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Evidence-based Series 9-7 EDUCATION AND INFORMATION 2013

Gliadel® Wafers in the Treatment of Malignant Glioma

J Perry, A Chambers, K Spithoff, N Laperriere,
and 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

Report Date: August 15, 2006

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Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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Evidence-based Series 9-7: Section 1

Gliadel® Wafers in the Treatment of Malignant Glioma: A Clinical Practice Guideline

J Perry, A Chambers, K Spithoff, N Laperriere,
and the Neuro-Oncology Disease Site Group

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Report Date: August 15, 2006

Question

What is the safety and efficacy of Gliadel® (interstitial chemotherapy with carmustine-loaded polymers) in the treatment of newly diagnosed or recurrent malignant glioma (i.e., glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma)? The outcomes of interest for this guideline are overall survival, adverse effects, and quality of life.

Target Population

The recommendations apply to adult patients undergoing surgery for newly diagnosed or recurrent malignant glioma.

Recommendations

- Gliadel®, followed by standard radiotherapy, is an option for selected patients with newly diagnosed malignant glioma where a near-gross total excision is possible; however, the majority of patients with malignant glioma will not be eligible for various reasons (ie. non-resectable tumours or contact with the ventricular system).
- The current standard of care for patients with newly diagnosed glioblastoma multiforme is radiotherapy with concurrent and adjuvant temozolomide. No evidence is currently available to support the sequential combination of Gliadel® with temozolomide; however, the DSG does not feel that the placement of Gliadel® should preclude the administration of systemic therapy. Decisions to use Gliadel® with subsequent temozolomide should be made on an individual patient basis, recognizing that there is little clinical experience with such combined treatment, and patients should be made aware of the possibility of increased toxicity. When new evidence becomes available, the DSG will revise these recommendations as necessary.
- Gliadel® is an option in patients with surgically resectable recurrent malignant gliomas.

Qualifying Statements

- The patient population (based on age, histology, performance status, etc.) that would benefit from Gliadel® is unclear and needs to be further investigated.
- There is no evidence available comparing the efficacy of Gliadel® to systemic chemotherapy, therefore no comment can be made regarding the relative efficacy of Gliadel® compared to alternative treatment options. For recommendations of adjuvant systemic chemotherapy for newly diagnosed malignant glioma, refer to Evidence-based Series #9-2.

Evidence

Newly Diagnosed Malignant Glioma

- One RCT of newly diagnosed malignant glioma reported a significant improvement in median overall survival in patients who received Gliadel® compared to those who received the placebo (13.8 months in the Gliadel® arm versus [vs.] 11.6 months in the placebo arm, p=0.017). The estimated mortality hazard ratio for Gliadel® compared to control was 0.73 (95% confidence interval 0.56-0.95, p=0.018), representing a 27% decrease in risk of death over the course of the study for patients who received Gliadel®. There was no statistically significant difference in one-year overall survival or progression-free survival between the two treatment arms.
- Another RCT was limited to only 32 patients newly diagnosed with malignant glioma, because halfway through the trial the researchers were unable to obtain Gliadel®.

Recurrent Malignant Glioma

- One RCT compared Gliadel® to placebo in patients with recurrent malignant glioma. Median survival was 7.2 months in the Gliadel® arm compared to 5.3 in the placebo arm; however, six month overall survival was not significantly different (60% in the Gliadel® arm and 47% in the placebo arm, p=0.061).
- A cohort study reported a survival benefit in favour of patients who did not receive Gliadel®; however, this study was affected by selection bias and used a retrospectively-identified control cohort.

- All of the studies reported similar adverse effects in the treatment and control arms. The most common adverse effects associated with Gliadel® were hemiplegia, convulsions, confusion, and brain edema. The most commonly reported adverse effects among patients receiving the placebo were convulsions, confusion, brain edema, and aphasia. The largest RCT of 240 patients reported a greater occurrence of intracranial hypertension in patients who received Gliadel® compared to those who received placebo (9.2% vs. 1.7%, p=0.019).

