Guidelines for the Use of Temozolomide in Malignant Gliomas
QEII Health Sciences Centre

Guideline Questions:
• Does temozolomide exhibit activity against high grade malignant gliomas (Grade III and IV) at first relapse?
• Should temozolomide be used as primary therapy at first relapse instead of procarbazine and/or nitrosourea-based therapy?
• Is there sufficient evidence to use temozolomide as adjuvant therapy to surgery and radiation in high grade malignant gliomas?
• Does temozolomide have any impact on overall survival in patients with refractory or relapsing high-grade malignant gliomas?

Objectives:
• To make recommendations regarding the use of temozolomide in patients with malignant gliomas.

Outcome Measures:
• To review response, progression-free survival (PFS) and overall survival.
• Quality of life (QOL) issues are discussed.

Quality of Evidence:
- Phase I and Phase II studies in malignant gliomas have been reported.
  - Phase I studies were reported in advanced solid malignancies in children, adolescents and adults. Dose escalation and pharmacokinetic studies were included.
  - Trials reflecting the Charing Cross Hospital experience with both primary and recurrent glioma patients (Level V evidence) (Published).
  - Phase II adult trials included: Cancer Research Campaign (CRC) trial of patients with progressive or recurrent Grade III-IV gliomas (Level IV evidence) (Published); multicentre trial of patients with anaplastic astrocytoma (AA) or anaplastic oligoastrocytoma (AOA) at first relapse (Level IV evidence) (Published); study of glioblastoma multiforme (GBM) patients in relapse (Level III evidence) (Not Published – data on file at Schering-Plough); randomized trial of temozolomide versus procarbazine in GBM (Level II) (Published in abstract form).
  - Quality of life (QOL) benefits in patients with recurrent AA (Published in abstract form).
  - QOL benefits of treatment with temozolomide versus procarbazine in patients with GBM (Published in abstract form).

Benefit:
• Prognosis for high-grade malignant gliomas is poor. The nitrosourea analogs are among the most useful chemotherapeutic agents in the treatment of malignant gliomas. Patients with high-grade gliomas do recur after surgery and radiotherapy with or without adjuvant chemotherapy. In order to stabilize disease, previous treatment modalities cannot always be used again. The chance that additional treatment with nitrosoureas will provide response is low and the risk of toxicity is high. Temozolomide, a prodrug, degrades to form a product that resembles dacarbazine but does not require metabolic activation. It is an oral alkylating agent with demonstrated clinical antitumor activity.
• The benefit of temozolomide treatment in 75 consecutive patients at the Charing Cross Hospital has been reported. Forty-eight patients with recurrent glioma reported an objective response (OR) rate of 25%, stable disease (SD)38%, and response duration of 6.1 months. The response rate was 30% in the newly diagnosed group. Only 7% of these patients ever received previous chemotherapy plus radiotherapy. The CRC Phase II trial reported on 103 eligible high grade glioma patients with an 11% OR rate, 47% SD and median duration of response (MDR) of 4.6 months. Response rates were similar for AA and GBM tumors. Thirty one percent of these patients had previous surgery, radiotherapy and chemotherapy. A Phase II trial reported the response of 111/162 patients with histologies of AA or AOA at first relapse. The OR rate was 35% with SD in 26% of patients. The median progression-free survival (PFS) was 5.5 months with an overall survival (OS) of 14.5
**Temozolomide in Malignant Gliomas**

months. Nitrosourea-based chemotherapy had been previously administered to 60% of the total group.

- Another Phase II trial sponsored by Schering-Plough (not published) enrolled 128 GBM confirmed patients in relapse. The OR was 8% with 43% of patients having SD. The median PFS was 2.1 months and OS was 5.4 months. A randomized Phase II trial of temozolomide versus procarbazine in GBM at first relapse was reported in abstract form in 1999. One hundred and twelve patients were randomized to the temozolomide arm and 113 to procarbazine. The number of patients with prior nitrosourea-based chemotherapy was 65% for temozolomide and 68% for procarbazine. A statistically significant median PFS was reported for temozolomide (2.89 months) versus procarbazine (1.88 months), with \( p = 0.0063 \). At 6 months 21% of the temozolomide-treated patients were progression-free compared to 9% of the procarbazine group (\( p=0.016 \)). The median OS was 7.3 months and 5.8 months in favour of the temozolomide arm (\( p=0.337 \)). The temozolomide-treated patients showed improved or stable health related QOL over the procarbazine-treated patients at 3 and 6 months.

