Ontario
Cancer Care Ontario
Action Cancer Ontario

Evidence-based Series 9-2 EDUCATION AND INFORMATION 2013

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

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

J. Perry, N. Laperriere, L. Zuraw, A. Chambers, K. Spithoff, G. Cairncross, and members of the Neuro-oncology Disease Site Group

Report Date: November 1, 2006

An assessment conducted in November 2013 put Evidence-based Series (EBS) 9-2 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

EBS 9-2 consists of:

Section 1: Clinical Practice Guideline
Section 2: Systematic Review
Section 3: Guideline Development and External Review

and is available on the CCO website (http://www.cancercare.on.ca)

PEBC Neuro-Oncology DSG page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/neuro-ebs/

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

Journal Citation (Vancouver Style): Perry J, Laperriere N, Zuraw L, Chambers A, Spithoff K, Cairncross JG. Adjuvant chemotherapy for adults with malignant glioma: a systematic review. Can J Neurol Sci 2007;34:402-10.

Guideline Citation (Vancouver Style): Perry J, Laperriere N, Zuraw L, Chambers A, Spithoff K, Cairncross G, et al. Adjuvant systemic chemotherapy, following surgery and external beam radiotherapy, for adults with newly diagnosed malignant glioma. Toronto (ON): Cancer Care Ontario; 2006 Nov 1 [Education and Information Dec 2013]. Program in Evidence-based Care Evidence-based Series No.: 9-2 Education and Information 2013.

Education and Information

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-based Series 9-2: Section 1

Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma: A Clinical Practice Guideline

J. Perry, N. Laperriere, L. Zuraw, A. Chambers, K. Spithoff, G. Cairncross, and members of the Neuro-oncology Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Neuro-oncology Disease Site Group

Original Report Date: March 10, 2004
Current Report Date: November 1, 2006

Education and Information

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

- The use of concurrent temozolomide during radiotherapy 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 other malignant gliomas, although no randomized trials were identified that compared temozolomide to no adjuvant chemotherapy in these patients.
- 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.
- The combination of procarbazine, lomustine, and vincristine (PCV) is not recommended for patients with anaplastic oligodendroglioma or oligoastrocytoma.
- Patients should be provided with information about the controversies surrounding the benefit and optimal timing of adjuvant 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.
- 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 RCTs suggest that patients with MGMT gene promoter methylation had a greater benefit from temozolomide than did patients without a methylated MGMT promoter.

Key Evidence

- Twenty-six out of 28 randomized trials, and two meta-analyses incorporating some of those 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 radiotherapy or radiotherapy 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 radiotherapy compared to those receiving radiotherapy 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 radiotherapy versus 12.1 months for patients treated with radiotherapy alone). A smaller phase II randomized controlled trial reported similar results.
- Two randomized trials comparing radiotherapy plus PCV chemotherapy to radiotherapy alone in patients with newly diagnosed anaplastic oligodendroglioma and oligoastrocytoma reported no survival advantage for PCV chemotherapy. Patients receiving PCV experienced significant toxicity, particularly hematologic toxicity, in both trials.

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.

Related Guidelines

- Practice Guideline Report #9-3 Radiotherapy for Newly Diagnosed Malignant Glioma in Adults.

Education and Information

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

Copyright

This evidence-based series is copyrighted by Cancer Care Ontario; the series and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series 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 guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Contact Information

For further information about this series, please contact:

Dr. James Perry, co-Chair, Neuro-oncology Disease Site Group, Sunnybrook and Women's College Health Science Centre, Rm A-402, 2075 Bayview Avenue, Toronto, Ontario, Canada, tel: (416) 480 4766; fax: (416) 480 5054.

or

Dr. Normand Laperriere, co-Chair, Neuro-oncology Disease Site Group, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, Canada, tel: (416) 946-2127; fax: (416) 946-2038.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

Education and Information

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-based Series 9-2: Section 2

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

J. Perry, N. Laperriere, L. Zuraw, A. Chambers, K. Spithoff, G. Cairncross, and members of the Neuro-oncology Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Neuro-oncology Disease Site Group

Original Report Date: March 10, 2004
Current Report Date: November 1, 2006

For Education and Information

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?