Alternative Treatments

Newly Diagnosed Malignant Glioma
• Concurrent and adjuvant temozolomide
Recurrent Malignant Glioma
• Surgical resection
• Systemic chemotherapy

Related Guidelines

- Evidence-based Series #9-2 *Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma.*

Future Research

- A direct comparison between Gliadel® and systemic chemotherapy has not been undertaken and would be helpful in defining the role of this local therapy in comparison to a systemic therapy. The comparison of outcomes including toxicity, quality of life, and survival would be useful.
- Clinical trials investigating Gliadel® in combination with other drugs would also be useful.

Funding

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Evidence-based Series #9-7

Gliadel® Wafers in the Treatment of Malignant Glioma: A Systematic Review

J Perry, A Chambers, K Spithoff, N Laperriere,
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QUESTION

What is the safety and efficacy of Gliadel® in the treatment of newly diagnosed or recurrent malignant glioma (i.e. glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligoastrocytoma, and anaplastic oligodendroglioma)?

The outcomes of interest for this guideline were overall survival, adverse effects, and quality of life.

INTRODUCTION

Malignant glioma is the most common type of primary brain tumour in adults, with approximately 5 new cases per 100,000 people diagnosed each year. The current standard treatment for malignant glioma consists of surgical resection followed by radiation therapy. On recurrence, regimens of systemic chemotherapy delivered via the intravenous or oral routes are used. Median survivals remain poor despite refinement in surgical techniques and radiation therapy delivery.

Nitrosoureas, especially carmustine (BCNU), and more recently temozolomide are most frequently used in systemic chemotherapy. The use of chemotherapy in malignant gliomas is reviewed in Practice Guideline #9-2. While the use of temozolomide concurrently with radiotherapy and as adjuvant therapy has shown promising survival benefit with low toxicity, the clinical effectiveness of systemic therapy in general has been disappointing. Systemic toxicities, short half-life, and limitations in the ability to traverse the blood-brain barrier are common problems in the clinical effectiveness of systemic agents. Novel methods to treat malignant gliomas are needed and should be evaluated to assess their role in the treatment of this devastating disease.

Gliadel® wafers represent a novel approach to the delivery of chemotherapy in malignant gliomas. Recurrence of malignant glioma is often local, suggesting a role for a regional therapy. Gliadel® wafers contain carmustine and are designed to release this agent over a two to three week period. Gliadel® wafers are placed on the surface of the resected tumour beds in recurrent tumours and after initial resections. Efficacy data has been based on small trials that demonstrate marginal survival benefits in selected subgroups of patients with recurrent disease

(1-3). A larger randomized controlled trial (RCT) in newly diagnosed malignant gliomas (4) has recently become available.

The Neuro-Oncology Disease Site Group (DSG) felt that an evidence-based series was warranted in order to provide an interpretation of the available clinical trials with respect to survival advantage, adverse effects, and quality of life.

METHODS

This practice guideline was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by two members of the PGI's Neuro-Oncology DSG and methodologists. All reports are reviewed and approved by the Neuro-Oncology DSG, which comprises medical and radiation oncologists, neuro-oncologists, neurosurgeons, a neuro-radiologist, an oncology nurse, and a patient representative. Members of the Neuro-Oncology DSG disclosed potential conflict of interest information.

This practice guideline is a convenient and up-to-date source of the best available evidence on the use of Gliadel® wafers in the treatment of malignant glioma. The body of evidence in this review is primarily comprised of mature RCT data. That evidence forms the basis of a clinical practice guideline developed by the Neuro-Oncology DSG. This systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

MEDLINE (1990 to March 2006, week 3), EMBASE (1990 to 2006, week 11), CANCERLIT (1990 to October 2002), and the Cochrane Library (2006, Issue 1) were searched. The terms "glioma" (Medical subject heading [MeSH]) and "brain neoplasms" were combined with the text words "Gliadel", "carmustine" and "BCNU". In addition, the Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/clinical_trials/) and the proceedings of the 1997 to 2005 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, and the reference lists from these sources were searched for additional trials.

