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Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma

Practice Guideline Report #9-2

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ORIGINAL GUIDELINE: March 10, 2004
MOST RECENT LITERATURE SEARCH: June 2004
NEW EVIDENCE ADDED TO GUIDELINE REPORT: June 2004
RECOMMENDATIONS MODIFIED: June 2004

Based on new evidence that has emerged since completion of the original guideline, the Neuro-oncology Disease Site Group has modified this practice guideline report. The revised recommendations and supporting evidence are labelled **Update**.

SUMMARY

Guideline Question

Should chemotherapy be recommended, following surgery and external beam radiotherapy, to adults with newly diagnosed malignant glioma in order to improve overall survival and/or quality of life?

Target Population

These recommendations apply to adults with newly diagnosed malignant glioma who have undergone surgery and external beam radiotherapy.

Recommendations

- **Update**
  The use of concurrent temozolomide during radiation therapy and postradiation adjuvant temozolomide is recommended for all patients with newly diagnosed glioblastoma multiforme who are fit for radical therapy. Temozolomide should be considered in patients with malignant gliomas.
- Younger patients, patients with anaplastic (grade 3) astrocytoma, and patients with pure or mixed oligodendroglioma, are more likely to harbour chemosensitive tumours, and adjuvant chemotherapy may be an option in these cases. 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.
- Patients should be provided with information about the controversies surrounding the benefit and optimal timing of such treatment.

Qualifying Statements

- This guideline considers chemotherapy in the adjuvant setting only and should not discourage the consideration of chemotherapy for selected patients at the time of tumour progression or in the context of clinical trials evaluating new treatment regimens at any point in the disease.
- **Update**
  The recommendation regarding the use of adjuvant temozolomide is based on abstract data from one randomized trial. There may be subgroups of patients who will benefit more or less from adjuvant temozolomide; thus the Neuro-oncology Disease Site Group will revise their recommendations as necessary as subgroup data emerges.

Methods

Entries to MEDLINE (1966 to June 2004), EMBASE (1980 to week 25, 2004), CANCERLIT (1983 to October 2002), and the Cochrane Library (2004, Issue 2) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1997 to 2004) were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by members of the Practice Guidelines Initiative's Neuro-oncology Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Neuro-oncology Disease Site Group, which is comprised of neuro-oncologists, neurosurgeons, radiation oncologists, medical oncologists, an oncology nurse, and a patient representative.

External review by Ontario practitioners is obtained for all practice guidelines through a mailed survey. Final approval of the practice guideline report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Twenty-four heterogeneous randomized controlled trials, and two meta-analyses incorporating some of these trials, variably detected either no advantage or a small survival advantage in favour of adjuvant chemotherapy. These studies often did not consider quality of life as an outcome variable. The most contemporary and largest trial reported a slight survival advantage in favour of adjuvant chemotherapy compared with no-chemotherapy controls in patients with anaplastic astrocytoma or glioblastoma.
- **Update**
  One randomized controlled trial (abstract) randomized 573 patients with newly diagnosed glioblastoma multiforme to receive either temozolomide and radiation therapy or radiation therapy alone. The trial reported a significant improvement in median progression-free survival, overall survival, and two-year survival in the patients receiving temozolomide with radiation therapy compared to those receiving radiation therapy alone ($p<0.001$). There was a three month difference in median overall survival between the treatment arms (15 months for patients treated with temozolomide and radiation therapy versus 12 months for patients treated with radiation therapy alone).

Future Research

- Planned and ongoing therapeutic and clinical-molecular correlative studies with quality-of-life outcomes may clarify the role of chemotherapy in the subgroups of patients most likely to benefit from treatment. Participation in these trials is encouraged.

For further information about this evidence summary report, please contact

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:
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FULL REPORT

I. QUESTION

Should chemotherapy be recommended, following surgery and external beam radiotherapy, to adults with newly diagnosed malignant glioma in order to improve overall survival and/or quality of life?

II. CHOICE OF TOPIC AND RATIONALE

Surgery and external beam radiotherapy (RT), when compared with basic supportive care, are known to improve survival time and quality of life for many patients with malignant glioma. Surgery provides tissue for definitive diagnosis and may reduce bulk disease prior to adjuvant therapy. The roles of surgery and RT for newly diagnosed malignant glioma are discussed in detail in a companion practice guideline report that is being developed by the Neuro-oncology Disease Site Group (DSG). Eventually, the guideline reports will be merged.

