REVIEW ARTICLE

Adjuvant Chemotherapy for Adults with Malignant Glioma: A Systematic Review

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ABSTRACT: ***Objective:*** This systematic review examines the role of chemotherapy following surgery and external beam radiotherapy for adults with newly diagnosed malignant glioma. ***Methods:*** MEDLINE, EMBASE, and the Cochrane Library databases were searched to August 2006 to identify relevant randomized controlled trials (RCTs) and meta-analyses. Proceedings from the 1997 to 2006 annual meetings of the American Society of Clinical Oncology were also searched. ***Results:*** Two RCTs reported a survival advantage in favour of radiotherapy with concomitant and adjuvant temozolomide compared with radiotherapy alone in patients with anaplastic astrocytoma or glioblastoma. Twenty-six RCTs and two meta-analyses detected either no advantage or a small survival advantage in favour of adjuvant chemotherapy. ***Conclusion:*** Concomitant temozolomide during radiotherapy and post-radiation adjuvant temozolomide is recommended for all patients ages 18-70 with newly diagnosed glioblastoma multiforme who are fit for radical therapy (ECOG 0-1). Temozolomide may be considered in other situations (i.e., ECOG 2, biopsy only, age >70, intermediate grade glioma), but there is no high-level evidence to support this decision. Moreover, there are few data on long-term toxicities or quality of life with temozolomide. Adjuvant chemotherapy may be an option for younger patients with anaplastic (grade 3) astrocytoma and patients with pure or mixed oligodendroglioma. However, there is no evidence of a survival advantage from adjuvant chemotherapy in these patients, and treatment-related adverse effects and their impact upon quality of life are poorly studied. The combination of procarbazine, lomustine, and vincristine (PCV) is not recommended for patients with anaplastic oligodendroglioma and oligoastrocytoma.

RÉSUMÉ: Chimiothérapie adjuvante chez les adultes porteurs d'un gliome malin : revue systématique. ***Objectif :*** Cette revue systématique examine le rôle de la chimiothérapie administrée après la chirurgie et la radiothérapie externe chez les adultes porteurs d'un gliome malin dont le diagnostic est récent. ***Méthodes :*** Nous avons identifié les essais contrôlés randomisés (ECRs) pertinents ainsi que les méta-analyses dans les bases de données MEDLINE, EMBASE et la Cochrane Library jusqu'en août 2006. Nous avons également révisé les comptes rendus des réunions annuelles de l'American Society of Clinical Oncology. ***Résultats :*** Deux ECRs ont rapporté un bénéfice quant à la survie avec le témozolomide comme traitement adjuvant administré en même temps que la radiothérapie par rapport à la radiothérapie seule chez des patients porteurs d'un astrocytome anaplasique ou d'un glioblastome. Vingt-six ECRs et deux méta-analyses n'ont pas mis en évidence d'avantage ou ont démontré un faible avantage quant à la survie avec la chimiothérapie adjuvante. ***Conclusion :*** L'administration de témozolomide pendant la radiothérapie et son administration adjuvante après l'irradiation est recommandée chez tous les patients entre 18 et 70 ans chez qui on vient de poser un diagnostic de glioblastome multiforme et dont l'état général le permet (ECOG 0-1). On peut envisager le traitement par le témozolomide dans d'autres situations (c'est-à-dire ECOG 2, biopsie seulement, âge > 70 ans, gliome de grade intermédiaire), mais il n'existe pas de données probantes à cet effet. De plus, il existe peu de données sur la toxicité à long terme du témozolomide ou sur la qualité de vie. La chimiothérapie adjuvante peut être une option chez les patients plus jeunes qui sont porteurs d'un astrocytome anaplasique (grade 3) et les patients porteurs d'un oligodendrogliome pure ou mixte. Cependant, un avantage quant à la survie n'a pas été démontré avec l'administration de la chimiothérapie adjuvante chez ces patients et les effets secondaires et leur impact sur la qualité de vie ont été mal étudiés. La combinaison procarbazine, lomustine et vincristine (PCV) n'est pas recommandée chez les patients porteurs d'un oligodendrogliome ou d'un oligoastrocytome anaplasique.

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Malignant glioma is the most prevalent type of primary brain tumour in adults. Surgery and external beam radiotherapy (RT), when compared with basic supportive care, are known to improve survival time and quality of life (QOL) for many patients with malignant glioma. Surgery provides tissue for definitive diagnosis and may reduce bulk disease prior to adjuvant therapy. However, despite the effectiveness of surgery and RT, prognosis remains poor for these patients, and the

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likelihood of tumour relapse remains high. Historically, the value of adjuvant chemotherapy (CT) for patients with malignant glioma has been controversial, and until recently, there was considerable practice variation in the province of Ontario.