Study Inclusion Criteria

Articles were selected for inclusion if they:

1. Were fully published reports of RCTs comparing treatment with Gliadel® wafers to placebo or alternative treatment in patients with malignant glioma. Prospective cohort studies were also included.
2. Included results regarding the safety or efficacy (i.e., survival) of Gliadel®.

Study Exclusion Criteria

1. Letters and editorials were not considered.
2. Papers published in a language other than English were not considered.

Synthesizing the Evidence

The DSG decided not to pool the two RCTs that included patients with newly diagnosed malignant glioma (4,6) because of the methodological limitations of the smaller trial (6). Only 16 patients were included in each arm of the trial and there were imbalances in key prognostic factors such as tumour histology and performance status between treatment groups. The DSG did not believe that pooling data from the trials of newly diagnosed malignant glioma with the trial of recurrent malignant glioma (5) was reasonable due to the clinical heterogeneity between these patient groups.

RESULTS

Literature Search Results

No existing practice guidelines examining the role of Gliadel® in patients with newly diagnosed or recurrent malignant glioma were identified. In 2000, Engelhard published a review describing the role of interstitial BCNU chemotherapy in patients with malignant glioma (7). Engelhard included five studies in his review, two phase I studies (1,8), one prospective cohort study with historical controls (2), and two RCTs (5,6). Since his review, one large RCT was published evaluating the role of Gliadel® in patients with malignant glioma (4).

Three RCTs (4-6) and one prospective cohort study with historical controls (2) were eligible for inclusion in this systematic review (Table 1). A long-term follow-up study (9) for one of the RCTs (4) was also included. The RCTs compared patients treated with Gliadel® to patients treated with a placebo and were all supported by pharmaceutical funding. Two of the RCTs studied patients with newly diagnosed malignant glioma (4,6), and the other RCT (5) and the prospective study (2) investigated patients with recurrent malignant glioma. In addition to the studies comparing Gliadel® to placebo, there was one prospective phase II study identified that compared several dosages of carmustine (3). No studies that compared Gliadel® to alternative treatment were identified.

Table 1. Overview of studies included in this systematic review.

Study year (ref)	Study Design	Number of Patients (% with GBM)	Experimental/ Control	Additional Treatment	Number Undergoing Re-operation	Number Receiving CT	Median Survival	p-value	Mortality Hazard Ratio	p-value
Patients with newly diagnosed malignant glioma										
Westphal 2003 (4,9)	RCT	120 (84% GBM) 120 (88% GBM)	3.85% BCNU Placebo	EBRT (2 wks after surgery)	36 (30%)* 30 (25%)*	35 (29%)* 28 (23%)*	59.8 wks 50.3 wks	p=0.017	0.73 (95% CI 0.56-0.95)	p=0.018
Valtonen 1997 (6)	RCT	16 (69% GBM) 16 (100% GBM)	3.85% BCNU Placebo	standard RT after surgery	subsequent operations allowed	NR	58.1 wks 39.9 wks	p=0.012	0.27 (95% CI 0.11-0.68)‡	p=0.006[II]
Patients with recurrent malignant glioma										
Subach 1999 (2)	cohort-control	17 (100% GBM) 45 (100% GBM)	BCNU No treatment	100% prior RT	76% prior craniotomy 71% prior craniotomy	88% prior CT 96% prior CT	58 wks 97 wks	NR	NR	p<0.001 *in favour of control*
Brem 1995 (5)	RCT	110 (65% GBM) 112 (65% GBM)	3.85% BCNU Placebo	100% prior RT	no difference in # of prior surgeries p=0.17	52.7% prior CT 48.2% prior CT	31 wks 23 wks	NR	0.83 (95% CI 0.63-1.10) [0.67 (95% CI 0.51-0.90)] †	p=0.19 [p=0.006] †

Note: BCNU, carmustine; CI, confidence interval; CT, chemotherapy; EBRT, external beam radiotherapy; GBM, glioblastoma multiforme; NR, not reported; NS, not significant; RCT, randomized controlled trial; ref, reference; RT, radiotherapy; wks, week(s).