**Adverse Effects:**
Myelosuppression is the dose limiting toxicity. It is not cumulative and usually predictable with platelet and neutrophil nadirs between day 21 to 28. Other adverse events reported in glioma patients include fatigue (23%), nausea (41%), vomiting (34%), constipation (15%), and headache (11%). In the Phase II malignant glioma trials, hematologic toxicity – Grade 3 or 4 thrombocytopenia or neutropenia were the most common serious adverse events. Dose reductions are required for patients previously treated with chemotherapy.

**Evidence Based Recommendation:**
Temozolomide, an oral alkylating agent, has shown promising activity in relapsed AA and GBM. Temozolomide has been approved by the Health Protection Branch (HPB) and Food and Drug Administration (FDA) as an alternate therapy in those patients who have progressed or relapsed following standard chemotherapy. Presently, no randomized controlled trials have compared temozolomide to PCV chemotherapy as patients may have received adjuvant nitrosoureas. Procarbazine has been used as the single agent in the standard arm in trials comparing temozolomide in GBM.

The benefits of temozolomide have been promising in terms of disease stabilization in GBM. The QOL scores were maintained in the group of AA patients with SD and improved in the responding patients. In the randomized trial in relapsed GBM, a statistically higher proportion of patients treated with temozolomide experienced improvement in social functioning, motor dysfunction, and communication deficit. Temozolomide is recommended as a treatment option for patients with recurrent high grade gliomas who have previously been treated with chemotherapy. In the circumstances where patients are chemo-naïve at first relapse, nitrosourea-based chemotherapy will remain standard therapy.
Temozolomide in Malignant Gliomas

GUIDELINES FOR THE USE OF TEMOZOLOMIDE IN MALIGNANT GLIOMAS
QEII HEALTH SCIENCES CENTRE

Background
Primary brain tumors represent approximately 2% of all adult cancer in the U.S.A. In adults, primary brain tumors rank thirteenth in frequency of all cancers. It is estimated that in 1999 in Canada, approximately 2300 new cases of brain tumors will present. Of these, 1250 new cases will be males compared to 1000 for females. The estimated number of deaths will be 1500. The total of new cases in 1995 in Nova Scotia for males and females were 37 cases each. Malignant gliomas represent 1% of all adult cancers and cause 2.5% of all cancer deaths in the U.S.A.

The age-related incidence of primary brain tumors exhibit an early peak in infancy and childhood, a gradual rise in young adulthood, and a sustained peak from the fifth to eighth decade. The most common primary brain tumor in adults are glial neoplasms and represent approximately 50% of primary brain tumors. Gliomas include astrocytomas, oligodendrogliomas, ependymomas, and mixed oligoastrocytomas.

Standard tumor, nodal and metastatic (TNM) classification of brain tumors is not appropriate. The size of tumor is much less important than the tumor grade. Metastatic involvement outside the central nervous system (CNS) is extremely rare. Using the St. Anne-Mayo system, there are four essential elements that are identified when classifying astrocytic tumors. These include nuclear atypia, mitotic activity, endothelial proliferation and necrosis. Tumors are given a numerical grade based on presence or absence of these features: Grade I- absence of all; Grade II – one feature; Grade III – two features; Grade IV – three features present. Tumor grade correlates highly with survival in astrocytomas.

A practical classification system can be employed. Grades I-II tumors are low grade astrocytomas; Grade III are malignant or anaplastic astrocytomas (AA) and Grade IV lesions are referred to as glioblastoma multiforme (GBM).

Low-grade astrocytomas represent one-third of all gliomas. Grade I astrocytomas are well circumscribed tumors unusual in that they are potentially curable with surgery and will not be discussed further. Grade II tumors have a median survival of 5-7 years. The limited knowledge on the natural history of these lesions is of concern. It is estimated that one half of these low-grade tumors convert to higher-grade lesions within 3-4 years after diagnosis. The median survival from initial diagnosis is 11 months for GBM compared with 27 months for AA. The mean age of presentation for AA is 45 years and 45-65 years of age for GBM.
$\textit{Temozolomide in Malignant Gliomas}$

**Standard Treatment**
The primary therapies used in the management of malignant gliomas include surgery, radiotherapy and chemotherapy. Surgical resection of the tumor provides a tissue diagnosis, cytotheresection and effect on intracranial pressure. Low-grade gliomas pose a particular problem with the lack of randomized trials definitively addressing the issue of timing and extent of surgery. This same issue is controversial with radiotherapy as well. Chemotherapy is not used in adults in Grade II tumors.