There are no other therapies known to influence survival time to the degree seen with primary surgical resection and RT. In particular, the value of adjuvant chemotherapy is controversial, and practice variation exists in Ontario. An informal poll of members of the Neuro-oncology DSG indicated that some institutions recommend adjuvant chemotherapy to most patients with malignant glioma, yet others tend to recommend chemotherapy only at the time of tumour recurrence, if at all.

In large part, the modest results of clinical trials of 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 chemotherapy 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 chemotherapy than do purely astrocytic gliomas (1,2). 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 chemotherapy. 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 malignant glioma treatment timely.

For the purposes of our review, we felt that overall survival was the chief outcome of interest to patients. We recognized, however, that, even in the face of a survival advantage in favour of adjuvant chemotherapy, there are adverse effects associated with treatment. The overall benefit to an individual patient in terms of perceived health status and quality of life must also be considered. We were aware of conflicting evidence from a multitude of randomized trials, a meta-analysis, and a recently completed large randomized controlled trial; these data made the issue of the appropriate use of adjuvant chemotherapy an obvious question for our group. Overall survival was the outcome of greatest interest, but quality of life, even though poorly studied in this disease, is clearly important and was also considered. We also examined the evidence suggesting that there may be certain patients more likely to be sensitive to treatment, and we incorporated these data into our analyses.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (3). Evidence was selected and reviewed by members

of the PGI's Neuro-oncology Disease Site Group (Neuro-oncology DSG) and methodologists. Members of the Neuro-oncology DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 to January 2004), CANCERLIT (1983 to October 2002), and the Cochrane Library (2003, Issue 3) databases were searched with no language restrictions. "Glioma" (Medical subject heading [MeSH]) was combined with "chemotherapy, adjuvant" (MeSH). These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses and randomized controlled trials. In addition, the Physician Data Query (PDQ) clinical trials database (www.cancer.gov/search/clinical_trials, searched May 21, 2003) and the proceedings of the 1997 to 2003 meetings of the American Society of Clinical Oncology (ASCO) were searched for reports of new or ongoing trials. Relevant articles and abstracts were selected and reviewed by one reviewer, and the reference lists from these sources were searched for additional trials.

Update

The original literature search has been updated using MEDLINE (through June 2004), EMBASE (through week 25, 2004), the Cochrane Library (2004 Issue 2) and the 2004 proceedings of the annual meeting of the American Society of Clinical Oncology.

Inclusion Criteria

1. We included all randomized controlled trials (RCTs) of adjuvant chemotherapy for malignant glioma. Trials could be of single- or multi-agent regimens, but these regimens had to be compared with a no-chemotherapy control arm. We elected to include early studies that used what are now considered to be unacceptable methods of allocation (i.e., by birth-year or sequential assignment) because data from these studies are frequently cited and were used in a subsequent 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; we included these studies in order to judge their quality and any bias that their inclusion in subsequent overviews may have introduced.
2. As the primary outcomes of interest were overall survival, median survival or survival rates had to be reported. Quality of life (QOL) was also considered.
3. Full reports and abstracts were considered.

Exclusion Criteria

1. Phase I and 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-chemotherapy control arm.
3. Studies of non-systemic treatments, such as the intracavitary placement of carmustine wafers, were also excluded.

Synthesizing the Evidence

We considered performing our own meta-analysis of all relevant RCTs. However, we felt that the heterogeneity within these studies precluded a valid meta-analysis, if performed in the traditional fashion. Meta-analysis is open to misinterpretation when results are combined, even against better judgment, simply to create a large sample size. Heterogeneity of a meta-analysis results from variations in inclusion criteria, outcome measures, and interventions. However, the Medical Research Council (MRC-UK) had performed a meta-analysis by obtaining original individual patient data from the randomized trials (4).

IV. RESULTS

Literature Search Results

Two published meta-analyses (4,5) and 24 RCTs (6-29) were identified and included. One paper reported results from two separate RCTs (12). A single study used time to tumour progression as a surrogate for median survival time and was included in the analysis (12). We also included a report of a single institution experience (19) in a larger multicentre trial (11). Methodological and survival data from the 24 trials are provided in Table 1. The literature search also identified one consensus-based practice guideline for the treatment of a wide variety of adult brain tumours (30).

