

## Chemotherapy in Adults with Gliomas

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### Abstract

Treating patients with gliomas requires a multidisciplinary approach, which often includes surgery, radiation and chemotherapy. Recent developments have demonstrated the efficacy of chemotherapeutic agents in patients with newly diagnosed or recurrent gliomas. Large clinical studies have provided important information on the impact of chemotherapy for anaplastic oligodendrogliomas in the upfront setting. Randomised trials have demonstrated the benefit of chemoradiation for patients with glioblastoma. Investigations are also under way to clarify the role of chemotherapy for low-grade gliomas. This review article summarises the recent developments and approaches in the use of chemotherapy to treat adult patients with astrocytomas and oligodendrogliomas.

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**Key words:** Astrocytoma, Oligodendroglioma, Primary brain tumour

### Introduction

Gliomas are primary central nervous system (CNS) tumours originating from neuroglial cells. The term includes the various histologic grades of astrocytoma, oligodendroglioma and ependymoma. Although all are malignant, these tumours can be further separated into different grades according to their morphologic features that reflect their natural history or biologic behavior. Currently, the World Health Organization (WHO) classification is the most widely used system. Table 1 provides some details on the

WHO grading of gliomas frequently seen in adults and their long-term survival.<sup>2</sup> The biologic behaviour of the different grades of tumour can be markedly different, hence the need for varied treatment approaches. Grade I astrocytoma refers to a very specific histologic subtype, pilocytic astrocytoma as well as some rare, non-infiltrating tumours. These tumours are generally well-circumscribed, slowly growing and occurring mainly in children or very young adults (<20 years old). Pilocytic astrocytoma and ependymoma will not be addressed in this article.

Table 1. Grades of Astrocytoma and Oligodendroglioma<sup>1,2</sup>

Histologic type	WHO Grade	Features	5-year survival rate <sup>1</sup>	
Astrocytoma	II	Diffuse astrocytoma	Well-differentiated neoplastic astrocytes. Moderately increased cellularity, occasional nuclear atypia. Mitotic activity generally absent.	46.9%
	III	Anaplastic astrocytoma (AA)	Increased cellularity. Nuclear atypia. Marked mitotic activity. No microvascular proliferation or necrosis.	29.7%
	IV	Glioblastoma multiforme (GBM)	Poorly differentiated, pleomorphic astrocytic neoplastic cells, marked nuclear atypia. Brisk mitotic activity. Microvascular proliferation and/or necrosis.	3.4%
Oligodendroglioma	II	Oligodendroglioma (OD)	Moderately cellular. Marked nuclear atypia and occasional mitosis are compatible with grade II.	69.6%
	III	Anaplastic oligodendroglioma (AO)	Increased cellularity, marked cytological atypia, high mitotic activity. Microvascular proliferation and necrosis may be present	41.9%

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### Adjuvant Chemotherapy in Low-grade glioma

Patients with low-grade gliomas frequently experience anaplastic transformation of their tumours into a higher grade after a mean time interval of 4 to 5 years.<sup>3,4</sup> Progressive growth of low-grade gliomas can also occur without anaplastic transformation. Even without transformation into a higher grade tumour, further infiltration of neoplastic cells into normal brain or mass effect can lead to new or increased morbidity.

Treatment for newly diagnosed low-grade glioma generally includes maximal safe resection. Radiation therapy (RT) may be given immediately after surgery in high-risk patients or delayed until there is subsequent tumour progression.<sup>5</sup> Controversy exists regarding the optimal timing of radiation. Randomised trials demonstrate a prolongation of tumour control with early radiation treatment but no improvement in overall survival when compared with patients who undergo radiation only at the time of tumour regrowth. Despite interventions with modern surgical techniques and RT, control of low-grade gliomas remains suboptimal, with median progression-free survival (PFS) and survival at 5.3 years and 7.4 years, respectively. Even for patients who had received RT, recurrences occur mostly within the radiation field.<sup>5</sup> More treatment approaches are required to improve survival and reduce delayed neurotoxicity.