* No data available for patients in long-term follow-up study published in 2006 (9). Data presented are for the original 30-month follow-up period. All patients receiving chemotherapy in this period also underwent re-operation. When the patients who underwent re-operation and chemotherapy were removed from the analysis at 30 months follow-up, median survival was 64.1 weeks for the BCNU group and 49.4 weeks for the control group, p=0.02.

† After adjustment for prognostic factors.

‡See body of text for results for patients with grade IV tumours only.

Efficacy

Newly Diagnosed Malignant Glioma

Two RCTs compared Gliadel® to placebo in patients with newly diagnosed malignant glioma (4,6). Westphal et al. (4) conducted a multicentre, double-blind phase III RCT comparing 120 patients in each study arm at the time of surgery. The sample size was pre-specified and based on a two-tailed log-rank test with an alpha level of 0.05, and a power of 0.90 to detect an 18% difference in one-year survival between Gliadel® and placebo (68% vs. 50%). The original course of the trial was 30 months but a long-term follow-up study was later published, extending the follow-up to 56 months (9). Survival data for 58 patients who were known to be alive at the end of the original trial period were obtained retrospectively and were combined with data from the original study period for analysis. Over the 56-month period, only one patient was lost to follow-up.

Westphal et al (4,9) reported that overall survival at one year was 59.2% for Gliadel® patients and 49.2% for the placebo patients (9). Survival for the Gliadel® and placebo groups were 15.8% and 8.3%, respectively, at two years and 9.2% and 1.7%, respectively, at three years. The difference between the survival curves was statistically significant (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.56-0.95, p=0.018), with a 27% reduction in risk of death for patients receiving Gliadel® compared to placebo. Median survival was 13.8 months in the Gliadel® arm and 11.6 months in the placebo arm (p=0.017). Since the high number of patients undergoing reoperation could have confounded the results (29% of the Gliadel® arm and 25% of the placebo arm at 30 months), an analysis of the intention–to-treat population was performed, in which patients undergoing reoperation were censored at the time of reoperation. That analysis was performed at the end of the 30-month study period, as no data for reoperation were available for the 58 patients who were followed long-term after that time point. In that analysis, patients in the Gliadel® group survived longer than the placebo group (HR 0.64, 95% CI 0.45-0.92, p=0.01), with a median survival of 64.1 weeks compared to 49.4 weeks (4).

Westphal et al. (4,9) also analyzed the results in subgroups according to histology. There were 101 patients with glioblastoma multiforme (GBM) in the Gliadel® arm and 106 patients with GBM in the placebo arm. For that subgroup, the median survival was 13.1 months in the Gliadel® arm and 11.4 months in the placebo arm. No significant difference in survival between the two GBM subgroups was detected (HR 0.78, 95% CI 0.595-1.03, p=0.08) (9). When Westphal et al. corrected for the possible imbalance in prognostic factors, because the groups were not originally randomized according to histologic subgroup, no significant survival advantage was detected for the patients with GBM in the Gliadel® arm compared to the placebo arm (HR 0.78, 95% CI 0.58-1.05, p=0.10). However, it is important to note that this trial was not designed to detect differences between histologic subgroups.

Valtonen et al. (6) reported the results of a small double-blind randomized trial. Thirty-two patients with newly diagnosed malignant glioma were randomized to receive either Gliadel® or a placebo. Initially the trial was designed to recruit 100 patients; however, due to difficulty obtaining Gliadel®, the trial was terminated early. There was an imbalance in the histologies of the two arms: 16 patients in the placebo arm had GBM (100%) compared to 11 patients in the Gliadel® arm (69%). Valtonen et al. (6) reported a statistically significant overall survival benefit in the Gliadel® arm (HR 0.27, 95% CI 0.11-0.68, p=0.006) and increased median survival (58.1 weeks vs. 39.9 weeks, p=0.012). A subgroup analysis of the 27 patients with grade IV tumours revealed a similar benefit for Gliadel® in overall survival (HR 0.27, 95% CI 0.10-0.71, p=0.008). Median survival for that subgroup of patients was 53.3 weeks in the treatment arm and 39.9 weeks in the placebo arm (p<0.05). Those results need to be interpreted with caution because of the small number of patients and small variances in prognostic factors, which could have significantly influenced outcome.