Update

Since the completion of the original practice guideline, one RCT comparing temozolomide and radiation therapy was compared to radiation therapy alone (National Cancer Institute of Canada Clinical Trials Group [NCIC CTG] CE.3) (1u). The abstract results of the RCT were presented at ASCO 2004.

Table 1. Randomized controlled trials of adjuvant chemotherapy for malignant glioma.

Study (Reference)	# evaluated/ # entered	Treatment Groups	N	Median Survival Time (months)	2-Year Survival Rate (%)	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)	63/75	RT RT + CCNU	22 19	11.6 12.0	NR	Data from CCNU-only arm not shown.
Weir, 1976 (9)	28/28	RT RT + CCNU	15 13	6.2 8.4	NR	Patients crossed to CCNU at recurrence.
Garrett, 1978 (10)	69/74	RT RT + CCNU	35 34	8.0 13.0*	34.0 51.0 (1-year survival rates)	Patients randomized by birth year.
Walker, 1978 (11)	222/303	RT RT + BCNU	93 100	9.0 8.6	1.0 5.0	Data from "valid study group" only.
EORTC, 1978 (trial 26741) (12)	81/111	RT RT + CCNU	52 59	8.6 7.8	NR	Time to tumour progression used as a surrogate for median survival time. CCNU at recurrence in RT arm.
EORTC, 1978 (trial 26742) (12)	19/23	RT RT + CCNU	13 10	5.4 7.8*	NR	Unclear why patients were excluded from analysis.
Eagen, 1979 (13)	42/43	RT RT + DHG	20 22	8.8 16.7*	NR	Major problems with co-intervention.
Solero, 1979 (14)	102/105	RT RT + BCNU RT + CCNU	32 34 36	10.5 12.0 16.0*	NR	--
Cianfriglia, 1980 (15)	103/?	RT RT + CCNU	50 26	13.2 11.9	NR	Sequentially assigned, not randomized.
Walker, 1980 (16)	358/467	RT RT + BCNU RT + MeCCNU	118 120 118	9.3 12.3 10.8	14.1 19.2 19.2	Data shown for whole randomized population.
EORTC, 1981 (17)	116/116	RT RT + CCNU + VM-26	55 61	14.2 13.5	NR	--
Kristiansen, 1981 (18)	118/?	Support RT + placebo RT + Bleo	38 35 45	6.1 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	11.8 17.3* 23.0*	16.0 26.9 30.0	Subgroup of patients already reported in Walker, 1978.
Green, 1983 (20)	527/609	RT + steroid RT + BCNU RT + PCB RT + steroid + BCNU	156 147 153 153	10.3 12.5 10.8 10.3	8.0 19.5 22.2 18.0	? worse outcomes in patients treated with methylprednisolone.
Afra, 1983 (21)	84/91	RT RT + DBD RT + DBD + CCNU	30 26 28	10.0 14.3* 15.0*	3.3 19.0* 25.0*	Most of the excluded patients from the chemotherapy arms.

Table 1 Continued.

Study (Reference)	# evaluated/ # entered	Treatment Groups	N	Median Survival Time (months)	2-Year Survival Rate (%)	Comments
Ushio, 1984 (22)	?	RT RT + Bleo RT + MeCCNU RT + MeCCNU + Bleo	?15 ?16 ?16 ?13	7.8 10.6 14.0* 18.2*	NR	Data presented briefly in a review article.
Hatlevoll, 1985 (23)	244/280	RT RT + CCNU	118 126	8.0 – 12.0 8.0 – 12.0	NR	Median survival time not reported.
Takakura, 1985 (24)	77/105	RT RT + ACNU	48 57	17.0 17.0	NR	Response rate 47.5% in chemotherapy arm.
Nelson, 1988 (25)	538/626	RT RT + boost RT + BCNU RT + MeCCNU + DTIC	141 103 156 138	9.3 8.2 9.7 10.1	NR	Unknown if anaplastic astrocytoma or glioblastoma multiforme in 31% of patients.
Trojanowski, 1988 (26)	?	RT RT + CCNU	75 74	11.3 13.0	NR	--
EORTC, 1991 (27)	246/285	RT RT + CisPt	143 142	13.0 11.5	NR	--
Hildebrand, 1994 (28)	269/269	RT RT + DBD + CCNU	134 135	10.8 13.2	12.0% 21.0%	Results reported as significant for eligible group, not whole randomized population.
MRC, 1998 (29)	674/674	RT RT + PCV	339 335	9.5 10.0	NR	No increase in one- or two-year survival
Update NCIC-CTG CE.3, 2004 (1u) (abstract)	573	RT RT + temozolomide	286 287	12.0 15.0	8.0% 26.0%	RT + temozolomide significantly improved overall median survival and progression-free survival compared to RT alone (p<0.001)