The use of chemotherapy in low-grade glioma is controversial. Recently, evidence has become available to suggest that it may have a role in low-grade gliomas. Brada et al<sup>6</sup> treated 30 treatment-naïve low-grade glioma patients (17 with astrocytoma), all of whom had non-enhancing tumours on magnetic resonance imaging (MRI), with chemotherapy. The 2-year PFS rate achieved was 76%, comparable to PFS seen in radiation trial European Organisation for Research and Treatment of Cancer (EORTC) 22845.<sup>6,7</sup> Frenay and colleagues<sup>8</sup> reported their results in 10 patients with unresectable low-grade astrocytoma who were treated with a nitrourea-based chemotherapy regimen without any preceding RT. Clinical benefit and partial radiographic response was seen in 8 and 4 patients, respectively.<sup>8</sup> Radiation and chemotherapy-naïve low-grade oligodendrogliomas and mixed oligoastrocytoma are also responsive to chemotherapy; in one study, 51% of patients improved clinically and radiographic responses were seen in 31% of patients.<sup>9</sup>

Randomised clinical trials of chemotherapy for low-grade gliomas have been conducted. A small randomised study found no benefit in the addition of lomustine to RT in patients with low-grade glioma.<sup>10</sup> The Radiation Therapy Oncology Group (RTOG) 9802 randomised patients with unfavourable risk factors (age >40, or subtotal resection/biopsy) into either RT alone or PCV chemotherapy

(lomustine, procarbazine and vincristine) following the completion of RT. Patients with favourable characteristics were observed following resection. This study recruited 251 patients. Preliminary results were reported with 5-year survival and 5-year PFS rates of 61% and 42% in the RT alone arm and 71% and 60% in the RT PCV arm. The difference in outcomes between the 2 treatment arms (RT alone versus RT PCV) for patients with unfavourable risk factors was not statistically significant. However, the median follow-up duration in RTOG 9802 was only 4 years. Of note, the early data from the observation arm confirm the overall good prognosis in this group with a 5-year survival and 5-year PFS rate of 93% and 48%, respectively.<sup>11</sup>

The chemoradiation regimen developed for patients with newly-diagnosed glioblastoma multiforme (GBM) (discussed in detail below), where RT is administered along with daily temozolomide (TMZ) followed by 6 to 12 months of adjuvant TMZ, is being tested in low-grade glioma. The RTOG activated a phase II trial (RTOG 0424) earlier this year that will treat high-risk low-grade glioma patients with TMZ concurrently with RT followed by 12 cycles of 4-weekly chemotherapy. High-risk patients are defined as those who meet at least 3 of the following criteria: age ≥40 years, largest preoperative tumour diameter ≥6 cm, tumour crossing midline, tumour of astrocytoma histology or preoperative neurologic deficits (Neurologic Function Score >1).

Separately, the question of whether upfront chemotherapy can replace initial RT will be addressed by EORTC 22033-26033. Patients with low-grade gliomas will be randomised to receive either 50.4 Gy of radiation or TMZ (75 mg/m<sup>2</sup>/day for 21 days every 28-day cycle, total 12 cycles) alone.

Although there is increasing interest in evaluating chemotherapy in low-grade gliomas, it is difficult to measure tumour response. Low-grade gliomas are often non-contrast enhancing tumours with poorly-defined borders. The traditional method of measuring tumour response was designed for enhancing tumours where the cross-sectional area (product of the 2 largest perpendicular diameters) was used.<sup>12</sup> Non-contrast enhancing tumours are better seen on T2 or FLAIR MRI sequences. However, T2 signal changes may also result from peritumoral oedema, surgical scars or brain injury resulting from prior treatments, particularly RT. In practice, responses shown by non-contrast enhancing tumours with a reduction in mass visible with visual inspection are not well-quantified by measuring the dimensions of T2 signal changes.<sup>13</sup> This may explain the disparity in the frequency of clinical versus radiographic responses reported by investigators such as Brada et al.<sup>6</sup>