High-grade glioma therapy consists of surgery and radiotherapy. Trials have reported that median survival is doubled with the addition of radiotherapy to surgery. The major controversy arises in the area of addition of adjuvant chemotherapy. Highly lipophilic agents such as carmustine (BCNU), lomustine (CCNU) and procarbazine with the ability to penetrate the blood-brain barrier have been used. A meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults was reported by Fine et al (1993). This analysis included 16 studies between 1975 and 1989 of more than 3000 patients. Prognostic factors such as age and histology were included and a survival benefit was evident from the addition of chemotherapy to treatment for patients with high-grade gliomas. The benefit occurs earlier in AA than in patients with GBM. A report published by Levin et al (1990) compared BCNU alone versus procarbazine, CCNU and vincristine (PCV) chemotherapy after radiation. Results indicated that PCV chemotherapy produced longer survival and time to progression than BCNU but only with patients with AA. However a recent publication by Prados et al (1999) reported that patients with AA treated with adjuvant BCNU or PCV show no survival benefit to PCV chemotherapy over BCNU. This was a retrospective review of 432 patients (257 treated with BCNU; 175 patients treated with PCV) in the Radiation Therapy Oncology (RTOG) database. An abstract by Prada et al (1998) reported preliminary data from the Medical Research Council in the United Kingdom suggest no survival benefit from PCV chemotherapy in GBM or AA. These patients were randomized to surgery plus radiation versus surgery, radiation plus adjuvant PCV. The definitive answer of adjuvant use of chemotherapy in this setting still awaits completion of clinical trials.

Treatment strategies for recurrent malignant gliomas are now the focus of discussion. Despite the use of aggressive treatment, high-grade gliomas almost always recur and low-grade gliomas progress. As with many other disease sites, the management of gliomas is based on previous surgery, radiotherapy and/or chemotherapy. Some patients may benefit from additional surgery. The most common chemotherapy regimens include the use of combination PCV or single agent carmustine. Second line chemotherapy includes platinum-based regimens, such as carboplatin or cisplatin. Procarbazine is an agent which is used in relapsed GBM. High dose tamoxifen has been used in patients not responsive to previous therapy. Response rates vary between 10-40% and progression-free survival is very short, often only several months.

It is recognized that new therapeutic approaches to the treatment of malignant gliomas are
Temozolomide in Malignant Gliomas

needed. Clinical trials are on-going which include signal transduction inhibitors, matrix metalloproteinase inhibitors and angiogenesis inhibitors.

Presently, a new cytotoxic chemotherapeutic agent, temozolomide has been approved by the Health Protection Branch (HPB) in October 1999 for the treatment of adult patients with GBM or AA who have documented evidence of recurrence or progression after standard therapy. In the USA, the Food and Drug Administration (FDA) approved temozolomide as a cancer treatment for adults diagnosed with AA who have relapsed following chemotherapy, including a nitrosourea drug and procarbazine. Temozolomide was approved under the FDA accelerated approval process.

Temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine. It has virtually complete oral bioavailability and crosses the blood brain barrier. It does not require hepatic metabolism like dacarbazine to convert to the active compound. In chemotherapy-naive patients, temozolomide is orally administered at a dose of 200 mg/m² once daily for 5 days every 28 days. The dose is decreased to 150 mg/m² initially, in previously treated patients.

