in 167 glioblastoma patients demonstrated 6-month PFS rates of 42.6% with monotherapy and 50.3% with combination therapy [83]. The median duration of response was 4.3–5.6 months. Importantly, with bevacizumab, the use of steroids either stabilized or decreased in this patient population. Bevacizumab was generally well tolerated, although grade 3 or greater side effects were common (46.4% of patients in the monotherapy arm); adverse effects included hypertension, seizure, and thromboembolic events.

Alternative dosing regimens using bevacizumab have been studied (10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks plus irinotecan) with reported 6-month PFS rates of 29%–64% [84–86]. In addition to being used as monotherapy, bevacizumab has been combined with other drugs in the recurrent setting. Recently, a combination of bevacizumab and oral etoposide was observed to be no more effective and more toxic than bevacizumab monotherapy [87].

Another anti-angiogenic agent, cediranib, was recently evaluated in a phase II trial of 31 subjects with recurrent GBM, and an encouraging 6-month PFS of 25.8% was observed [88]. Grades 3 and 4 toxicities included hypertension, diarrhea, and fatigue. Toxicities were generally manageable, with dose reductions or drug interruptions being reported in 15 of 31 patients. The phase III REGAL trial of cediranib in combination with lomustine is ongoing and will further clarify the role of that agent in recurrent GBM. Other anti-angiogenic agents, such as thalidomide and pazopanib, appear to offer only modest benefits [89,90].

Although the foregoing results indicate an encouraging clinical effect with selected anti-angiogenic agents, some concerns have also been raised about their use. A pooled analysis of recurrent glioblastoma patients treated with bevacizumab or cediranib found that anti-angiogenic therapies benefited PFS but not OS [91]. Also, anti-angiogenic agents may directly interfere with Gd uptake in tumours, making it difficult to ascertain tumour margins and to evaluate clinical response [92]. A further concern is the effect of anti-angiogenic agents on tumour biology. A preliminary study found that, when exposed to anti-angiogenic therapy, glioblastoma upregulates other pro-angiogenic factors and invades normal brain tissue through upregulation of matrix metalloproteinases, thereby shifting glioblastoma to a more infiltrative phenotype that is undetectable with enhancing MRI [93,94]. Indeed, a non-enhancing pattern of tumour progression appears to be correlated with worse survival [95]. Overall, early data regarding the use of anti-angiogenic agents are promising, but additional research is needed to clarify the effects of these agents used alone or in combination with conventional chemotherapies.

3.6.3 Combination Therapy and Nitrosourea-Based Regimens

Combination therapy is still experimental, and optimal drug combinations and sequencing have not been established.

Two phase II trials reported improved efficacy with the combination of temozolomide 150–200 mg/m^2 daily for 5 of 30 days and either short-acting IFNα2b 4×10^6 U for 3 of 7 days (6-month PFS: 31%) or pegylated IFN 0.5 μg/kg weekly (6-month PFS: 38%) [96]. Use of this regimen may be limited by the frequency of grades 3 and 4 toxicities such as fatigue, leucopenia, and thrombocytopenia. Temozolomide has also been combined with conventional chemotherapeutic agents

such as mitoxantrone [97], irinotecan [98], and pegylated doxorubicin, and appears to be well tolerated [99]. A phase II trial of cisplatin (40 mg/m^2 on days 1 and 2) and temozolomide (200 mg/m^2 on days 2–6) every 4 weeks in heavily pretreated patients with recurrent glioblastoma reported a 6-month PFS of 35%, but grades 4 and 5 side effects were not uncommon [100]. Another report evaluating that combination suggested that temozolomide was better tolerated when fractionated (70 mg/m^2 every 12 hours, days 2–6 every 4 weeks), although it should be noted that subjects in that study were chemotherapy-naïve [101]. An important clinical consideration is that temozolomide does not appear to be cross-resistant with other chemotherapeutic agents [102–104]. Thus, selected patients with continued progression on a temozolomide regimen may respond to salvage chemotherapy or may be considered for entry into a clinical trial.

