Complete Summary

GUIDELINE TITLE

Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma: a clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

Perry J, Zuraw L, Neuro-Oncology Disease Site Group. Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma: a clinical practice guideline. Toronto (ON): Cancer Care Ontario (CCO); 2006 May 8. 23 p. (Evidence-based series; no. 9-2). [38 references]

GUIDELINE STATUS

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

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SCOPE

DISEASE/CONDITION(S)

Newly diagnosed malignant glioma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Neurology
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate whether chemotherapy should 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

Adults with newly diagnosed malignant glioma who have undergone surgery and external beam radiotherapy

INTERVENTIONS AND PRACTICES CONSIDERED

Chemotherapy using temozolomide, either concurrent with radiation therapy or as post-radiation adjuvant therapy

Chemotherapy regimens that were considered but not recommended include bleomycin, cisplatin, 5-fluorouracil, nitrosourea, lomustine (CCNU), carmustine (BCNU), dibromodulcitol (DBD), methyl-CCNU, dianhydrogalactitol (DHG), dacarbazine (DTIC), procarbazine, lomustine, vincristine (PCV), epipodophyllotoxin (VM-26), and nimustine (ACNU)

MAJOR OUTCOMES CONSIDERED

- Overall survival
- Adverse effects
- Health status
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

MEDLINE (1966 to October 2005), EMBASE (through week 44, 2005), CANCERLIT (1983 to October 2002), and the Cochrane Library (2005, Issue 4) 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 proceedings of the 1997 to 2004 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.

Inclusion Criteria

1. All randomized controlled trials (RCTs) of adjuvant chemotherapy for malignant glioma were included. Trials could be of single- or multi-agent regimens, but these regimens had to be compared with a no-chemotherapy control arm. The Neuro-oncology Disease Site Group members 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; these studies were included 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 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-chemotherapy control arm.
3. Studies of non-systemic treatments, such as the intracavitary placement of carmustine wafers, were also excluded.

NUMBER OF SOURCE DOCUMENTS

Two published meta-analyses and 26 randomized controlled trials were identified and included.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The guideline developers considered performing their own meta-analysis of all relevant randomized controlled trials (RCTs). However, they 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.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

This evidence-based series was developed by the Neuro-oncology of Cancer Care Ontario's (CCO's) Program in Evidence-Based Care (PEBC). The series 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 review, evidence synthesis, and input from practitioners in Ontario.

Members of the Neuro-oncology Disease Site Group (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 randomized controlled trials (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 randomized controlled trials will help to clarify the optimal timing of procarbazine, lomustine, vincristine (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. 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.

In light of the new evidence from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) CE.3 trial, the Neuro-Oncology DSG decided to revise its original recommendation which did not recommend the routine use of adjuvant chemotherapy.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External Review

Following review and discussion of sections 1 and 2 of the original guideline document, the Neuro-oncology Disease Site Group (DSG) circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback.

Practitioner feedback was obtained in 1999 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.

Practice Guideline 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 randomized controlled trial as the most compelling source of evidence. The Neuro-oncology DSG revised the Interpretative Summary to reflect the importance of BR-05 as the most compelling source of evidence.

This report reflects the integration of the draft recommendations with feedback obtained from the external review process and new evidence emerging from the latest literature search since the development of the original report.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- The use of concurrent temozolomide during radiation therapy and post-radiation 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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by meta-analyses and randomized controlled trials (RCTs).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Twenty-four randomized 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 and were heterogeneous in terms of patient selection, treatment and method of analysis.

- One recent phase III trial 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 concurrent and adjuvant temozolomide with radiation therapy compared to those receiving radiation therapy alone ($p<0.001$). There was a 2.5 month difference in median overall survival between the treatment arms (14.6 months for patients treated with temozolomide and radiation therapy versus 12.1 months for patients treated with radiation therapy alone). A smaller phase II randomized controlled trial (RCT) reported similar results.

POTENTIAL HARMS

- Scales for toxicity assessment were commonly used in the early trials (prior to 1994). 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 randomized controlled trials excluded from the analysis patients with the most severe toxicity. Most chemotherapy regimens used in these studies were associated with acceptable myelotoxicity; however, nausea and vomiting were often problematic.
- As with previous trials, the latest three randomized trials provided no specific information about quality of life (QOL) but no overall impact upon general performance status was seen. The Medical Research Council (MRC) trial of procarbazine, lomustine, vincristine (PCV) therapy did not carry out a formal assessment of quality of life but clinical performance status and neurologic status were assessed at each follow-up point. While toxicity in general was moderate, 50% of patients required delay of at least one chemotherapy cycle, mainly due to hematologic toxicity. No grade 3 or grade 4 neurotoxicity was reported. The National Cancer Institute of Canada (NCIC) trial of concurrent and adjuvant temozolomide administered quality of life questionnaires to patients but this data has not yet been published. Grade 3/4 hematological toxicity was observed in 7% of patients during concomitant temozolomide and radiation therapy treatment, and in 14% of the patients during the adjuvant temozolomide treatment. No grade 3/4 hematologic toxicity was reported for the patients receiving radiation therapy 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. reported that the main side effect of temozolomide with radiotherapy was reversible myelosuppression. Late side effects have not yet been assessed.

QUALIFYING STATEMENTS

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.
- The recommendation regarding the use of concurrent and adjuvant temozolomide is based on data from two randomized trials. There may be subgroups of patients who will benefit more or less from temozolomide, thus the Neuro-oncology Disease Site Group will revise their recommendations as necessary as subgroup data emerges. Data from a companion study to one of the randomized controlled trials (RCTs) suggest that patients with O^6-methylguanine–DNA methyltransferase (MGMT) gene promoter methylation had a greater benefit from temozolomide than patients without a methylated MGMT promoter.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Mar 10 (revised 2006 May 8)

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Neuro-oncology Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Neuro-oncology Cancer Disease Site Group (DSG) involved in the development of this systematic review were polled for potential conflicts of interest.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma: a clinical practice guideline summary. Toronto (ON): Cancer Care Ontario (CCO), 2006 May 8. Various p. (Practice guideline; no. 9-2). Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- 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.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on June 30, 2004. The information was verified by the guideline developer on July 19, 2004. This NGC summary was updated by ECRI on August 16, 2006. The updated information was verified by the guideline developer on August 23, 2006.

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