The modest results of clinical trials of most newer brain tumour therapies reflect a resilient and largely treatment-resistant disease. However, the histological and molecular features of brain tumours that confer an increased probability of response to CT are becoming better known.[1] For example, young patients with malignant glioma may respond to treatment more frequently than do older patients, grade 3 astrocytomas may be more treatment-sensitive than their grade 4 counterparts, and oligodendrogliomas and mixed oligoastrocytomas respond more frequently to CT than do purely astrocytic gliomas.[1,2] Additionally, recent results of clinical trials examining the use of temozolomide with RT in the treatment of newly diagnosed malignant glioma have been promising, although benefits are usually short-lived. In addition to the biological advances, experts have identified several methodological issues concerning trial design and analysis that may have contributed to the uncertainties about the role of CT in the past. For example, many early brain tumour studies were flawed by inappropriate inclusion criteria, lack of recognition of important prognostic variables affecting outcomes, and biased analyses.[2] Increasing awareness of both the molecular substrates of treatment response and the methodological issues affecting the interpretation of clinical trials make an evidence-based review of CT for patients with malignant glioma timely.

For the purposes of this review, overall survival was the chief outcome of interest. It is important to recognize, however, that even in the face of a survival advantage in favour of adjuvant CT, there are adverse effects associated with treatment. The overall benefit to an individual patient in terms of perceived health status and QOL must also be considered, even though poorly reported and challenging to study in this disease setting.

Methods

This systematic review was prepared as part of an evidence-based series developed by the Cancer Care Ontario's Program in Evidence-based Care (PEBC) using methods of the Practice Guidelines Development Cycle.[3] Evidence was selected and reviewed by members of the PEBC's Neuro-oncology Disease Site Group (DSG) and methodologists. The initial data extraction was performed by a single reviewer, and the results were verified in a data audit procedure. Any disagreements were resolved by consensus, making the final agreement 100%. Members of the DSG disclosed potential conflict of interest information.

MEDLINE (1966 to August 2006), EMBASE (1980 to week 36, 2006), and the Cochrane Library (2006, Issue 3) databases were searched. "Glioma" (Medical subject heading [MeSH]) was combined with "chemotherapy, adjuvant" (MeSH) or "brain neoplasms/ dt [drug therapy]". In addition, text words for glioma and chemotherapy were used. These terms were then combined with search terms for the following study designs or publication types: meta-analyses and randomized controlled trials. In addition, the National Cancer Institute (NCI) clinical trials database (www.cancer.gov/search/clinical_trials) and the proceedings of the 1997 to 2006 meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Reference lists from relevant articles were searched for additional trials.

Inclusion Criteria

1. Randomized controlled trials (RCTs) of adjuvant CT for malignant glioma were included. Trials could be of single- or multi-agent regimens, but these regimens had to be compared with a no-CT control arm. Early studies that used what are now considered to be unacceptable methods of allocation (i.e., by birth year or sequential assignment) were also included because data from these studies are frequently cited and were included in a published meta-analysis. In some instances, a randomized trial was reported in more than one publication or as a single-institution experience within a larger multicentre trial. These studies were included so that their quality and any bias that their inclusion in subsequent overviews may have introduced could be judged.
2. As the primary outcome of interest was overall survival, median survival or survival rates had to be reported. Quality of Life was also considered.
3. Meta-analyses of relevant RCTs were included.
4. Full reports and abstracts were considered.

Exclusion Criteria

1. Phase I and single-arm phase II studies were not included because of the availability of randomized trials. Letters, editorials, and review articles were not considered.
2. Trials were excluded if they compared active regimens rather than having a no-CT control arm.
3. Studies of non-systemic treatments such as the intracavitary placement of carmustine wafers were excluded.

Synthesizing the Evidence

The heterogeneity within these studies precluded a valid meta-analysis if performed in the traditional fashion. Heterogeneity results from variations in inclusion criteria, outcome measures, and interventions. The Medical Research Council (MRC-UK) has performed a meta-analysis by obtaining original individual patient data from randomized trials.[4]

Results

Literature Search Results

The literature search yielded 462 results, 31 of which were retained and included in this review. Two trial reports were identified through a search of reference lists from relevant articles.[10,22] The majority of the excluded reports were not randomized trials, did not include a no-chemotherapy control arm, were not studies of patients with malignant glioma or were not studies of systemic chemotherapy. Where more than one report of a single study was identified, only the most recent publication of results was included.