INTRODUCTION

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 has been developed by the Neuro-oncology Disease Site Group (DSG).

Historically, the value of adjuvant chemotherapy for patients with malignant glioma was controversial, and, until recently, there was considerable practice variation in Ontario. In 2002, an informal poll of members of the Neuro-oncology DSG indicated that some institutions recommended adjuvant chemotherapy to most patients with malignant glioma, yet others tended to recommend chemotherapy only at the time of tumour recurrence, if at all.

In large part, the modest results of clinical trials of 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). Additionally,

recent results of clinical trials examining the use of temozolomide with radiotherapy in the treatment of newly diagnosed malignant glioma have been promising. 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 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 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, even though poorly studied in this disease. 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. The evidence suggesting that there may be certain patients more likely to be sensitive to treatment was also examined and incorporated into our analyses.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by members of the PEBC Neuro-oncology DSG and methodologists.

This systematic review 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. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Neuro-oncology DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1966 to August 2006), EMBASE (through week 36, 2006), CANCERLIT (1983 to October 2002), and the Cochrane Library (2006, 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 proceedings of the 1997 to 2006 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. We included all randomized controlled trials (RCTs) of adjuvant chemotherapy for malignant glioma. Trials could be of single- or multi-agent regimens, but those 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 those studies are frequently cited and were used in a subsequent published meta-analysis. In some instances, a randomized trial was

For Decision and Information

reported in more than one publication or as a single-institution experience within a larger multicentre trial; we included those 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 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.

Synthesizing the Evidence

We considered performing our own meta-analysis of all relevant RCTs. However, we felt that the heterogeneity within those 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).

RESULTS

Literature Search Results

Two published meta-analyses (4,5) and 28 randomized trials (6-33) 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). A report of a single institution experience (19) in a larger multicentre trial (11) was also included. Two RCTs compared radiotherapy with temozolomide to radiotherapy alone (30,31), three RCTs compared radiotherapy with procarbazine, lomustine, and vincristine (PCV) to radiotherapy alone (29,32,33), and 24 older trials (1994 and earlier) compared radiotherapy with other adjuvant chemotherapy to radiotherapy alone (6-28). Methodological and survival data from the 28 trials are provided in Table 1. Quality of life data from one of the RCTs (30) were published separately and were included in the review (34). The literature search also identified one consensus-based practice guideline for the treatment of a wide variety of adult brain tumours (35).

Education and Information

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)	41/41	RT RT + CCNU	15 13	6.2 8.3	NR	Patients crossed to CCNU at recurrence.
Garrett, 1978 (10)	69/74	RT RT + CCNU	35 34	8.0 13.0	34.0 52.0 (1-year survival rates)	Patients randomized by birth year.
Walker, 1978 (11)	222/303	RT RT + BCNU	93 100	8.3 8.0	1.0 5.0	Data from "valid study group" only.
EORTC, 1978 (trial 26741) (12)	81/111	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)	19/23	RT RT + CCNU	13 10	5.0 7.2*	NR	Unclear why patients were excluded from analysis.
Eagen, 1979 (13)	42/43	RT RT + DHG	20 22	8.1 15.5*	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	8.0 12.0	NR	Sequentially assigned, not randomized.
Walker, 1980 (16)	358/467	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.
Green, 1983 (20)	527/609	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)	84/91	RT RT + DBD RT + DBD + CCNU	30 26 28	9.2 13.2* 13.8*	3.3 19.0* 25.0*	Most of the excluded patients from the chemotherapy arms.

Education and Information

Table 1 Continued.

Study (Reference)	# evaluated/ # entered	Treatment Groups	N	Median Survival Time (months)	2-Year Survival Rate (%)	Comments
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)	244/280	RT RT + CCNU	118 126	8.0 – 12.0 8.0 – 12.0	NR	Median survival time not reported.
Takakura, 1986 (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	10.4 12.0	NR	--
EORTC, 1991 (27)	246/285	RT RT + CisPt	143 142	12.0 10.6	NR	--
Hildebrand, 1994 (28)	269/269	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	NR	No increase in one- or two-year survival
Stupp EORTC-NCIC CE-3, 2005 (30)	573/573	RT RT + temozolomide	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)	110/130	RT RT + temozolomide	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 RT + PCV significantly improved progression-free survival
Cairncross, 2006 (33)	289/289	RT RT + PCV	142 147	56.4 58.8	74 70	Patients had anaplastic oligodendroglioma or oligoastrocytoma RT + PCV significantly improved progression-free survival

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; GBM, glioblastoma multiforme; MeCCNU, methyl-CCNU; N, sample size; NR, not reported; PCB, procarbazine; PCV, procarbazine, lomustine, and vincristine; RT, radiotherapy; VM-26, epipodophyllotoxin.
*Statistically significant difference in favour of adjuvant chemotherapy (p<0.05).