Note: ?, unclear; 5-FU, 5-fluorouracil; ACNU, nimustine; BCNU, carmustine; Bleo, bleomycin; CCNU, lomustine; CisPt, cisplatin; DBD, dibromodulcitol; DHG, dianhydrogalactitol; DTIC, dacarbazine; EORTC, European Organization for Research and Treatment of Cancer; MeCCNU, methyl-CCNU; N, sample size; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; NR, not reported; PCB, procarbazine; PCV, procarbazine, lomustine, vincristine; RT, radiotherapy; VM-26, epipodophyllotoxin.
*Statistically significant difference in favour of adjuvant chemotherapy (p<0.05).

Meta-analyses

The MRC-UK conducted a meta-analysis using individual patient data from 12 randomized trials of radiotherapy alone compared with radiotherapy plus chemotherapy in 3004 patients with high-grade glioma (4). Most of the chemotherapy regimens involved nitrosoureas, either alone or in combination. The meta-analysis (4) included both published and unpublished data. They chose to include unpublished data because they wanted to avoid publication bias, but ensuring the quality of unpublished data is difficult. However, the MRC meta-analysis did state that "all data were thoroughly checked for consistency, plausibility, and integrity of randomisation and follow-up."

The results of the MRC meta-analysis detected a significant overall survival benefit favouring chemotherapy and radiotherapy over radiotherapy alone (mortality hazard ratio [HR], 0.85; 95% CI, 0.78 to 0.91; p<0.0001). There was a 5% (95% CI, 2% to 8%) absolute improvement in survival at two years (from 15% to 20%), which corresponds to a 15% relative reduction in the risk of death with chemotherapy. Data available from 2022 patients (from eight RCTs) showed that, similar to overall survival, there was a significant reduction (17%) in the risk of disease progression in the patients treated with chemotherapy and radiotherapy compared to

radiotherapy alone (HR, 0.83, 95% CI, 0.75 to 0.91m p<0.0001). The effect of chemotherapy was not related to age, sex, histology, performance status, or extent of resection.

The results of the MRC meta-analysis need to be interpreted with caution. There were differences in the designs of the RCTs included in the meta-analysis, including various radiotherapy regimens. Also, of the 12 studies included in the meta-analysis, eight were published 20 or more years ago.

Of the four RCTs published in the last 20 years included in the MRC meta-analysis (4), one is unpublished, two reported that chemotherapy offers no survival advantage (26,29), and one reported a survival benefit in patients treated with chemotherapy (28). A trial published in 1994 by the European Organization for Research and Treatment of Cancer (EORTC) compared radiotherapy alone to radiotherapy plus a radiosensitizing agent with adjuvant chemotherapy using carmustine (28). The study was designed to detect a 50% increase in median survival and stratified patients according to degree of surgical resection. When all randomized patients were considered, the median survival time was 10.8 months in the RT alone arm and 13.2 months in the RT plus radiosensitizer plus chemotherapy arm (p=0.058). When only eligible patients were analyzed, this value reached conventional levels of statistical significance (p=0.044). This promising trend in improved survival could not be attributed solely to the use of adjuvant carmustine, because the experimental arm also included a radiosensitizer. Thus, the age of the RCTs, the variances among the RCTs, and the inherent inconsistencies of each RCT reduces the clinical utility of the results from the MRC meta-analysis (4).

The other meta-analysis (5), published in 1993, pooled survival data from 16 of the 24 identified RCTs comparing RT with RT plus adjuvant chemotherapy of some type (8,10,11,13-22,24-26). 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 chemotherapy (absolute increase in one-year survival rate, 10.1%; 95% CI, 6.8% to13.3%; p-value not reported).