Two published meta-analyses[4,5] and 28 RCTs[6-33] were identified and included. One paper reported results from two separate RCTs.[12] One study used time-to-tumour progression as a surrogate for median survival time and was included in the analysis.[12] A report of a single institution experience[19] in a larger multicentre trial[11] was also included. Two RCTs compared RT

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with temozolomide to RT alone,[30,31] three RCTs compared RT with procarbazine, lomustine, and vincristine (PCV) to RT alone,[29,32,33] and 24 older trials (1994 and earlier) compared RT with other adjuvant CT to RT alone.[6-28] Data from the 28 trials are provided in the Table. Quality of Life data from one of the RCTs[30] were published separately and were included in the review.[34]

Outcomes

Survival

Randomized Trials

Virtually all of the early RCTs (1994 and earlier) suffered from methodological or analytical flaws. The four pre-treatment prognostic variables of age, performance status, degree of surgical resection, and tumour grade are key determinants of patient outcome. Analyses have shown that various combinations of these prognostic factors have more influence upon patient survival than does treatment itself.[35] Current recommendations for the design of RCTs include stratification for these important variables.[2] Only eight of the early RCTs demonstrated equal distribution of these variables across treatment arms.[6,9,16,21,24,25,28] Up to 30% of patients in many of these RCTs had indeterminate histology (grade 3 versus grade 4 versus oligodendroglioma). An intention-to-treat analysis was performed in only seven of the early studies.[6,7,9,17,23,25,28] Moreover, most studies excluded patients from the valid study group because of early death, CT-related toxicity, or a combination of death and loss to follow-up. In one trial,[28] an observed trend in improved survival could not be attributed solely to the use of adjuvant CT since the experimental arm also included a radiosensitizer.

Most of the early RCTs were powered to detect only relatively large survival differences. Using conventional levels of statistical significance and assuming a median survival of 9.4 months for glioblastoma (from Fine et al[5]), 136 patients are required per treatment group to demonstrate a 50% increase in median survival (two-sided alpha=0.05, beta=0.20, accrued over two years).[2,36] Only three of the early RCTs had sufficient statistical power to detect a 50% increase in median survival time,[20,25,27] and the results of each of these studies were negative. Using similar statistical assumptions, 411 patients per treatment group would be required to detect a 25% difference in median survival; none of the studies eligible for this overview had such power.

A trial published in 2001 by the Medical Research Council (BR-05) overcame some of the methodological obstacles of prior work.[29] This trial 1) used a contemporary CT regimen, namely PCV, for up to 12 cycles, 2) excluded oligodendroglioma and mixed oligoastrocytoma, when recognized histologically, as this chemosensitive subtype of glioma might bias results in favour of CT, 3) used an intention-to-treat analysis, and 4) was the largest RCT to date with 90% power to detect a 10% increase in survival at two years (from approximately 15% to 25%). In BR-05, 674 patients were randomized to receive RT alone or RT plus PCV CT following the diagnosis of a grade 3 or grade 4 astrocytic glioma. The trial failed to detect a difference between study arms in median survival time or proportionate survival at one or two years. Subgroup analysis demonstrated no identifiable patient characteristics or other variables associated with improved survival.

Two recent RCTs by van den Bent et al[32] and Cairncross et al[33] compared RT plus PCV CT to RT alone in patients with newly diagnosed anaplastic oligodendroglioma and oligoastrocytoma. Patients in both trials who were randomized to the RT-alone arm were encouraged to receive PCV at disease progression. One RCT administered six cycles of PCV starting within six weeks after RT[32] and one RCT administered up to four cycles of intensive PCV every six weeks before RT.[33] Neither RCT reported a significant difference in overall survival between treatment groups. The RCT by van den Bent et al[32] reported a median survival of 30.6 months in the RT arm and 40.3 months in the RT plus PCV arm (HR 0.85; 95% confidence interval [CI], 0.65 to 1.11; p=0.23), while the RCT by Cairncross et al[33] reported a median survival of 56.4 months in the RT arm and 58.8 months in the RT plus PCV arm (HR 0.90; 95% CI, 0.66 to 1.24; p=0.26). Both RCTs reported a significant benefit for RT plus PCV in progression-free survival. Van den Bent et al[32] reported a median progression-free survival of 13.2 months in the RT arm and 23.0 months in the RT plus PCV arm (HR 0.68; 95% CI, 0.53 to 0.87; p=0.0018), while Cairncross et al[33] reported a median progression-free survival of 20.4 months in the RT arm and 31.2 months in the RT plus PCV arm (HR 0.69; 95% CI, 0.52 to 0.91; p=0.004). In the van den Bent RCT,[32] 82% of patients with disease progression in the RT-alone arm received CT. Similarly, 80% of patients with disease progression in the RT-alone arm of the Cairncross RCT received salvage CT.[33]