### Chemotherapy in High-grade Astrocytomas

High-grade astrocytoma includes anaplastic astrocytomas

(AA) (WHO grade III) and glioblastoma (GBM, WHO grade IV). A meta-analysis of 12 clinical trials, conducted between 1965 and 1997 randomising patients who had undergone surgery and subsequently randomised to receiving RT alone versus RT plus chemotherapy, reported only a small benefit in survival when chemotherapy was added to radiotherapy.<sup>14</sup> However, many of the trials conducted before the mid-1990s included a variable mix of patients with grade III or IV tumours, and/or a mix of astrocytic and oligodendroglial gliomas. As the histologic subtype and grade of tumour have a strong impact on outcomes, it was difficult to decipher the contribution of chemotherapy to the outcomes for individual tumour types.

Between 1988 and 1997, the Medical Research Council (MRC) Brain Tumor Working Party randomised 674 patients with high-grade astrocytoma into 2 arms, one undergoing RT alone and the other receiving adjuvant PCV chemotherapy (lomustine, procarbazine and vincristine) after RT. No significant difference in survival was seen between the 2 arms. When survival was analysed according to histologic grade, there was no difference in the outcomes; the hazard ratio for death was 0.86 (95% confidence interval, 0.58-1.30) for patients with AA and 0.93 (95% confidence interval, 0.77-1.12) for those with GBM.<sup>15</sup>

More recently, the EORTC and the National Cancer Institute of Canada (NCIC) Clinical Trials Group (EORTC 26981/22981-NCIC CE3) randomised 573 patients with GBM to receive RT alone or RT with TMZ. Patients receiving chemotherapy were given 75 mg/m<sup>2</sup> of TMZ daily, concurrent with RT. After a 4-week rest period following the end of RT, TMZ was resumed at 150 to 200 mg/m<sup>2</sup> per day for 5 consecutive days every 28-day cycle. A total of 6 cycles were administered in the trial. The RT plus chemotherapy arm demonstrated a significant superior survival rate of 26.5% at 2 years compared to 10.4% in the RT alone group.<sup>16</sup> Combined treatment was well-tolerated, with grade 3 and 4 haematologic toxic effects seen in 7% of the patients. At tumour progression, treatment was administered at the discretion of patients' primary physician and 60% of patients in the RT alone group received salvage TMZ. The difference in survival may have been narrowed by this treatment following tumour progression in the RT alone group. This study was the first to demonstrate a survival benefit with the addition of chemotherapy to RT for the treatment of GBM.

The RTOG started a similar phase III trial (RTOG 98-13) for patients with grade 3 astrocytoma, combining TMZ with RT in 2002. Patients with AAs or anaplastic oligoastrocytomas (AOAs) will be randomised to RT plus TMZ versus RT plus nitrosourea (carmustine or lomustine).

The long-term outcomes for patients with AAs are significantly better than those for patients with GBM.<sup>17</sup> It remains unknown whether patients with AA will experience a similar level of benefit from combined RT plus TMZ treatment. Little is known about the potential delayed neurologic effects of concurrent RT plus TMZ, which may be unmasked in patients with a more protracted course of illness. Hence, caution is required in extrapolating the benefits of RT plus TMZ found in patients with GBM to other tumour types and grades.