A known problem with meta-analysis in a heterogeneous patient population is the difficulty of combining data from studies that have varying inclusion criteria, outcome measures, and interventions. The RCTs in the meta-analysis by Fine et al (5) were small, had varying consideration of important prognostic variables, used different chemotherapy regimens, and had different primary outcomes. Most of these RCTs reported results for a “valid study group”—patients who received at least one cycle of chemotherapy—rather than reporting results on an intention-to-treat basis. Although Fine et al went to great lengths to overcome some of these biases, their analysis may have been biased by these and other factors. For example, the study by Chin et al (19) was a single-institution report of a multicentre RCT (11). The multicentre study was negative, but the results from Chin et al were strongly in favour of chemotherapy. Thus, this group of patients was reported twice in the meta-analysis. The meta-analysis may also have been biased by the inclusion of two studies that were not truly randomized. One trial allocated patients by date of birth (10) while another appeared to have sequentially assigned patients (15). Both of these techniques may have led to bias in the study results. These methodological concerns and the now out-of-date nature of this meta-analysis do not allow us to reach definite conclusions about the role of adjuvant chemotherapy.

Randomized Controlled Trials (prior to 1994)

Survival

Virtually all of the early RCTs suffered from methodological or analytical flaws that preclude consideration as high-quality evidence for use in our guideline development process. The four pre-treatment prognostic variables of age, performance status, degree of surgical resection, and tumour grade are key determinants of patient outcome. Various combinations of these prognostic factors had more influence upon patient survival than did treatment itself in many analyses (31). Current recommendations for the design of RCTs include stratification for

these important variables (2). Only seven of the early RCTs detected equal distribution of these variables across treatment arms (6,9,16,21,24,25). 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 six of the early studies (6,7,9,17,23,25). However, most excluded patients from the valid study group because of early death, chemotherapy-related toxicity, or a combination of death and loss to follow-up.

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) (2,32). 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.

Quality of Life

Global performance and job status were reported in the first RCT evaluating chemotherapy for malignant glioma in 1971, but no subsequent brain tumour therapy trial has evaluated QOL in a comprehensive fashion. Quality of life was usually not pre-defined 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, the 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 chemotherapy were well tolerated by most patients; unfortunately, many of the early RCTs excluded from the analysis patients with the most severe toxicity. Most chemotherapy regimens used in these studies were associated with acceptable myelotoxicity. Nausea and vomiting were often problematic.

Randomized Controlled Trials (1994 and after)

Survival

There have been two RCTs published since 1994. A trial published in 1994 by the EORTC compared RT alone with RT plus a radiosensitizing agent and adjuvant chemotherapy using carmustine (28). The study was designed to detect a 50% increase in median survival and stratified patients according to degree of surgical resection. When all randomized patients were considered, the median survival time was 10.8 months in the RT-alone arm and 13.2 months in the RT plus radiosensitizer plus chemotherapy arm (p=0.058). When only eligible patients were analyzed, the value reached conventional levels of statistical significance. That promising trend in improved survival could not be attributed solely to the use of adjuvant carmustine, since the experimental arm also included a radiosensitizer.

A large trial by the MRC (BR-05) appeared to overcome some of the methodological obstacles of prior work (29). The trial 1) used a contemporary chemotherapy regimen, PCV (procarbazine, CCNU [lomustine], and vincristine), for up to 12 cycles, 2) excluded oligodendroglioma and mixed oligoastrocytoma, when recognized histologically, as that chemosensitive subtype of glioma might bias results in favour of chemotherapy, 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%). No other RCT has had these features, making the study an important source of high-quality evidence upon which to base our recommendations. In BR-05, 674 patients were randomized to receive radiotherapy alone or radiotherapy plus PCV chemotherapy 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 detected no identifiable patient characteristics or other variables associated with improved survival.

Update

The RCT comparing temozolomide with radiation therapy to radiation therapy alone in 573 with glioblastoma multiforme has been reported in abstract form (NCIC CTG CE.3) (1u). Patients in the temozolomide and radiation therapy arm were treated with concomitant temozolomide and radiation therapy, and then up to six cycles of adjuvant temozolomide. After a median of two-year follow-up, 436 patients had died (76%). There was no significant difference between the treatment arms in terms of median age, extent of tumour resection, or performance status. There was a significant three-month difference in median overall survival between the temozolomide with radiation therapy arm and the radiotherapy-alone arm (15 months versus 12 months, respectively, $p<0.001$). Significant improvements in progression-free survival and two-year survival were also observed in the temozolomide and radiation therapy arm compared to the radiation therapy arm alone ($p<0.001$). The full publication of the trial is expected by the end of 2004.