A phase III RCT by the National Cancer Institute of Canada (NCIC) -Clinical Trials Group and the European Organisation for Research and Treatment of Cancer (EORTC) has shown the most promise of all adjuvant CT trials for newly diagnosed malignant glioma to date (EORTC-NCIC CE-3).[30] This trial compared temozolomide with RT to RT alone in 573 patients with glioblastoma multiforme (GBM). Patients in the temozolomide and RT arm were treated with concomitant temozolomide and RT, followed by up to six cycles of adjuvant temozolomide. There was no significant difference between the treatment arms in terms of median age, extent of tumour resection, or performance status. After a median of 28 months follow-up, 480 patients had died (84%). The hazard ratio for death between the temozolomide group and the RT alone group was 0.63 (95% CI, 0.52 to 0.75; p<0.001) compared with the RT alone group. There was a significant 2.5-month difference in median overall survival between the temozolomide with RT arm and the RT-alone arm (14.6 months versus 12.1 months, respectively). Significant improvements in progression-free survival and two-year survival were also observed in the temozolomide and RT arm compared to the RT-alone arm (p<0.001). A similar phase II randomized trial of 130 patients with GBM by Athanassiou et al also demonstrated a statistically significant benefit in median and overall one-year survival for RT plus concomitant and adjuvant temozolomide compared to RT alone.[31]

Meta-analyses

The MRC-UK conducted a meta-analysis in 2002 using individual patient data from 12 randomized trials of RT alone compared with RT plus CT in 3004 patients with high-grade glioma.[4] Most of the CT regimens involved nitrosoureas, either alone or in combination. Only trials with proper randomization

Table: Randomized controlled trials of adjuvant chemmotherapy for malignant glioma

Study	# patients (eligible)	Treatments	n	Median Survival (months)	2-year survival (%)	Comments
Edland, 1971 (6)	32 (32)	RT RT + 5-FU	17 15	11.7 11.5 (mean)	NR	-
Brisman, 1976 (7)	33 (33)	RT RT+nitrosourea	16 17	6.3 6.1	NR	Data from randomized arm; multiple regimens used.
Reagan, 1976 (8)	75 (63)	RT RT + CCNU	22 19	11.6 12.0	NR	Data from CCNU-only arm not shown.
Weir, 1976 (9)	41 (41)	RT RT + CCNU	15 13	6.2 8.3	NR	Patients crossed to CCNU at recurrence.
Garrett, 1978 (10)	74 (69)	RT RT + CCNU	35 34	8.0 13.0	34.0 52.0 (1-year survival)	Patients randomized by birth year.
Walker, 1978 (11)	303 (222)	RT RT + BCNU	68 72	8.3 8.0	1.0 5.0	Data from “valid study group” only.
EORTC, 1978 (trial 26741) (12)	111 (81)	RT RT + CCNU	52 59	7.2 8.0 (mean)	NR	Time to tumour progression used as a surrogate for median survival time. CCNU at recurrence in RT arm.
EORTC, 1978 (trial 26742) (12)	23 (19)	RT RT + CCNU	13 10	5.0 7.2*	NR	Unclear why patients were excluded from analysis.
Eagan, 1979 (13)	43 (42)	RT RT + DHG	20 22	8.1 15.5*	NR	Major problems with co-intervention.
Solero, 1979 (14)	105 (102)	RT RT + BCNU RT + CCNU	32 34 36	10.5 12.0 16.0*	NR	-
Cianfriglia, 1980 (15)	? (103)	RT RT + CCNU	50 26	8.0	12.0	Sequentially assigned, not randomized.
Walker, 1980 (16)	467 (358)	RT RT + BCNU RT + MeCCNU	118 120 118	8.5 11.3 9.9	14.1 19.2 19.2	Data shown for whole randomized population.
EORTC, 1981 (17)	116 (116)	RT RT + CCNU + VM-26	55 61	14.1 13.4	NR	-
Kristiansen, 1981 (18)	? (118)	 RT + placebo RT + Bleo	 35 45	 10.5 10.3 (mean)	NR	Excluded from analysis if severe toxicity occurred.
Chin, 1981 (19)	? (61)	RT RT + BCNU RT + MeCCNU	25 26 10	10.8 15.9 21.2	16.0 26.9 30.0	Subgroup of patients already reported in Walker, 1978 (11).
Green, 1983 (20)	609 (527)	RT + steroid RT + BCNU RT + PCB RT + steroid + BCNU	156 147 153 153	9.5 11.5 9.9 9.5	8.0 19.5 22.2 18.0	Worse outcomes in patients treated with methylprednisolone.
Afra, 1983 (21)	91 (84)	RT RT + DBD	30 26	9.2 13.2*	3.3 19.0*	Most of the excluded patients from the chemotherapy arms.