Recurrent Malignant Glioma

One RCT examined the role of Gliadel® in recurrent gliomas (5). Brem et al. compared 110 patients with recurrent malignant glioma receiving Gliadel® to 112 patients with recurrent malignant glioma receiving a placebo. Each trial arm had a similar proportion of GBM patients: 65.5% were GBM patients in the Gliadel® arm, and 65.2% were GBM patients in the placebo arm. The analysis of overall treatment effect showed no significant benefit for Gliadel (HR 0.83, 95% CI 0.63-01.10, p=0.19). However, once adjustment was made for the effects of prognostic factors, the overall treatment effect favoured Gliadel (HR 0.67, 95% CI 0.51-0.90, p=0.006). The median survival was 31 weeks for the Gliadel® arm and 23 weeks for the placebo arm. Six-month overall survival was 60% in patients in the Gliadel® arm and 47% in patients in the placebo arm. That difference was not significant (p=0.061).

Similar to the RCT by Westphal et al. (4), Brem et al. (5) compared histologic subgroups of the Gliadel® and placebo arms. The results of the subgroup analysis need to be interpreted with caution, however, because the study was not designed to detect survival differences according to subgroups. Brem et al. (5) reported that six-month overall survival for GBM patients was 56% in the Gliadel® arm and 36% in the placebo arm (p=0.020). The estimated hazard ratio showed no significant difference between treatment arms (HR 0.81, p=0.22) but did show a benefit for Gliadel® after an adjustment for treatment group and prognostic factors (HR 0.67, 95% CI 0.48-0.95, p=0.02).

One prospective cohort study with historical control examining the role of Gliadel® in patients with recurrent malignant glioma was identified (2). Seventeen patients underwent surgery for recurrent malignant glioma and received Gliadel® wafers. A cohort of 45 patients who underwent surgery for recurrent malignant glioma during the same time period was retrospectively identified to act as a control group. Subach et al. reported a median survival from diagnosis of 58 weeks for the Gliadel® group versus 97 weeks for the control group. While authors reported no significant difference in prognostic factors between groups, a possible selection bias was suggested, since patients offered Gliadel® had no remaining treatment options while patients in the control cohort received established adjuvant treatment. The potential for bias in non-randomized studies with historical controls prevents any conclusions being made from the results of that study.

Safety

One prospective phase II study examined various dosages of BCNU in the wafers to establish the maximum tolerated dose (MTD) (3). Forty-four patients were included in the study and received 6.5%, 10.05%, 14.5%, 20.0%, or 28.0% BCNU. No dose-limiting toxicities were identified in the 18 patients who received $\leq$14.5% BCNU. Three of the initial six patients in the 20% BCNU group experienced the following adverse effects: seizures, brain edema, wound infection, wound drainage, and a bone flap infection. Six more patients were included in the 20% BCNU group to see if those adverse effects were consistent with patients undergoing craniotomies or whether 20% BCNU is intolerable. The six patients did not experience similar adverse effects. Olivi et al. then treated four patients with 28% BCNU. Three of those patients developed major adverse effects (seizures and brain edema). Olivi et al. (3) thereby concluded that 20% interstitial BCNU was the MTD.

Westphal et al. (4) reported that the number of deaths, adverse events, and laboratory abnormalities were high, as expected in that patient population. Both the Gliadel® arm and placebo arm experienced similar adverse events. The most frequently reported adverse effects among the patients receiving Gliadel® were hemiplegia, convulsions, confusion, and brain edema. The most commonly reported adverse effects among the patients in the placebo arm were convulsions, confusion, brain edema, and aphasia. The only difference between groups in the Westphal et al. (4) study was that more patients in the Gliadel® arm experienced intracranial hypertension (11 patients vs. two patients in the placebo arm, p=0.019).