Quality of Life

As with previous trials, these two studies provided no specific information about QOL but no overall impact upon general performance status was seen. The MRC trial collected patient self-reports of QOL; however, these data are unavailable at present.

Update

The CE.3 trial has not published any quality-of-life data as of yet. Grade 3/4 hematological toxicity was observed in 7% of patients during concomitant temozolomide and radiation therapy treatment and in 16% of the patients during the adjuvant temozolomide treatment. No toxicity results were reported for the patients receiving radiation therapy alone.

Guidelines Developed by Other Groups

The National Comprehensive Cancer Centre Network (NCCN) developed practice guidelines for the treatment of a wide variety of adult brain tumour types (30). These guidelines were based on expert opinion and a consensus process, but the meta-analysis by Fine et al was also cited (5). Adjuvant chemotherapy for malignant glioma is left to the practitioner's discretion: "As chemotherapy is of marginal benefit and is not curative, it may be administered as adjuvant therapy or be withheld until the time of tumour recurrence. In general BCNU is administered to patients with glioblastoma multiforme and PCV is given to patients with anaplastic astrocytoma, although the data supporting PCV over BCNU in the latter situation are meager." These guidelines, although reflective of expert opinion rather than being evidence-based, are concordant with our evidence-based recommendation.

V. INTERPRETIVE SUMMARY

High-quality evidence from a large RCT (BR-05) showed no evidence of a survival advantage in favour of treatment for adjuvant chemotherapy with PCV in patients with anaplastic astrocytoma or glioblastoma (29). However, two meta-analyses reported a survival advantage in favour of adjuvant chemotherapy (4,5).

There are criticisms regarding both the RCT and the meta-analyses. Criticisms of the BR-05 trial include the use of a somewhat less intensive PCV regimen than conventionally used

by others. The Neuro-oncology DSG felt that these treatment differences were relatively minor and were unlikely to change the implications of the study.

The most recent meta-analysis by MRC (4) included unpublished studies; studies with various study designs (including various therapy regimens); and studies that were published 20 or more years ago (8 of 12). Of the four RCTs published in the last 20 years included in the MRC meta-analysis (4), one is unpublished, two reported that chemotherapy offers no survival advantage (26,29), and one reported a survival benefit in patients treated with chemotherapy and radiotherapy compared to radiotherapy alone (p=0.044) (28). However, that trial also included a radiosensitizer in the treatment arm; thus the promising trend in improved survival could not be attributed solely to the use of chemotherapy. The RCTs included in the meta-analysis by Fine et al (5) were small, had varying consideration of important prognostic variables, used different chemotherapy regimens, and had different primary outcomes.

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 astrocytome and glioblastoma multiforme. However, the Neuro-oncology DSG felt that because temozolomide shares common mechanisms of both action and resistance with other alkylators, it is unlikely to be more effective than older regimens when used in conventional single-agent doses in the adjuvant setting. Ongoing trials using newer schedules of temozolomide, particularly protracted schedules, and in combination with radiotherapy may clarify the utility of this drug.

There may be subgroups of patients more likely to benefit from chemotherapy. However, the nature of these subgroups is unclear, and at present, chemosensitivity cannot be accurately predicted prior to therapy. Younger patients, patients with grade 3 astrocytoma, and patients with pure or mixed oligodendrogliomas that contain chromosome 1p loss (32) may be more likely to harbour chemosensitive tumours. In practice, adjuvant chemotherapy is reasonable to consider for these patients; however, a definite survival advantage is unproven and, if one exists, may be small. In addition, the impact of treatment-related adverse effects upon quality of life 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.

Update

The NCIC CTG CE.3 trial comparing temozolomide and radiation therapy to radiation therapy alone in patients with glioblastoma multiforme is the first of its kind (1u). The trial reports a significant median survival difference of three months between the temozolomide and radiation therapy arm and the radiation therapy alone arm (15 months versus 12 months, respectively). The data from that trial have recently been released in abstract form, and the Neuro-oncology DSG is awaiting the full publication to review the complete results, particularly in terms of comparing toxicity and quality of life between the treatment arms (data which has not been published yet).