Clinical Studies:
Several Phase I oral and intravenous studies have been reported on the use of temozolomide in a variety of malignancies, such as melanoma, high-grade glioma and low-grade Non-Hodgkin’s lymphoma. Temozolomide was developed as an alternate to dacarbazine due to its antitumor activity, improved toxicity profile and high degree of oral absorption. A five-day oral schedule as well as an extended continuous oral schedule were reviewed. Myelosuppression was the dose limiting toxicity in both settings. Phase II trials proceeded with the 5-day oral regimen. At the Charing Cross Hospital in London, U.K., patients were enrolled in Phase I and Phase II trials. Results reported by Newlands et al 1996, on 75 patients with malignant gliomas. There were 48 patients with recurrent disease following radiotherapy and 27 newly diagnosed patients. In the entire group only 5 patients (7%) had previous radiotherapy plus chemotherapy. The OR in the recurrent group treated with temozolomide was 25% with a median response duration of 6.1 months. There were an additional 18 patients (38%) with disease stabilization. Patients who were newly diagnosed had a higher response rate of 30% and 48% reported SD. Temozolomide was well tolerated when given with the 5HT 3 antagonist ondansetron and the Grade 3 / 4 myelosuppression was predictable as described in Phase I trials. The median number of courses in the overall group was 7.

The CRC reported a Phase II trial of temozolomide in progressive or recurrent high-grade gliomas in 1997. (Bower et al). There were 103 eligible patients and the response rates were similar for AA and GBM tumors. The OR was 11% with an additional 47% of patients with SD. The MDR was 4.6 months. Myelosuppression was the major toxicity including 16 episodes of Grade 4 lymphopenia which were generally asymptomatic and 7 episodes of Grade 4 thrombocytopenia. The median number of courses received per patient was 4.
In a non-comparative trial reported by Yung et al (1999), the OR rate to temozolomide was 35% in patients with recurrent AA or AOA at first relapse. An additional 26% of patients reported SD. One hundred and sixty two patients entered the study but 111 patients had confirmed AA or AOA after central review. Sixty percent (97 patients) of the total group (162 patients) had previous nitrosourea-based chemotherapy. The OR rate in the prior chemotherapy versus chemotherapy-naïve groups were 30% and 43% respectively. The MDR for the 111 patients was 5.5 months and median OS was 14.5 months. Myelosuppression was noncumulative and nausea/vomiting were the most frequently reported adverse events. The median number of cycles in the overall group was 5. QOL was measured using the QLQ-C30 functioning and symptom scores and the BCM-20 symptom scale scores. Maintenance of progression-free status and objectively assessed response were both associated with health-related QOL benefits.

A similar study of 138 GBM patients in relapse (not yet published) reported an OR rate of 8% and median PFS of 2.1 months. The OS was 5.4 months. QOL scores were higher in responding patients.

A randomized comparative trial with procarbazine versus temozolomide in patients with recurrent GBM was reported in abstract form by Yung et al (1999). Patients with GBM have been treated with many agents but procarbazine has generally been accepted as a reasonable therapy for GBM in first relapse, particularly in patients previously exposed to a nitrosourea. Patient characteristics between the two groups were similar with prior exposure to nitrosourea-based chemotherapy, 65% versus 68% for the temozolomide and procarbazine group respectively. Objective partial responses were seen in 5% of patients in both groups but SD was observed in 46% (temozolomide) and 33% (procarbazine) of patients. The median PFS was 3 months for temozolomide and 2 months for procarbazine (p=0.0065). The median overall survival was 7.3 months (temozolomide) and 5.8 months (procarbazine) (p=0.337). QOL scores were at least maintained more often in temozolomide patients than in procarbazine patients. In an abstract reported by Osoba et al (1999) at the American Society of Clinical Oncology (ASCO), a statistically significant higher proportion of patients treated with temozolomide experienced improvement in social function, motor dysfunction and communication deficit and showed a trend of improvement in other domains than did patients treated with procarbazine. Major hematologic toxicity was thrombocytopenia, while nausea, vomiting and constipation were the common non-hematologic toxicities.

Other Phase II studies are on-going reviewing activity in AA and GBM in relapse. Unfortunately there are presently no randomized trials comparing temozolomide to PCV chemotherapy. As with other chemotherapeutic agents, the movement of such active agents into the adjuvant setting is the next step to hopefully extend the survival of such an aggressive disease. The National Cancer Institute of Canada (NCIC) Clinical Trials Group plans to become involved with an adjuvant randomized Phase III trial for newly diagnosed GBM. Presently, it is too early to assume the benefits of temozolomide in this setting.
**Temozolomide in Malignant Gliomas**

**Approved Use:**

1. Patients must have recurrent high-grade malignant glioma.
2. Karnofsky performance status ≥60.
3. First Relapse and beyond
   - Patients demonstrating disease progression who have been treated with chemotherapy in the adjuvant setting (ie procarbazine and/or nitrosourea based chemotherapy).
   - Patients demonstrating disease progression during treatment with chemotherapy such as procarbazine and/or nitrosourea combination.