Table: continued

Study	# patients (eligible)	Treatments	n	Median Survival (months)	2-year survival (%)	Comments
		RT + DBD + CCNU	28	13.8*	25.0*	
Ushio, 1984 (22)	? 91	RT RT + Bleo RT + MeCCNU RT + MeCCNU + Bleo	?15 ?16 ?16 ?13	7.7 9.8 18.2 26.5	NR	Data presented briefly in a review article.
Hatlevoll, 1985 (23)	280 (244)	RT RT + CCNU	118 126	8.0 – 12.0 8.0 – 12.0	NR	Median survival time not reported.
Takakura, 1986 (24)	105 (77)	RT RT + ACNU	48 57	17.0 17.0	NR	Response rate 47.5% in chemotherapy arm.
Nelson, 1988 (25)	626 (538)	RT RT + boost RT + BCNU RT + MeCCNU + DTIC	141 103 156 138	9.3 8.2 9.7 10.1	14.3 15.5 19.5 20.6	Unknown if anaplastic astrocytoma or GBM in 31% of patients.
Trojanowski, 1988 (26)	? (198)	RT RT + CCNU	75 74	10.4 12.0	NR	-
EORTC, 1991 (27)	285 (246)	RT RT + CisPt	143 142	12.0 10.6	NR	-
Hildebrand, 1994 (28)	269 (255)	RT RT + DBD + BCNU	134 135	10.8 13.2	12.0 21.0	Results reported as significant for eligible group, not whole randomized population.
MRC, 2001 (29)	674 (674)	RT RT + PCV	339 335	9.5 10.0	14.2 15.5	No difference in one- or two-year survival
Stupp, 2005 (30)	573 (573)	RT RT + TMZ	286 287	12.1 14.6*	10.4 26.5*	Patients had GBM. RT + temozolomide significantly improved overall median survival and progression-free survival compared to RT alone ($p<0.001$).
Athanassiou, 2005 (31)	130 (110)	RT RT + TMZ	53 57	7.7 13.4*	NR	Patients had GBM.
van den Bent, 2006 (32)	368 (368)	RT RT + PCV	183 185	30.6 40.3	55 62	Patients had anaplastic oligodendroglioma or oligoastrocytoma. A significant increase in PFS was reported for RT + PCV.
Cairncross, 2006 (33)	289 (289)	RT RT + PCV	142 147	56.4 58.8	74 70	Patients had anaplastic oligodendroglioma or oligoastrocytoma. A significant increase in PFS was reported for RT + PCV.

Note: ?, unclear; 5-FU, 5-fluorouracil; ACNU, nimustine; BCNU, carmustine; Bleo, bleomycin; CisPt, cisplatin; CCNU, lomustine; DBD, dibromodulcitol; DHG, dianhydrogalactitol; DTIC, dacarbazine; EORTC, European Organisation for Research and Treatment of Cancer; GBM, glioblastoma multiforme; MeCCNU, semustine; N, sample size; NR, not reported; PCB, procarbazine; PCV, procarbazine, lomustine, vincristine; PFS, progression-free survival; RT, radiotherapy; TMZ, temozolomide; VM-26, epipodophyllotoxin.
*Statistically significant difference in favour of adjuvant chemotherapy ($p<0.05$).

and allocation concealment procedures were accepted for inclusion. The meta-analysis included both published trials[9,11,14,16,17,20,21,26,28,29] and unpublished data. Unpublished data were included to avoid publication bias; however, inclusion of an unpublished study makes it difficult to ensure the quality of the data. The MRC meta-analysis did state that "all data were thoroughly checked for consistency, plausibility, and integrity of randomisation and follow-up".[4]