Valtonen et al. (6) reported similar results to Westphal et al. (4). They found that 12 patients in the treatment group reported adverse effects and nine patients in the placebo group reported adverse effects. The most common adverse effects amongst the patients in the Gliadel® group were hemiparesis, convulsion, visual field defect, and aphasia.

Brem et al. (5) also found that both groups had a similar amount of adverse effects. They found that two percent of patients in each group developed thrombocytopenia, and that one percent of the patients in the Gliadel® group developed leukopenia. Brem et al. (5) also compared seizures between the groups. They found that 41 patients in the Gliadel® group experienced seizures, and 32 patients in the placebo group experienced seizures (p=0.199). The overall incidence of serious intracranial infection was 2.2%, but was more common in the Gliadel® arm compared to the placebo arm (3.6% versus 0.89%, respectively). This difference was not statistically significant.

DISCUSSION

Newly Diagnosed Malignant Glioma

Two RCTs compared the efficacy of Gliadel® versus placebo in patients with newly diagnosed gliomas (4,6). In the largest RCT to date, a two-month improvement in median survival for patients with newly diagnosed malignant glioma receiving Gliadel® compared to patients who received a placebo was reported (p=0.017) (9). In addition, the analysis of the survival curves revealed a significant 27% reduction in risk of mortality for patients who received Gliadel® (p=0.018). A survival advantage of Gliadel® for patients with GBM was not detected, although the trial was not designed to make comparisons between histological subgroups. Another randomized trial only included 32 patients newly diagnosed with malignant glioma, because the researchers were unable to obtain Gliadel® during the trial (6). While a survival benefit was reported for Gliadel® in the entire patient population and for patients with GBM, no conclusions could be reached based on this small number of patients.

Both studies reported similar adverse effects in the treatment and control arms. The most common adverse effects associated with Gliadel® were hemiplegia, convulsions, confusion, and brain edema. The most commonly reported adverse effects among patients receiving the placebo were convulsions, confusion, brain edema, and aphasia. A significantly higher number of patients experienced intracranial hypertension in the Gliadel® arm of the Westphal trial (4). Since neither trial included a comparison with systemic therapy, it is unclear how the adverse effect rates associated with interstitial chemotherapy wafers compares to the rates expected with systemic chemotherapy.

As the largest trial does demonstrate a survival advantage in the Gliadel® treatment arm, Gliadel® may be considered an option in the subgroup of patients with newly diagnosed resectable malignant gliomas. However, the patient population (based on age, histology, performance status, etc.) that would benefit from Gliadel® is unclear and needs to be further investigated. In addition, no comparison has been performed between the efficacy of interstitial and systemic chemotherapy; therefore, clinicians should review the latest evidence for the benefit of systemic chemotherapy in patients with newly diagnosed malignant glioma. (See Practice Guideline #9-2 *Adjuvant Systemic Chemotherapy, Following Surgery and External Beam Radiotherapy, for Adults with Newly Diagnosed Malignant Glioma*).

Recurrent Malignant Glioma

One RCT compared the efficacy of Gliadel® versus placebo in patients with recurrent gliomas (5). The overall result of that trial was negative, with no significant survival advantage seen in the primary analysis; however, a survival advantage for Gliadel® in the entire patient population and in patients with GBM was observed after the adjustment for prognostic factors. As there were no *a priori* subgroups identified, the results of the subgroup analysis of GBM patients should be interpreted with caution. While no survival advantage for Gliadel® was detected in the

cohort study with historical control (2), no conclusions can be reached due to the heterogeneity between patients and potential for bias in such studies. The positive results of the RCT (5) after the adjustment for prognostic factors suggest that Gliadel® may increase overall survival in some patients with recurrent resectable malignant glioma. Since those patients generally have a poor outlook, any treatment that has the potential for prolonging life without significant adverse effects should be considered as an option.

ONGOING TRIALS

The National Cancer Institute's (NCI) database of clinical trials (www.cancer.gov/clinicaltrials) was searched for reports of relevant ongoing trials. One ongoing randomized trial examining the role of Gliadel® in adults with malignant glioma was identified.