**Note:** Special approval of temozolomide as a single agent for patients outside the approved use can be sought through the Request for Non-Formulary or Restricted Drug process. Requests should be submitted in writing with specific references included. Guidelines will be updated and modifications made on the basis of published studies only.
**Temozolomide in Malignant Gliomas**

**Side Effects:**
The side effect profile is based on pooled data from 400 patients who received temozolomide for glioma. A total of 1030 patients with advanced malignancies were treated with temozolomide in clinical trials.

<table>
<thead>
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<th>TOTAL PATIENT GROUP/ALL GRADES</th>
<th>GLIOMA PATIENTS</th>
<th>Recommend:</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>43%</td>
<td>Antiemetics</td>
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<td></td>
<td>Grade 3 5%</td>
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<td>Vomiting</td>
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<td>Grade 4 0%</td>
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<td>Grade 4 0%</td>
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<tr>
<td>Anorexia</td>
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<td>Diarrhea</td>
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<td>Grade 3 &lt;1%</td>
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<td>Rash, fever, somnolence</td>
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<td>Changes from Grade 0-2 to Grade 3-4</td>
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<td>Anemia</td>
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</tbody>
</table>

**Dosing:**
- Hepatic insufficiency: No formal studies
- Renal Dysfunction: No formal studies
- Use in Elderly: >70 yo may be at increased risk of neutropenia and thrombocytopenia
**Temozolomide in Malignant Gliomas**

**Expected Patient Numbers:**

It is estimated that for:

Temozolomide (based on 1.7 m$^2$) 150 mg/m$^2$ = 255 mg daily x 5 days q28 days

Approximately: **$1818.10** / cycle

Temozolomide – 10 patients / year will be treated

<table>
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<th>Drug</th>
<th>Estimated Number of cycles / patient</th>
<th>Average Cost / patient</th>
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<td>Temozolomide</td>
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<td><strong>$10,900.00</strong></td>
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**Approximate Drug Cost Per Year**

Temozolomide = **$109,000** *

- It is anticipated that some patients will have third party drug coverage.

Current estimates from the Department of Health (DOH) suggest that 40% of the Nova Scotia population is covered by private drug insurance, 40% by public insurance and 20% non-insured. Based on these estimates and realization that not all programs would include this drug on their respective formularies, the approximate drug cost to the QEII Health Sciences Centre would be in the order of **$50,000.00**.
**Temozolomide in Malignant Gliomas**

**Summary:**
High-grade malignant gliomas represent a group of brain tumors that offer a definite challenge from a treatment perspective. Surgery, radiotherapy and chemotherapy represent the three treatment modalities presently available. Unfortunately, effective chemotherapeutic agents have been limited. A large portion of patients recur after surgery and radiotherapy and are not eligible for additional treatment from those sources. Several chemotherapy agents or regimens have been explored to gain stabilization of the neurological symptoms of the disease and improve overall QOL. Temozolomide offers a new orally bioavailable prodrug which appears to have a positive effect on progression-free survival, disease stabilization, and QOL in malignant glioma patients at first relapse.

**Restrictions for Use**
Restricted to Neuro-Oncologist for the treatment of recurrent malignant gliomas at first relapse and beyond if previously treated with a chemotherapy agent or regimen.

**Treatment Location**
Patients will be treated on an out-patient basis at home. A small portion of patients may initiate therapy as hospital in-patients.

**Original Date Prepared:** February 2000

**Review Date:** February 2001

**Prepared by:** Dr. S. Kirby, Neuro-Oncologist
Marlene Sellon, Pharmacist

**Reviewed by:** Brain Tumor Site Group
Temozolomide in Malignant Gliomas

Bibliography

4. Manufacturer’s Published Literature (Product monography and/or package insert) – Schering Canada Inc. - Temodal® - 1999.
**Temozolomide in Malignant Gliomas**