The results of the MRC meta-analysis demonstrated a significant overall survival benefit favouring CT and RT over RT alone (HR 0.85; 95% CI, 0.78 to 0.91; p<0.0001), which corresponds to a 15% relative reduction in the risk of death with CT.[33] There was a five percent (95% CI, 2% to 8%) absolute improvement in survival at two years (from 15% to 20%). There were also data available from 2022 patients (from eight RCTs) on disease progression. Similar to overall survival, the HR for disease progression indicated a significant reduction (17%) in the risk of disease progression in the patients treated with CT and RT compared with those treated with RT alone (HR 0.83; 95% CI, 0.75 to 0.91; p<0.0001). The effect of CT was not related to age, sex, histology, performance status, or extent of resection.

The meta-analysis published in 1993 by Fine et al[5] pooled survival data of more than 3000 patients from 16 of the 24 identified RCTs comparing RT to RT plus adjuvant CT of some type.[8,10,11,13-22,24-26] One study included by Chin et al[19] was a single-institution report of a multicentre RCT,[11] meaning that this patient group was reported twice in the meta-analysis. The multicentre study was negative, but the results from Chin et al were strongly in favour of CT. The meta-analysis also included two studies that were not properly randomized. One trial allocated patients by date of birth,[10] while another appeared to have sequentially assigned patients.[15] Survival data were extracted from the published survival curves for each RCT. The authors reported a slight increase in one- and two-year survival in favour of adjuvant CT (absolute increase in one-year survival rate, 10.1%; 95% CI, 6.8% to 13.3%; p-value not reported).

The results of the two meta-analyses need to be interpreted with caution. Nine out of 12 studies included in the MRC meta-analysis,[4] and 14 out of 16 studies in the Fine et al. meta-analysis[5] were published more than 20 years ago. A known difficulty with meta-analysis in a heterogeneous patient population is the combining of data from studies that have varying inclusion criteria, outcome measures, and interventions. The RCTs in these meta-analyses were small, had varying consideration of important prognostic variables, used different CT regimens, and had different primary outcomes. Many of these RCTs reported results for a "valid study group"—patients who received at least one cycle of CT—rather than reporting results on an intention-to-treat basis. The age of the trials included in the analyses, the variances among the trials, and the inherent inconsistencies between studies reduces the clinical utility of the results from the meta-analyses.

Quality of Life and Adverse Effects

Global performance and job status were reported in the first RCT evaluating CT for malignant glioma in 1971,[6] but few subsequent brain tumour therapy trials have evaluated QOL in a comprehensive fashion. Quality of Life was usually not predefined as an endpoint of interest in the early RCTs. Karnofsky performance status (KPS), an eligibility criterion for many RCTs and an important prognostic factor, correlates poorly with QOL.[2] Where KPS was recorded as an outcome measure for QOL, no differences in KPS scores were found between treatment groups.

Scales for toxicity assessment were commonly used in the early trials. However, brain tumour patients may have disease-specific acute and delayed adverse effects not captured in all-purpose toxicity scales such as the National Cancer Institute Common Toxicity Criteria. For example, impairment of neurocognitive function likely represents an important outcome to patients and may reflect the impact of disease or the impact of treatment. In general, the acute adverse effects of CT were well tolerated by most patients; however, many of the early RCTs excluded patients with the most severe toxicity from the analysis. Most CT regimens used in these studies were associated with acceptable myelotoxicity. Nausea and vomiting were often problematic.

As with previous trials, four of the latest five RCTs[29,31-33] provided no specific information about QOL, but no overall impact upon general performance status was seen. The MRC trial of PCV therapy did not carry out a formal assessment of QOL, but clinical performance status and neurologic status were assessed at each follow-up point.[29] While toxicity in general was moderate, 50% of patients required delay of at least one CT cycle, mainly due to hematologic toxicity including anemia, leukopenia or thrombocytopenia. No grade 3 or grade 4 neurotoxicity was reported. The two RCTs comparing RT alone to RT plus PCV CT[32,33] in anaplastic oligodendroglioma and oligoastrocytoma reported significant toxicity in patients who received PCV. Van den Bent et al[32] reported that 46% of patients in the experimental arm experienced grade 3/4 hematologic toxicity, including leukopenia in 30%, neutropenia in 32%, thrombocytopenia in 21% and anemia in 7%, and only 37% of patients completed at least five out of six cycles of PCV. Grade 3 nausea and vomiting each occurred in 6% of patients. In the RCT by Cairncross et al,[33] 65% of patients had grade 3/4 toxicity during PCV treatment: 56% had grade 3/4 hematologic toxicity including neutropenia, thrombocytopenia or anemia, 13% had grade 3/4 neurologic toxicity including cognitive change, affective disturbance, peripheral neuropathy or autonomic neuropathy, and 9% had grade 3/4 gastrointestinal toxicity. During RT, 8% of patients in the PCV plus RT arm and 5% in the RT alone arm had grade 3/4 toxicity.