Education and Information

Outcomes

Survival

Randomized Trials

Virtually all of the early randomized trials suffered from methodological or analytical flaws that preclude consideration as high-quality evidence for use in our guideline development process. (See Table 1 for trial details and results). 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 (36). Current recommendations for the design of RCTs include stratification for these important variables (2). Only eight of the early trials detected equal distribution of these variables across treatment arms (6,9,16,21,24,25,28). Up to 30% of patients in many of these studies had indeterminate histology (grade 3 versus grade 4 versus oligodendroglioma). An intention-to-treat analysis was performed in only seven of the early trials (6,7,9,17,23,25,28). 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. In one trial (28), an observed trend in improved survival could not be attributed solely to the used of adjuvant chemotherapy since the experimental arm also included a radiosensitizer.

Most of the early randomized trials 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) (2,37). Only three of the early trials 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 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) had 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 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.

Two more recent RCTs by van den Bent et al (32) and Cairncross et al (33) compared radiotherapy plus PCV chemotherapy to radiotherapy alone in patients with newly diagnosed anaplastic oligodendroglioma and oligoastrocytoma. Patients in both trials who were randomized to the treatment arm containing radiotherapy alone were encouraged to receive PCV at disease progression. One RCT administered six cycles of PCV starting within six weeks after radiotherapy (32), and one RCT administered up to four cycles of intensive PCV every six weeks before radiotherapy (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 radiotherapy arm and 40.3 months in the radiotherapy plus PCV arm (hazard ratio [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 radiotherapy arm and 58.8 months in the radiotherapy plus PCV arm (HR 0.90; 95% CI, 0.66 to 1.24; p=0.26). Both RCTs reported a significant benefit for radiotherapy plus PCV in progression-free survival. Van den Bent et al

For consultation purposes only

(32) reported a median progression-free survival of 13.2 months in the radiotherapy arm and 23.0 months in the radiotherapy 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 radiotherapy arm and 31.2 months in the radiotherapy 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 in the radiotherapy alone arm received chemotherapy at disease progression. Similarly, 80% of patients in the radiotherapy alone arm of the Cairncross RCT received salvage chemotherapy (33).

A phase III RCT by the National Cancer Institute of Canada (NCIC) -Clinical Trials Group and the European Organization for Research and Treatment of Cancer (EORTC) has shown the most promise of all adjuvant chemotherapy trials for newly diagnosed malignant glioma to date (EORTC-NCIC CE-3) (30). This trial compared temozolomide with radiotherapy to radiotherapy alone in 573 patients with glioblastoma multiforme (GBM). Patients in the temozolomide and radiotherapy arm were treated with concomitant temozolomide and radiotherapy, 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 HR for death in the temozolomide group was 0.63 (95% CI, 0.52 to 0.75; log-rank p<0.001) compared with the radiotherapy alone group. There was a 2.5 month difference in median overall survival between the temozolomide with radiotherapy arm and the radiotherapy alone arm (14.6 months versus 12.1 months, respectively). Significant improvements in progression-free survival (log-rank p<0.001) and two-year survival were also observed in the temozolomide and radiotherapy arm compared to the radiotherapy arm alone. A similar randomized phase II trial of 130 patients with glioblastoma multiforme by Athanassiou et al. also demonstrated a statistically significant benefit in median and overall 1-year survival for radiotherapy plus concurrent and adjuvant temozolomide compared to radiotherapy alone (31).

Meta-analyses

The MRC-UK conducted a meta-analysis in 2002 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. Only trials with proper randomization 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 was included to avoid publication bias, but ensuring the quality of unpublished data is difficult. However, the authors stated that “all data were thoroughly checked for consistency, plausibility, and integrity of randomisation and follow-up” (4).