Protocol IDs	Trial Information	Status
NEOPHARM-IL13PEI-301 NEOPHARM-IL13PEI-301-RO1 PRECISE UCLA-040305101 NCT00090948	Phase III randomized evaluation of convection enhanced delivery of Interleukin-13 PE38QQR Immunotoxin compared to Gliadel® Wafer (Polifeprosan 20 with carmustine implant) in glioblastoma multiforme patients at first recurrence Outcomes: overall survival, safety and toxicity, health-related quality of life Projected accrual: 200 for IL-13 PE38QQR and 100 for Gliadel® wafer	Active First published: 8/24/2004 Last modified: 8/9/2005

CONFLICT OF INTEREST

The members of the Neuro-Oncology DSG were polled for conflicts of interest relating to the topic of this systematic review and meta-analysis. No conflicts were declared.

JOURNAL REFERENCE

Perry J, Chambers A, Spithoff K, Laperriere N. Gliadel wafers in the treatment of malignant glioma: a systematic review. Curr Oncol 2007;14(5):189-94.

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Evidence-based Series 9-7: Section 3

Gliadel® Wafers in the Treatment of Malignant Glioma: Guideline Development and External Review: Methods and Results

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and 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

Report Date: August 15, 2006

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 Gliadel® wafers in the treatment of malignant glioma, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to submission of this evidence-based series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included:

- A statement should be included indicating whether treatment with Gliadel® should be followed by radiation therapy (RT) and whether any modifications from standard RT are required.
- The DSG needs to include a statement placing some perspective on the options of Gliadel versus systemic therapy. If the placement of Gliadel® precludes treatment with temozolomide, it would be helpful for the DSG to advise by consensus which intervention is more desirable. If subsequent temozolomide is not precluded, a statement indicating the DSG's consensus about its use would again be helpful.
- Better justification for not pooling data should be provided.
- In the description of the Westphal study (3), the DSG has interpolated the one-year values for overall survival, deduced the difference between study groups, and then compared this difference with the delta used to calculate the sample size to suggest that the statistical significance for one-year overall survival was not reached. The DSG needs to verify whether this is valid and whether the primary outcome of the Westphal trial has been properly described.

Modifications/Actions

In response to feedback from the Report Approval Panel, the DSG made the following modifications to the document:

- The DSG added a statement to the recommendations that Gliadel® placement in patients with newly diagnosed malignant glioma should be followed by standard radiotherapy.
- A statement was added to the recommendations that, although there is currently no evidence to support the combination of Gliadel® with systemic therapy such as temozolomide, the DSG does not feel that the placement of Gliadel® should preclude administration of systemic therapy. The DSG emphasized that there is little clinical experience with such combined treatment and decisions should be individualized, recognizing that increased toxicity is possible.
- The DSG clarified its decision not to pool the data under Synthesizing the Evidence in Section 2 of this series.

- The DSG revised its description of the primary outcome, focusing on the Kaplan Meier survival analysis, as it was not clear from the published report that one-year overall survival was the original primary outcome for the trial.

External Review by Ontario Clinicians

Following review and discussion of sections 1 and 2 of this evidence-based series and review and approval of the report by the PEBC Report Approval Panel, the Neuro-oncology DSG 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.

BOX 1:
DRAFT RECOMMENDATIONS (approved for external review May 1, 2006)

Target Population

The recommendations apply to adult patients undergoing surgery for newly diagnosed or recurrent malignant glioma.

Recommendations

- Gliadel® is an option for selected patients with newly diagnosed malignant glioma where a near-gross total excision is possible; however, the majority of patients with malignant glioma will not be eligible for various reasons (ie. non-resectable tumours or contact with the ventricular system). Where considered technically possible, Gliadel® should be offered to patients as an option, followed by standard radiotherapy.
- The current standard of care for patients with newly diagnosed glioblastoma multiforme is radiotherapy with concurrent and adjuvant temozolomide. No evidence is currently available to support the sequential combination of Gliadel® with temozolomide; however, the DSG does not feel that the placement of Gliadel® should preclude the administration of systemic therapy. Decisions to use Gliadel® with subsequent temozolomide should be made on an individual patient basis, recognizing that there is little clinical experience with such combined treatment, and patients should be made aware of the possibility of increased toxicity. When new evidence becomes available, the DSG will revise these recommendations as necessary.
- Gliadel® is an option in patients with surgically resectable recurrent malignant gliomas.