In the EORTC-NCIC CE-3 trial[30] of radiotherapy with concurrent and adjuvant temozolomide, grade 3/4 hematological toxicity was observed in 7% of patients during concomitant temozolomide and radiotherapy treatment and in 14% of the patients during the adjuvant temozolomide treatment. Over the entire study period, grade 3/4 hematologic toxicity included leukopenia in 7%, neutropenia in 7%, thrombocytopenia in 12% and anemia in 1%. No grade 3/4 hematologic toxicity was reported for the patients receiving radiotherapy alone. Thirty three percent of patients in the temozolomide group experienced moderate to severe fatigue compared to 26% in the radiotherapy-alone group. Similarly, Athanassiou et al[31] reported that the main side effect of temozolomide with radiotherapy was reversible myelosuppression. Late side effects have not yet been assessed.

The EORTC-NCIC CE-3 trial[30] administered QOL questionnaires to patients and those data have been published

separately.[34] Health-related QOL was assessed by administering the EORTC core-30 questionnaire (QLQ-C30, version 3) and the EORTC brain cancer module questionnaire (QLQ-BN20) at baseline, during radiotherapy at four weeks, four weeks after radiotherapy, at the end of the third and sixth cycle of adjuvant temozolomide, and then every three months until disease progression. Seven scales were chosen for primary analysis: fatigue, overall health-related QOL, social function, emotional function, future uncertainty, insomnia, and communication deficit, with additional scales analyzed on an exploratory basis only. Baseline QOL data were available for 248 patients in the radiotherapy-alone group and 242 patients in the radiotherapy plus temozolomide group, and these patients were included in the analysis. At baseline, patients had impaired overall health-related QOL, impaired emotional and social functioning, substantial fatigue, insomnia, communication deficits, and uncertainty regarding the future. At first follow-up, patients in the radiotherapy-alone arm had significantly greater social functioning than patients in the temozolomide arm; however, the treatment arms did not differ for any of the seven scales in subsequent follow-up assessments. Only minor variations in the seven scales were observed over time; however, nearly all scales showed improvement. In the exploratory analysis of additional QOL scales, only nausea and vomiting, appetite loss, and constipation were significantly increased in patients who received radiotherapy plus temozolomide compared to patients who received radiotherapy alone.

Discussion

Temozolomide, a new well-tolerated oral alkylating agent, has just started to be tested in the adjuvant setting. Temozolomide has significant anti-glioma activity, and is commonly used in the treatment of recurrent anaplastic astrocytoma (AA) and GBM. The EORTC-NCIC CE-3 trial comparing temozolomide and RT to RT alone in patients with GBM was the first of its kind.[30] The trial reported a significant median survival difference of 2.5 months between the temozolomide and RT arm and the RT-alone arm (14.6 months versus 12.1 months, respectively). Data comparing toxicity and QOL between the treatment arms indicated no substantial negative effect of temozolomide on health-related QOL. The results of a smaller trial by Athanassiou et al[31] demonstrated a similar benefit.

Evidence from a large RCT (BR-05) detected no evidence of a survival advantage in favour of treatment for adjuvant CT with PCV in patients with AA or glioblastoma.[29] This finding is concordant with many early RCTs, most of which were of lower quality, and a meta-analysis which pooled results from 16 of 24 studies included in this systematic review. Criticisms of the BR-05 trial[31] include the use of a somewhat less-intensive PCV regimen than conventionally used by others. A second concern is that the power of the study was still insufficient to detect small, but perhaps important, survival differences in subgroups of patients most likely to benefit from treatment. For example, a doubling of median survival in young patients or patients with grade 3 tumours could not be excluded.