The results of the MRC meta-analysis detected a significant overall survival benefit favouring chemotherapy and radiotherapy over radiotherapy alone (HR 0.85; 95% CI, 0.78 to 0.91; p<0.0001) (4). 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 studies) 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 0.91; p<0.0001). The effect of chemotherapy was not related to age, sex, histology, performance status, or extent of resection.

The other meta-analysis by Fine et al. (5), published in 1993, pooled survival data of more than 3000 patients from 16 randomized trials comparing RT with RT plus adjuvant chemotherapy of some type (8,10,11,13-22,24-26). One included 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 also included two studies that were not

for education and information

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 study. 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).

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 16 studies in the Fine et al. meta-analysis (5) were published more than 20 years ago. 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 randomized trials in these meta-analyses were small, had varying consideration of important prognostic variables, used different chemotherapy regimens, and had different primary outcomes. Many of these studies 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. 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

Global performance and job status were reported in the first randomized trial evaluating chemotherapy for malignant glioma in 1971 (6), but few subsequent brain tumour therapy trials have evaluated QOL in a comprehensive fashion. QOL was usually not pre-defined as an endpoint of interest in the early trials. Karnofsky performance status (KPS), an eligibility criterion for many studies 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; however, nausea and vomiting were often problematic.

As with previous trials, four of the latest five randomized trials (29,31-33) provided no specific information about QOL; however, 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 chemotherapy cycle, mainly due to hematologic toxicity. No grade 3 or grade 4 neurotoxicity was reported. The two RCTs comparing radiotherapy alone to radiotherapy plus PCV chemotherapy (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, and only 37% of patients completed at least five out of six cycles of PCV. In the RCT by Cairncross et al (33), 65% of patients had grade 3/4 toxicity: 56% of patients had grade 3/4 hematologic toxicity, 13% had grade 3/4 neurologic toxicity, and 9% had grade 3/4 gastrointestinal 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. No grade 3/4 hematologic toxicity was reported for the

Education and Information

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 using the EORTC core-30 questionnaire (QLQ-C30, version 3) and the EORTC brain cancer module questionnaire (QLQ-BN20), administered 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.

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 in 1997 (35). Those 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 meagre." Those guidelines are reflective of expert opinion rather than being evidence-based and do not reflect the latest results of trials for newer chemotherapy regimens such as temozolomide.

DISCUSSION

Temozolomide, a new, well-tolerated, oral alkylating agent, has recently 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 radiotherapy to radiotherapy alone in patients with glioblastoma multiforme was the first of its kind (30). The trial reported a significant median survival difference of 2.5 months between the temozolomide and radiotherapy arm and the radiotherapy alone arm (14.6 months versus 12.1 months, respectively). Data comparing QOL between the treatment arms indicate no substantial negative effect of temozolomide on health-related QOL (34). The results of a smaller trial by Athanassiou et al. (31) demonstrated a similar survival benefit.

Evidence from a large RCT (BR-05) detected no evidence of a survival advantage in favour of treatment for adjuvant chemotherapy with PCV in patients with anaplastic astrocytoma or glioblastoma (29). That finding is concordant with many early RCTs, most of which were of lower quality, and a meta-analysis that pooled results from 16 of 24 studies included in this

For Education and Information

systematic review. 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 those treatment differences were relatively minor and were unlikely to change the implications of the study. However, although the largest RCT to date, the power of the study is 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 studies 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 radiotherapy-alone arms of both trials received PCV or other chemotherapy at disease progression, it could be argued that these RCTs compared early PCV to delayed chemotherapy at progression rather than radiotherapy plus PCV to radiotherapy 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 chemotherapy than 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 tumours with co-deletion of 1p and 19q live longer regardless of treatment and have a greater response to chemotherapy. 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 in a post hoc analysis that progression-free survival in the PCV arm was only significantly increased in the subset of patients with 1p and 19q loss. These results indicate that tumours with co-deletion of 1p and 19q are biologically and clinically distinct and should be studied separately in future RCTs (32,33).