Qualifying Statements

- The patient population (based on age, histology, performance status, etc.) that would benefit from Gliadel® is unclear and needs to be further investigated.
- There is no evidence available comparing the efficacy of Gliadel® to systemic chemotherapy, therefore no comment can be made regarding the relative efficacy of Gliadel® compared to alternative treatment options. For recommendations of adjuvant systemic chemotherapy for newly diagnosed malignant glioma, refer to Evidence-based Series #9-2.

Methods

Feedback was obtained through an electronic survey of 55 practitioners in Ontario (medical oncologists, radiation oncologists, neurologists and neurosurgeons). The survey consisted of

items evaluating the methods, results, and discussion used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was emailed on June 22, 2006. Follow-up reminders were sent on July 21 and August 4, 2006. The Neuro-oncology DSG reviewed the results of the survey.

Results

Two responses were received out of the 55 surveys sent (4% response rate). One of the responses was received via fax and one respondent filled out the electronic survey. Key results of the practitioner feedback survey are summarized in Table 2.

Table 2. 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 guideline, as stated in the "Introduction" section of the report, is clear.	2 (100)		
There is a need for a guideline on this topic.	2 (100)		
The literature search is relevant and complete.	2 (100)		
The results of the trials described in the report are interpreted according to my understanding of the data.	1 (50)	1 (50)	
The draft recommendations in the report are clear.	1 (50)	1 (50)	
I agree with the draft recommendations as stated.	1 (50)		1 (50)
This report should be approved as a practice guideline.	1 (50)		1 (50)
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**
	1 (50)		1 (50)

Summary of Written Comments

One respondent (33%) provided written comments. The main points contained in the written comment were:

- The respondent felt that the recommendation would best be phrased "Gliadel could be offered" not "should be offered". How does one go about offering the wafers to the patient when one is unsure ahead of time if a resection amenable to wafer placement will be achieved? There will be some preoperative uncertainty, which is the only practical time when patients could be "offered" the treatment.
- There is nothing in the Qualifying Statements to reflect relative costs of the two treatments. Both Gliadel and temozolomide are very expensive but are they equally expensive?
- The recommendation that Gliadel shouldn't preclude adding temozolomide seems a bit risky in the absence of any evidence saying they are safe to give together (and would be very expensive). The recommendations should stick to the established regimens (i.e. Gliadel or temozolomide) until someone does the trial that says they are safe to give together and more effective than either alone.

Modifications/Actions

In response to the written comments from the practitioner feedback survey, the following modifications were made:

- The authors deleted the statement "Where considered technically possible, Gliadel should be offered to patients as an option, followed by standard radiotherapy" from the first bullet of the Recommendations. The recommendation states that Gliadel is an option for selected

patients with newly-diagnosed malignant glioma. The authors agree that there will be some preoperative uncertainty whether placement of Gliadel wafers will be possible.
- The issue of cost of treatment is beyond the scope of this evidence-based practice guideline.
- The authors felt that the lack of evidence for the efficacy or safety of combining Gliadel with temozolomide has been sufficiently acknowledged in the second bullet of the Recommendations. The Recommendations emphasize that there is little evidence or clinical experience to support or refute the addition of systemic therapy to placement of Gliadel and there is a possibility of increased toxicity. Decisions to use Gliadel with subsequent temozolomide should be made on an individual patient basis.

ONGOING DEVELOPMENT AND MAINTENANCE

This report reflects the integration of feedback obtained from the Report Approval Panel of the PEBC and through the external review process, with final approval given by the Neuro-oncology DSG. Updates of the report will be conducted as new evidence informing the question of interest emerges.

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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

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