VI. ONGOING TRIALS

A search of the Physician Data Query (PDQ) database revealed three ongoing RCTs of interest (www.cancer.gov/search/clinical_trials, searched June 24, 2004), each designed to test the role of adjuvant chemotherapy in a specific brain tumour type. These trials reflect the increasing importance of histology-specific brain tumour studies, especially for the subgroups of patients expected to harbour chemosensitive gliomas.

Anaplastic Astrocytoma (World Health Organization [WHO] grade 3)

EORTC-26882 (J. Hildebrand, Principal Investigator) is a randomized trial of standard external beam RT compared with RT plus a radiosensitizer followed by adjuvant carmustine

(BCNU) chemotherapy for patients with newly diagnosed anaplastic astrocytoma. The study may help to answer the question of whether or not patients with grade three astrocytomas represent a subgroup of patients more likely to benefit from chemotherapy. Projected accrual is 212 patients. This trial is now closed.

Radiation Therapy Oncology Group (RTOG)-9813 (S. Chang, Principal Investigator) is a randomized trial of radiotherapy combined with temozolomide versus carmustine in patients with anaplastic astrocytoma or mixed gliomas. Projected accrual is 454 patients.

Anaplastic Oligodendroglioma

EORTC-26951 (M.J. van Den Bent, Principal Investigator) is a randomized trial comparing external beam RT with RT plus adjuvant PCV chemotherapy for patients with newly diagnosed pure or mixed anaplastic oligodendroglioma. Patients randomized to the arm containing RT alone are encouraged to receive PCV at relapse. Two hundred ninety-two patients will be entered. This trial will help to elucidate the optimal timing of PCV chemotherapy for this relatively uncommon, chemosensitive, malignant glioma. This trial is now closed.

V. DISEASE SITE GROUP CONSENSUS PROCESS

Members of the Neuro-oncology DSG agreed that, based upon the current evidence, it was reasonable not to recommend the routine use of adjuvant chemotherapy for patients with malignant glioma. Extensive consideration was given to the pre-treatment factors that might predict a higher chance of treatment response; nevertheless, even in patients with a predictably high probability of response to chemotherapy, there are no data from RCTs to confirm a survival advantage from adjuvant chemotherapy. In addition, the dilemma of expected survival gain versus treatment toxicity and impact upon quality of life remains unexplored. Ongoing RCTs will help to clarify the optimal timing of PCV chemotherapy for the most chemosensitive group of patients, those with anaplastic oligodendroglioma. Newer schedules and new chemotherapy agents, such as temozolomide, are also promising. Some astrocytic malignant gliomas are chemosensitive (a minority) but which ones, or why, is not yet clear (1). At present, allowing individualized consideration of adjuvant chemotherapy for patients with anaplastic oligodendroglioma, anaplastic astrocytoma and young patients with any type of malignant glioma is a reasonable option. Implicit in the designation of chemotherapy 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 chemotherapy. Participation in ongoing clinical trials should be encouraged.

Update

In light of the new evidence from the NCIC CTG CE.3 trial (1u), the Neuro-oncology DSG decided to revise its original recommendation not to recommend the routine use of adjuvant chemotherapy.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Neuro-oncology DSG drafted the following recommendations:

Target Population

These recommendations apply to adults with newly diagnosed malignant glioma who have undergone surgery and external beam radiotherapy.

Draft Recommendations

- The routine use of current adjuvant chemotherapy regimens for patients with malignant glioma is not recommended.

- Adjuvant chemotherapy is an option for selected patients who are most likely to harbour chemosensitive tumours. Examples include young patients, patients with anaplastic (grade 3) astrocytoma and patients with pure or mixed anaplastic oligodendroglioma. These patients may be offered adjuvant chemotherapy although there is no evidence of a survival advantage and treatment-related adverse effects and their impact upon quality of life are poorly studied.
- Patients should be provided with information about the controversies surrounding the benefit and optimal timing of such treatment.
- Planned and ongoing therapeutic and clinical-molecular correlative studies may clarify the role of chemotherapy in the subgroups of patients most likely to benefit from treatment. Participation in these trials is encouraged.

Practitioner Feedback

Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 67 practitioners in Ontario (13 medical oncologists, 15 radiation oncologists, 22 surgeons, 15 neurologists, one hematologist, and one pathologist). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Neuro-oncology DSG has reviewed the results of the survey.