A study conducted along side the EORTC-NCIC CE-3 trial (30) examined the association between methylation of the MGMT gene and response to treatment with temozolomide (38). 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 (log-rank $p<0.001$). The overall survival benefit for temozolomide compared to radiotherapy 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 radiotherapy 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 radiotherapy alone group. 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 chemotherapy. However, the nature of those 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 (37) may be more likely to harbour chemosensitive tumours. In practice, it is reasonable to consider adjuvant chemotherapy for those patients; however, it must be recognized that a definite survival advantage is unproven and, if it exists, may be small. In addition, the impact of treatment-related adverse effects upon quality of life has been poorly studied and, given the

Education and Information

small expected benefit of therapy, those toxicity issues might 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. These trials reflect the increasing importance of histology-specific brain tumour studies, especially for the subgroups of patients expected to harbour chemosensitive gliomas.

ONGOING TRIALS

A search of the National Cancer Institute (NCI) clinical trials database (www.cancer.gov/search/clinical_trials) on September 14, 2006 revealed one ongoing RCT of interest:

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 was 212 patients. This trial is now closed.

CONCLUSIONS

Based upon the current evidence, the use of concurrent temozolomide during radiotherapy 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. 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 chemotherapy for patients with pure or mixed oligodendroglioma, anaplastic (grade 3) astrocytoma and young patients with any type of malignant glioma. Implicit in the designation of chemotherapy as an "option" for those patient groups is the recommendation that patients are provided with information about the controversies surrounding the benefit and optimal timing of such chemotherapy. Participation in ongoing clinical trials should be encouraged.

CONFLICT OF INTEREST

Members of the Neuro-oncology Disease Site Group involved in the development of this systematic review were polled for potential conflicts of interest. Two authors (NL, GC) reported that they have received consultancy fees or honoraria from Schering Plough.

JOURNAL REFERENCE

The systematic review has been published in the peer-reviewed journal *The Canadian Journal of Neurological Sciences* (http://www.cjns.org/):

- Perry J, Laperriere N, Zuraw L, Chambers A, Spithoff K, Cairncross JG. Adjuvant chemotherapy for adults with malignant glioma: a systematic review. Can J Neurol Sci 2007;34:402-10.

ACKNOWLEDGEMENTS

The Neuro-oncology Disease Site Group would like to thank Dr. James Perry, Ms Lisa Zuraw, Ms Alexandra Chambers, and Ms Karen Spithoff for taking the lead in drafting, revising and updating this systematic review.

Education and Information

For a complete list of the Neuro-oncology Disease Site Group members and the Report Approval Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

Copyright

This evidence-based series is copyrighted by Cancer Care Ontario; the series and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series 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 guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Contact Information

For further information about this series, please contact **Dr. James Perry**, Chair, Neuro-oncology Disease Site Group, Sunnybrook and Women's College Health Science Centre, Rm A-402, 2075 Bayview Avenue, Toronto, Ontario, Canada,
Phone: (416) 480 4766; Fax: (416) 480-5054.
or
Dr. Normand Laperriere, co-Chair, Neuro-oncology Disease Site Group, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, Canada,
Phone: (416) 946-2127; Fax: (416) 946-2038