The two recent RCTs of PCV in patients with anaplastic oligodendrogliomas and oligoastrocytomas demonstrated prolonged time-to-progression in patients who received adjuvant PCV but no significant benefit in overall survival.[32,33] Since most patients in the RT-alone arm of each trial received PCV or other CT at disease progression, it could be argued that these RCTs compared early PCV to delayed CT at progression rather than RT plus PCV to RT alone. Both trials reported considerable PCV-related toxicity, particularly grade 3/4 hematologic toxicity; therefore, this does not seem to be an optimal regimen for this patient population. Although anaplastic oligodendrogliomas and oligoastrocytomas are more sensitive to CT than is glioblastoma, the more favourable natural history of these tumours may play a greater role in determining overall survival than treatment modality and timing of adjuvant treatment.[33] There is evidence that patients having tumours with codeletion of 1p and 19q live longer, regardless of treatment, and are more likely to respond to CT. In post hoc analyses, Van den Bent et al[32] reported that 1p and 19q loss was the most predictive factor of overall survival, and Cairncross et al[33] reported that progression-free survival in the PCV arm was only significantly increased in the subset of patients with 1p and 19q loss. These results indicated that tumours with 1p and 19q codeletion are biologically and clinically distinct and should be studied separately in future RCTs.[32,33]

A study conducted alongside the EORTC-NCIC CE-3 trial[30] examined the association between methylation of the MGMT gene and response to treatment with temozolomide.[37] The MGMT gene encodes a DNA-repair protein that decreases the effects of alkylating agents such as temozolomide when present in high levels. The silencing of this gene through promoter methylation may be a predictor of response to therapy in patients with glioblastoma. MGMT methylation status was evaluable in 36% of patients from the EORTC-NCIC CE-3 trial. Regardless of treatment assignment, a significant benefit in overall survival was detected for patients with MGMT promoter methylation compared to patients without promoter methylation (long-rank $p<0.001$). The overall survival benefit for temozolomide compared to RT alone was significant for patients who had MGMT promoter methylation (log-rank $p=0.007$) but was not significant for patients who did not have evaluable MGMT promoter methylation (log-rank $p=0.06$). In patients with MGMT promoter methylation, median progression-free survival was 10.3 months in the temozolomide group compared to 5.9 months in the RT-alone group. In patients without MGMT promoter methylation, median progression-free survival was 5.3 months in the temozolomide group compared to 4.4 months in the RT-alone group. Although only a subset of patients were evaluable for methylation status, these results suggest that MGMT promoter methylation status may be a good prognostic factor for survival and response to treatment with alkylating agents such as temozolomide.

There may be additional subgroups of patients more likely to benefit from CT. However, the nature of these subgroups is unclear and at present, chemosensitivity cannot be accurately predicted prior to therapy. In addition to patients with pure or mixed oligodendrogliomas that contain 1p and 19q loss,[36] younger patients and patients with grade 3 astrocytoma may also be more likely to harbour chemosensitive tumours. In practice, it is reasonable to consider adjuvant CT for these patients; however, it must be recognized that a definite survival advantage is unproven and, if it exists, may be small. In addition, the

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impact of treatment-related adverse effects upon QOL has been poorly studied and, given the small expected benefit of therapy, these toxicity issues may be a concern. Simple, valid, and reproducible instruments sensitive to changes in the health status of brain tumour patients are under development and, with further validation, are likely to be included in future trials.

Based upon the current evidence, the use of concomitant temozolomide during radiation therapy and post-radiation adjuvant temozolomide is recommended for all patients with newly diagnosed GBM who are fit for radical therapy (ECOG 0-1). Temozolomide may also be considered in patients with other malignant gliomas, patients with ECOG 2 or biopsy only, and patients over the age of 70; however, there is no high-level evidence to support this decision. The dilemma of expected survival gain versus treatment toxicity and impact upon QOL remains unexplored. Some astrocytic malignant gliomas are chemosensitive (a minority), but it is not yet clear which ones nor why.[1] At present, it is a reasonable option to allow individualized consideration of adjuvant CT for patients with pure or mixed oligodendroglioma or anaplastic (grade 3) astrocytoma and young patients with any type of malignant glioma. Implicit in the designation of CT as an "option" for these patient groups is the recommendation that patients be provided with information about the controversies surrounding the benefit and optimal timing of such CT. Participation in ongoing clinical trials should be encouraged.

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Conflict of Interest

The authors of this manuscript were polled for potential conflicts of interest and the following conflicts were declared: James Perry, Normand Laperriere and Gregory Cairncross have received consultancy fees or honoraria from Schering Plough within the last two years. James Perry and Normand Laperriere have also received grant or research support from Schering Plough.

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