Results

Key results of the practitioner feedback survey are summarized in Table 2. Forty-three (64%) surveys were returned. Of this sample, 32 (74%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey. Of this latter sample, 81% agreed that the document should be approved as a practice guideline, and 94% agreed that they would use it in their own clinical practice. Seventeen (53%) respondents provided written comments. The majority of the written comments were positive and reinforced the completeness of the data considered. Most reviewers felt that the recommendations reflected their own clinical practice and that they would be helpful in practice. One reviewer, who disagreed with approval of the recommendations, felt that it was a “lucid and useful” document. One reviewer commented that the recommendations will “make chemotherapy easier to refuse”. Two reviewers asked for clarification of the specific definition of the term “young patients”.

Summary of Main Findings

The great majority of reviewers supported the recommendations in this guideline, felt that the review was comprehensive and balanced, and recommended the approval of the report as a guideline. Outlying opinions were uncommon; one reviewer, who indicated that the document was “useful”, rejected the notion of approval, leading us to suspect an error in the interpretation of the question. One reviewer appeared not to appreciate that this document applied only to chemotherapy in the adjuvant setting.

Table 2. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	30 (94%)	2 (6%)	0
There is a need for a clinical practice guideline on this topic.	28 (88%)	2 (6%)	2 (6%)
The literature search is relevant and complete.	28 (88%)	3 (9%)	1 (3%)
The results of the trials described in the report are interpreted according to my understanding of the data.	29 (91%)	3 (9%)	0
The draft recommendations in this report are clear.	29 (91%)	3 (9%)	0
I agree with the draft recommendations as stated.	29 (91%)	3 (9%)	0
This report should be approved as a practice guideline.	26 (81%)	3 (9%)	2 (6%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	30 (94%)	2 (6%)	0

* Percentages may not add up to 100% due to missing data.

Modifications/Actions

The DSG discussed the practitioner feedback survey results. The second bullet of the draft recommendations, a statement concerning types of patients for whom adjuvant chemotherapy may be an option, was reworded to add clarity. It was not felt that the evidence could support a strict definition of the term "young age". A qualifying statement, indicating that this document pertains only to chemotherapy in the adjuvant setting, was added. Separate consideration of the various subtypes of malignant glioma could not be given at present. Distinguishing between oligodendroglioma and mixed gliomas is difficult and was not done in most of the trials,. The clarification of those special groups of patients will await clinical-molecular correlative studies as indicated in the amended Future Research statement.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All 11 members of the PGCC returned ballots. Ten PGCC members approved the practice guideline report as written, with two members providing suggestions for consideration by the DSG. One member conditionally approved the guideline, provided that the Neuro-oncology DSG include a firmer statement regarding the reliability of the recent BR-05 RCT (29) as the most compelling source of evidence.

Modifications/Actions

The Neuro-oncology DSG revised the Interpretative Summary to reflect the importance of BR-05 (29) as the most compelling source of evidence.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Neuro-oncology DSG.

Target Population

These recommendations apply to adults with newly diagnosed malignant glioma who have undergone surgery and external beam radiotherapy.

Recommendations

- **Update**
  The use of concurrent temozolomide during radiation therapy and postradiation adjuvant temozolomide is recommended for all patients with newly diagnosed glioblastoma multiforme who are fit for radical therapy. Temozolomide should be considered in patients with malignant gliomas.
- Younger patients, patients with anaplastic (grade 3) astrocytoma, and patients with pure or mixed oligodendroglioma, are more likely to harbour chemosensitive tumours, and adjuvant chemotherapy may be an option in these cases. However, there is no evidence of a survival advantage from adjuvant chemotherapy in those patients, and treatment-related adverse effects and their impact upon quality of life are poorly studied.
- Patients should be provided with information about the controversies surrounding the benefit and optimal timing of such treatment.

Qualifying Statements

- This guideline considers chemotherapy in the adjuvant setting only and should not discourage the consideration of chemotherapy for selected patients at the time of tumour progression or in the context of clinical trials evaluating new treatment regimens at any point in the disease.
- **Update**
  The recommendation regarding the use of adjuvant temozolomide is based on abstract data from one randomized trial. There may be subgroups of patients who will benefit more or less from adjuvant temozolomide, thus the Neuro-oncology Disease Site Group will revise their recommendations as necessary as subgroup data emerges.

X. ACKNOWLEDGEMENTS

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For a complete list of the Neuro-oncology Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO Web site at Whttp://www.cancercare.on.ca/access_PEBC.htm.

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