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

Education and Information

REFERENCES

1. Mason W, Louis DN, Cairncross JG. Chemosensitive gliomas in adults: which ones and why? *J Clin Oncol* 1997;15:3423-6.
2. Perry JR, DeAngelis LM, Schold SC, Jr., Burger PC, Brem H, Brown MT, et al. Challenges in the design and conduct of phase III brain tumor therapy trials. *Neurol* 1997;49:912-7.
3. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.
4. Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002;359:1011-8.
5. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP. Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. *Cancer* 1993;71:2585-97.
6. Edland RW, Javid M, Ansfield FJ. Glioblastoma multiforme. An analysis of the results of postoperative radiotherapy alone versus radiotherapy and concomitant 5-fluorouracil. (A prospective randomized study of 32 cases). *Am J Roentgenol Radium Therapy Nuclear Med* 1971;111:337-42.
7. Brisman R, Housepian EM, Chang C, Duffy P, Balis E. Adjuvant nitrosourea therapy for glioblastoma. *Arch Neurol* 1976;33:745-50.
8. Reagan TJ, Bisel HF, Childs DS, Jr., Layton DD, Rhoton AL, Jr., Taylor WF. Controlled study of CCNU and radiation therapy in malignant astrocytoma. *J Neurosurg* 1976;44:186-90.
9. Weir B, Band P, Urtasun R, Blain G, McLean D, Wilson F. Radiotherapy and CCNU in the treatment of high-grade supratentorial astrocytomas [abstract]. *J Neurosurg* 1976;45:129-34.
10. Garrett MJ, Hughes HJ, Freedman LS. A comparison of radiotherapy alone with radiotherapy and CCNU in cerebral glioma. *Clin Oncol* 1978;4:71-6.
11. Walker MD, Alexander E Jr, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *Journal of Neurosurgery* 1978;49:333-43.
12. Effect of CCNU on survival rate of objective remission and duration of free interval in patients with malignant brain glioma--final evaluation. E.O.R.T.C. Brain Tumor Group. *Eur J Cancer* 1978;14:851-6.
13. Eagan RT, Childs DS, Jr., Layton DD, Jr., Laws ER, Jr., Bisel HF, Holbrook MA, et al. Dianhydrogalactitol and radiation therapy. Treatment of supratentorial glioma. *J Am Med Assoc* 1979;241:2046-50.
14. Solero CL, Monfardini S, Brambilla C, Vaghi A, Valagussa P, Morello G, et al. Controlled study with BCNU vs. CCNU as adjuvant chemotherapy following surgery plus radiotherapy for glioblastoma multiforme. *Cancer Clin Trial* 1979;2:43-8.
15. Cianfriglia F, Pompili A, Riccio A, Grassi A. CCNU-chemotherapy of hemispheric supratentorial glioblastoma multiforme. *Cancer* 1980;45:1289-99.
16. Walker MD, Green SB, Byar DP, Alexander E Jr, Batzdorf U, Brooks WH, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med* 1980;303:1323-9.
17. Evaluation of CCNU, VM-26 plus CCNU, and procarbazine in supratentorial brain gliomas. Final evaluation of a randomized study. European Organization for Research on Treatment of Cancer (EORTC) Brain Tumor Group. *J Neurosurg* 1981;55:27-31.
18. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R, et al. Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of

For Information and Information

postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. *Cancer* 1981;47:649-52.
19. Chin HW, Young AB, Maruyama Y. Survival response of malignant gliomas to radiotherapy with or without BCNU or methyl-CCNU chemotherapy at the University of Kentucky Medical Center. *Cancer Treat Report* 1981;65:45-51.
20. Green SB, Byar DP, Walker MD, Pistenmaa DA, Alexander E Jr, Batzdorf U, et al. Comparisons of carmustine, procarbazine, and high-dose methylprednisolone as additions to surgery and radiotherapy for the treatment of malignant glioma. *Cancer Treatment Reports* 1983;67:121-32.
21. Afra D, Kocsis B, Dobay J, Eckhardt S. Combined radiotherapy and chemotherapy with dibromodulcitol and CCNU in the postoperative treatment of malignant gliomas. *J Neurosurg* 1983;59:106-10.
22. Ushio Y, Hayakawa T, Hasegawa H, Yamada K, Arita N. Chemotherapy of malignant gliomas. *Neurosurg Rev* 1984;7:3-12.
23. Hatlevoll R, Lindegaard KF, Hagen S, Kristiansen K, Nesbakken R, Torvik A, et al. Combined modality treatment of operated astrocytomas grade 3 and 4. A prospective and randomized study of misonidazole and radiotherapy with two different radiation schedules and subsequent CCNU chemotherapy. Stage II of a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. *Cancer* 1985;56:41-7.
24. Takakura K, Abe H, Tanaka R, Kitamura K, Miwa T, Takeuchi K, et al. Effects of ACNU and radiotherapy on malignant glioma. *J Neurosurg* 1986;64:53-7.
25. Nelson DF, Diener-West M, Horton J, Chang CH, Schoenfeld D, Nelson JS. Combined modality approach to treatment of malignant gliomas--re-evaluation of RTOG 7401/ECOG 1374 with long-term follow-up: a joint study of the Radiation Therapy Oncology Group and the Eastern Cooperative Oncology Group. *Natl Cancer Inst Monogr* 1988;279-84.
26. Trojanowski T, Peszynski J, Turowski K, Kaminski S, GoScinski I, Reinfus M, et al. Postoperative radiotherapy and radiotherapy combined with CCNU chemotherapy for treatment of brain gliomas. *J NeuroOncol* 1988;6:285-91.
27. Cisplatin does not enhance the effect of radiation therapy in malignant gliomas. EORTC Brain Tumor Group. *Eur J Cancer* 1991;27:568-71.
28. Hildebrand J, Sahmoud T, Mignolet F, Brucher JM, Afra D. Adjuvant therapy with dibromodulcitol and BCNU increases survival of adults with malignant gliomas. EORTC Brain Tumor Group. *Neurol* 1994;44:1479-83.
29. Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. *J Clin Oncol* 2001;19:509-18.
30. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Eng J Med* 2005; 352:987-96.
31. Athanassiou H, Synodinou M, Maragoudakis E, Paraskevaidis M, Verigos C, Misailidou D, et al. Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme. *J Clin Oncol*. 2005;23:2372-7.
32. van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJB, Bernsen HJJA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol* 2006;24:2715-22.
33. Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and