Although the chemoradiation regimen significantly improved survival, only 26% of patients survived beyond 2 years in the study reported by Stupp et al.<sup>16</sup> Resistance to radiation and chemotherapy often results from DNA repair mechanisms within tumour cells. O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT) is an enzyme responsible for repairing chlorethylation or methylation damage at the O<sup>6</sup>-position of guanine induced by nitrosoureas and TMZ. Cellular MGMT becomes depleted when it repairs DNA damage; the cell then has to replenish it. Theoretically, reduced levels of MGMT may lead to more effective triggering of cytotoxicity induced by alkylating agents. Expression of MGMT can be "turned off" by methylation of its promoter site. To elucidate the influence of MGMT promoter methylation on treatment response, Hegi and her colleagues<sup>18</sup> successfully determined the MGMT promoter methylation status of 206 GBM tumour specimens from patients recruited into EORTC 26981/22981-NCIC CE3 ("Stupp study"; see above). Approximately 45% of tumours had MGMT promoter methylation, i.e. no expression of MGMT. The presence of MGMT promoter methylation was associated with better survival in all patients regardless of treatment arms (RT versus RT plus TMZ) in the trial. Analysis according to MGMT promoter methylation and treatment arms suggested that GBM patients with MGMT promoter methylation benefited the most from the addition of TMZ to RT.<sup>18</sup> Although this study was retrospective, it supports the potential role of molecular profiling in risk stratification of patients or selection of therapy in the future. Currently, there are ongoing attempts to improve the efficacy of nitrosoureas and TMZ via pharmacologic depletion of MGMT. This includes the use of dose-intense TMZ regimens and the use of agents such as O<sup>6</sup>-benzylguanine.

### **Chemotherapy for Anaplastic Oligodendroglioma (AO)**

AOs are considered to be chemosensitive with response rates of 60% to 70% with chemotherapy.<sup>19,20</sup> Many of the studies demonstrating this high response rate used the PCV combination. Recent large randomised trials addressed the role of PCV chemotherapy as part of upfront treatment for patients with newly diagnosed AO. EORTC 26951 randomised 368 patients with newly diagnosed AO or

AOA to receive RT (59.4 Gy) alone or RT followed by 6 cycles of standard dose adjuvant PCV chemotherapy. RTOG 9402 (with 298 patients) was designed slightly differently with the control arm receiving RT alone and the experimental arm receiving 4 cycles of intensive dose PCV prior to RT (59.4 Gy). In both studies, the PFS was significantly longer in the arms receiving PCV chemotherapy; however, there was no difference in overall survival. In both studies, a large proportions (about 80%) of patients in the RT alone arms who progressed went on to receive chemotherapy, which consisted mainly of either PCV or TMZ. The investigators acknowledged that these studies may have effectively compared RT and upfront PCV versus RT and delayed chemotherapy at point of tumour progression, with the similarity in overall survival in all treatment arms suggesting that effective salvage chemotherapy can be administered when tumours progressed.<sup>21,22</sup>

Hence, it appears that for patients with AO and AOA, the timing of PCV chemotherapy may not be crucial as long as it is given. However, the toxicity of PCV regimen was significant; grade 3 or 4 haemotoxicity was seen in 56% of patients in RTOG 9402, while haemotoxicity was responsible for the cessation of PCV chemotherapy in one third of patients in EORTC 26951. Optimal timing of PCV chemotherapy becomes an issue of balance between impairment of quality of life from toxicity of PCV regimen versus risk of neurologic deficits from tumour progression. The question remains as to whether a less toxic chemotherapeutic agent may effect a better outcome if used upfront as it may permit lower attrition rates compared to PCV combination. Clinical trials addressing the viability of chemotherapy alone with TMZ with deferment of RT are in progress.<sup>23</sup> Despite the high response rate to chemotherapy, currently, RT remains the standard treatment for AOs following surgical resection.