Adjuvant nitrosourea-based regimens such as carmustine, lomustine, and PCV were commonly used before the advent of temozolomide. Some studies have reported a combined complete and partial response rate as high as 11% and a 25% rate of stable disease with adjuvant PCV [105], but a large trial by the U.K. Medical Research Council found no benefit with PCV plus radiotherapy as compared with radiotherapy alone [106].

Several recent studies have investigated salvage nitrosoureas in progressive glioblastoma post-temozolomide. Fotemustine has been studied most extensively in that setting, with the 6-month PFS reported to be 20.9%–52% [104,107,108]. The combination of fotemustine–procarbazine may provide some benefit with respect to partial response and stable disease, but it does not appear to improve 6-month PFS [103]. The use of nimustine is not advised because of its modest efficacy and high rate of hematologic toxicity [109]. Salvage cyclophosphamide at the time of first or second recurrence post-temozolomide has also been reported to have modest efficacy (6-month PFS: 20%) with more acceptable toxicity [110].

3.6.4 Novel Therapies

A number of novel therapies have been investigated, but have demonstrated little clinical benefit. A subset of glioblastomas exhibit overexpression of EGFR and *EGFR* gene amplification [111], and several trials have investigated the EGFR tyrosine kinase inhibitors erlotinib, gefitinib, and lapatinib. However, a phase II trial that compared erlotinib with active controls (temozolomide or carmustine) reported a 6-month PFS of only 11.4% as compared with 24% for controls [112]. Other trials have reported little or no benefit for erlotinib used as a single agent or in combination with carboplatin or sirolimus, a mammalian target of rapamycin (MTOR) inhibitor [113–115]. Similarly, little benefit was observed with gefitinib alone or in combination with the MTOR inhibitor everolimus [116,117]. A Canadian phase I/II trial of lapatinib was stopped early because of a lack of efficacy [118].

Other targeted therapies, such as the histone deacetylase inhibitor vorinostat [119] and the protein kinase C and phosphoinositide 3 kinase (PI3K)/Akt inhibitor enzastaurin [120,121], have demonstrated little antitumour effect when used as monotherapy. More promising is cilengitide, an inhibitor of $\alpha v\beta 3$ and $\alpha v\beta 5$ integrin receptors. A phase II trial reported a 6-month PFS of 15% with cilengitide 2000 mg twice weekly, and *in vitro* data suggest cilengitide may promote temozolomide delivery to tumour cells when used in a combination approach [122,123]. Other novel therapies currently being investigated target PI3K/Akt (to overcome radioresistance), tumour cell growth (by inhibiting the farnesyl transferase pathway—examples include tipifarnib, lonafarnib), and the angiogenesis and angiopoietin pathways (for example, PDGFR, Src, MTOR, Ras). Additional research is needed to determine the effectiveness of these agents alone and in combination with current therapies.

4. SUMMARY

Numerous genetic alterations that influence tumour cell growth and proliferation have been identified in newly-diagnosed and recurrent glioblastoma. These alterations may be targets for novel therapies. Significant research is now being conducted and is likely to provide important insights into treatment strategies that target multiple pathways and that better control tumour infiltration and progression. Currently, selected patients may benefit from repeat surgery, re-irradiation, salvage chemotherapy, and biologic agents. The recommendations presented here are consistent with those produced by the National Comprehensive Cancer Network [124]. Taking into account efficacy, ease of administration, and toxicity, many Canadian centers have opted for a metronomic dose schedule of temozolomide (for example, 50 mg/m^2 daily) as the initial choice of treatment. However, anti-angiogenic therapies are also promising, and further studies will help to clarify the controversies outlined earlier. Using advances in molecular profiling, clinicians will be able to stratify patients by their response to alkylating chemotherapies, thus highlighting those who would benefit from an alternative approach.

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6. CONFLICT OF INTEREST DISCLOSURES

All the authors declare that they have no conflicts to report.

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