For Evaluation and Information

mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol* 2006;24:2707-14.
34. Taphoorn MJB, Stupp R, Coens C, Osoba D, Kortmann R, van den Bent MJ, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. *Lancet Oncol* 2005;6:937-44.
35. NCCN adult brain tumor practice guidelines. *Oncol* 1997;11:237-77.
36. Curran WJ, Jr., Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al. Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. *J Natl Cancer Inst* 1993;85:704-10.
37. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 1998;90:1473-9.
38. Hegi ME, Diserens A, Gorlia T, Hamou M, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Eng J Med* 2005;352:997-1003.

Education and Information

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-based Series 9-2: Section 3

Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma: Guideline Development and External Review - Methods and Results

J. Perry, N. Laperriere, L. Zuraw, A. Chambers, K. Spithoff, G. Cairncross, and members of the Neuro-oncology Disease Site Group

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Neuro-oncology Disease Site Group

Original Report Date: March 10, 2004
Current Report Date: November 1, 2006

Education and Information

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series:
Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Neuro-oncology DSG of CCO's 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 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 (3). 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 EORTC-NCIC CE-3 trial, the Neuro-oncology DSG decided to revise its original recommendation which did not recommend the routine use of adjuvant chemotherapy.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series, the Neuro-oncology circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

Education and Information

BOX 1: DRAFT RECOMMENDATIONS (approved for external review September 1999)
Target Population These recommendations apply to adults with newly diagnosed malignant glioma who have undergone surgery and external beam radiotherapy.
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.

Methods

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 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."

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.

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.

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.

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 (4) as the most compelling source of evidence.

Modifications/Actions

The Neuro-oncology DSG revised the Interpretative Summary to reflect the importance of BR-05 (4) as the most compelling source of evidence.

ONGOING DEVELOPMENT AND MAINTENANCE

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. PEBC reports are reviewed within five years of completion and updated reports will be posted on the CCO Web site at: www.cancercare.on.ca.

For a complete list of the Neuro-oncology Disease Site Group members and the Report Approval Panel members, please visit the CCO Web site at http://www.cancercare.on.ca/

Education and Information

Funding

The PEBC is supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from its funding agencies.

Copyright

This evidence-based series is copyrighted by Cancer Care Ontario; the series and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the evidence-based series 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 guarantees of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

Contact Information

For further information about this series, please contact **Dr. James Perry**, Chair, Neuro-oncology Disease Site Group, Sunnybrook and Women's College Health Science Centre, Rm A-402, 2075 Bayview Avenue, Toronto, Ontario, Canada,
Phone: (416) 480 4766; Fax: (416) 480-5054.
or
Dr. Normand Laperriere, co-Chair, Neuro-oncology Disease Site Group, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, Canada,
Phone: (416) 946-2127; Fax: (416) 946-2038

For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

Education and Information

REFERENCES

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;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. *J Clin Oncol* 1998;16(3):1226-31.
3. Mason W, Louis DN, Cairncross JG. Chemosensitive gliomas in adults: which ones and why? *J Clin Oncol* 1997;15:3423-6.
4. Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. *J Clin Oncol* 2001;19:509-18.

Education and Information