In several series of patients with AO, loss of heterozygosity (LOH) of chromosome 1p and 19q was associated with better outcomes.<sup>24,25</sup> Both EORTC 26951 and RTOG 9402 described above were able to determine the 1p/19q status in 311 and 201 patients, respectively. This provided an opportunity to better elucidate the impact of these genetic changes in larger numbers of patients undergoing similar therapies. Deletion of both 1p and 19q was found in 25% and 46% of patients in EORTC 26951 and RTOG 9402 respectively. Presence of 1p and 19q LOH was associated with significantly longer overall survival and progression free survival regardless of treatment received (RT alone versus combination of RT and PCV). In the RTOG study, hazard ratios for death and progression for patients with 1p and 19q deletions compared to all other patients were 0.31 (95% CI 0.20- 0.47;  $P < 0.001$ ) and 0.44 (95% CI 0.32-

0.62;  $P < 0.001$ ) respectively. The 5-year survival and progression free rates of patients with 1p and 19q LOH compared to other patients ranged from 66% to 75% and 31% to 70% compared to 28% to 37% and 8% to 27%, respectively. Despite the marked increase in chemosensitivity associated with 1p and 19q LOH, in subgroup analysis according to chromosomal status, addition of PCV chemotherapy to RT in upfront treatment for patients with 1p and 19q LOH did not confer any survival benefit compared to upfront RT alone.<sup>21,22</sup>

Deletion of 1p and 19q predicts for improved outcomes regardless of treatment. This molecular marker distinguishes a group of patients with AO with good outcomes apart from others whose survival resembles the more aggressive astrocytic tumours. This prognostic factor impacts design of future clinical trials; mandating that this molecular marker be used as a stratification factor in randomised trials or to develop specific therapies, based on the 1p 19q LOH status. Although associated with a marked improvement in response to treatment and prognosis, the optimal treatment of patients with AO with 1p 19q LOH remains undefined. An upcoming international phase III trial will compare chemotherapy alone, RT alone or a chemoradiation regimen to better define the optimal frontline treatment for this disease.

### Chemotherapy Impregnated Wafers

Biodegradable carmustine (BCNU) impregnated wafers (Gliadel<sup>®</sup> wafers) was designed to be implanted along the surface of the surgical cavity and release BCNU over 2 to 3 weeks. Each 200 mg wafer contains 3.85% (7.7 mg) BCNU.<sup>26</sup> A multicentre phase 3 trial randomised a mixed group of 240 patients with malignant gliomas (207 GBM, 2 AA, 19 AO or AOA, 3 metastatic disease and 9 others) to receive BCNU wafers plus RT or placebo wafers plus RT. BCNU wafers were implanted at the time of initial tumour resection if frozen section confirmed the diagnosis of malignant glioma.

In the intention-to-treat (ITT) analysis, overall median survival in the experimental arm was significantly better at 13.8 months compared to 11.6 months in the control arm; hazard ratio, 0.73; 95% CI, 0.56-0.95;  $P = 0.018$ . In the subgroup analysis of GBM patients, median survival was 13.1 versus 11.4 months in the control arm with a hazard ratio of 0.78; 95% CI, 0.595-1.03;  $P = 0.08$ .<sup>27</sup>

The prognosis of grade 3 gliomas (AA, AO, and AOA) is markedly different from GBM; in addition, AOs are known to be more chemosensitive than other gliomas. Hence, the subgroup analysis of a homogenous group of patients with GBM provides imperfect but important information. Although not reported, the 2-year survival rate of patients with GBM in either treatment arms as

indicated by the Kaplan-Meier curve did not exceed 20%. In this trial, the PFS is similar in both treatment arms (5.9 months).<sup>28</sup>

### Chemotherapy for Recurrent High-grade gliomas

Despite aggressive multimodality treatment with currently available therapies, glioma recurrence or progression invariably occurs. Salvage treatment may include additional resection, RT and chemotherapy. Given the poor prognosis associated with malignant gliomas, quality of life (QOL) experienced by the patients is increasingly important. In patients with brain tumours, neurologic function greatly impacts QOL.<sup>29</sup> Clinical trials with QOL components had confirmed that prevention of further disease progression with appropriate chemotherapy was associated with improvement or maintenance of health-related QOL; likewise, a decline in QOL was observed at tumour progression.<sup>30</sup> However, many “second line” chemotherapeutic regimens are highly toxic. Therefore, appropriate and careful selection of patients and chemotherapy may be the key to achieving maximal benefit while minimising toxicity.

Although most studies of chemotherapy for malignant gliomas demonstrate a very low response rate, recurrent AOs remain chemosensitive.<sup>31</sup> Chemotherapy-naïve patients, whose AO or AOA tumours recurred following prior RT, were treated with TMZ in a phase II trial. The response rate (complete and partial responses) was 53% and the median progression free interval was of meaningful duration at 10.4 months.<sup>32</sup> In patients who were previously treated with RT and PCV chemotherapy, response rates of 13% to 44% and median survival of 16 to 26 months were reported following additional salvage chemotherapy with TMZ or carboplatin.<sup>33-35</sup>

The outcomes of patients with recurrent AA and GBM remain poor. Despite treatment, the survival of these patients following tumour recurrence was 47 weeks and 25 weeks for AA and GBM, respectively.<sup>35</sup> For recurrent high-grade astrocytoma, particularly GBM, various chemotherapeutic agents had gone through phase II clinical trials (Table 2). Only a few agents had shown sufficient promise to be assessed in comparison or phase III trials (Table 3). Besides conventional cytotoxic agents, newer agents include biologic agents such as inhibitors of epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), chimeric proteins, tumour vaccines and oncolytic viruses. Advances in the technology and science of cellular processes have led to novel approaches in cancer treatment. In addition to the expanding selection

of new treatments, there is increasing international collaboration that will hopefully lead to significant therapeutic advances in the near future.

Table 2. Some of the Pharmacotherapeutic Agents in Past and Present Phase II Clinical Trials for Recurrent Malignant Gliomas

Agents	Class
Cisplatin or carboplatin +/- etoposide	Platinum drugs and topoisomerase II inhibitor
Cis-retinoic acid	Retinoids
Tamoxifen	Protein C kinase inhibitor
Thalidomide	Anti-angiogenesis
Irinotecan	Topoisomerase I inhibitor
Procarbazine	Alkylating agent
Bevacuzimab	VEGFR inhibitor
Gefitinib	EGFR inhibitor
Erlotinib	EGFR inhibitor
Everolimus	mTor inhibitor
Sirolimus	mTor inhibitor
Romidepsin	Histone deacetylase inhibitor

EGFR: epidermal growth factor receptor; VEGFR: vascular endothelial growth factor receptor

Table 3. Some Agents in Phase III Clinical Trials for Recurrent Malignant Glioma

Agents	Class
Tf-CRM107	Adapted diphtheria toxin conjugated to human transferrin
Hydroxyurea plus imatinib	Imatinib (STI-571) is a platelet derived growth factor receptor inhibitor

### Appendix

#### Standard dose PCV combination chemotherapy:

Lomustine (CCNU) 110 mg/m<sup>2</sup> on day 1, procarbazine 60 mg/m<sup>2</sup> from day 8 to 21, intravenous vincristine at 1.4 mg/m<sup>2</sup> (maximum 2 mg) on day 8 and 29. Each cycle is 42 days.<sup>37</sup>

#### Intensive dose PCV combination chemotherapy:

Lomustine (CCNU) 130 mg/m<sup>2</sup> on day 1, procarbazine 75 mg/m<sup>2</sup> from day 8 to 21, intravenous vincristine at 1.4 mg/m<sup>2</sup> (maximum 2 mg) on day 8 and 29.<sup>22</sup>

#### Temozolomide “Stupp’s protocol”:

Concurrent with RT: Daily temozolomide (TMZ) 75 mg/m<sup>2</sup> administered 1 hour prior to radiation treatment. TMZ is continued Saturdays and Sundays until completion of RT.

Four weeks after completion of RT, TMZ is administered at a dose of 150 to 200 mg/m<sup>2</sup>/day for 5 consecutive days per cycle. Each cycle is 28 days.<sup>16</sup>

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