The Role of BCNU Polymer Wafers (Gliadel) in the Treatment of Malignant Glioma

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KEYWORDS

• Gliadel • BCNU wafers • Local chemotherapy • Glioma

After surgical removal, direct delivery of anti neoplastic agents to the tumor site is the oldest strategy of adjuvant cancer therapy. Brachytherapy, the direct delivery of radiation via an encapsulated source, was first used at the turn of the twentieth century to treat a wide variety of cancers. It was not commonly used to treat brain tumors, however. In the 1950s and 1960s systemic chemotherapies became available, but were quickly found to be ineffective against gliomas. The inability of most drugs to penetrate the blood-brain barrier and the subsequent dose-limiting systemic toxicity when attempting to reach therapeutic drug levels in brain led clinicians to revisit the concept of local drug delivery.

Clinicians used intracarotid injection,[1] direct application of drug to the cavity,[2,3] and diffusion via semipermeable silastic rubber membranes[4] with drugs, such as cyclophosphamide, vincristine, and methotrexate. These proved largely ineffective and no better than systemic administration, probably because the drugs had little activity against glioma.

In the mid-1970s, the nitrosoureas, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU; carmustine) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU; lomustine), were introduced and had moderate efficacy against gliomas.[4,5] Unfortunately, doses that produced response rates as high as 50% caused significant leukopenia or thrombocytopenia,[6] as well as a non–dose-related pulmonary fibrosis. The half-life of BCNU is only 15 to 30 minutes, but patients may need six weeks or longer between doses to allow adequate bone marrow recovery. Attempts to deliver BCNU intra-arterially and by direct injection into the postresection surgical cavity yielded results no better than systemic therapy. Patients who received intra-arterial BCNU had an increased risk of blindness.[7]

In the late 1970s, Langer and Folkman[8] demonstrated that polymers could provide a sustained release of proteins and other macromolecules. This mechanism could theoretically deliver chemotherapy beyond the blood-brain barrier. The initial polymers were nonbiodegradable and the rate of drug release slowed with time, making them unattractive for use in brain. In the 1980s, completely degradable polymers became available and were rapidly incorporated into surgical practice, in the form of absorbable sutures. The newer polymers work by surface erosion, with the layers being resorbed one after the other, analogous to peeling layers from an onion, and allowing more constant drug delivery.[9] Ultimately, these polymers were used to create the Gliadel wafer.

ANIMAL AND PHARMACOKINETIC STUDIES

Tamargo and colleagues[10] published the first paper using BCNU-embedded wafers in 1993. Rats with intracranial 9L gliosarcomas implanted with the wafers had 2- to 3-fold longer survivals than those treated with intraperitoneal BCNU

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injections. They tested 2 different polymer bases using this model, ultimately choosing polifeprosan 20 (copolymer of 1,3-bis(*p*-carboxyphenoxy)propane and sebacic acid in a 20:80 M ratio) because it better protects BCNU from degradation before it is released.[11]

The initial pharmacokinetic studies on BCNU wafers were performed in rabbits, using radiolabeled BCNU. Grossman and colleagues[12] demonstrated that BCNU was distributed widely in the brain ipsilateral to the implants, at distances up to 12 mm from the wafers. Follow-up studies in monkeys measured the drug concentration at the site of implantation on day 1 at 3.5 mmol/L, decreasing to approximately 1.0 mmol/L at a distance of 3 mm from implantation. Seven days postimplant, only the area within 0.5 mm had a concentration greater than 1 mmol/L.[13] The inhibitory concentration of BCNU on human glioma lines in vitro has been reported as from 15 to 300 μmol/L,[14,15] implying that the area adjacent to the implant receives well in excess of the therapeutic drug levels for at least 7 days. Further studies in monkeys demonstrated the safety of BCNU wafers with radiation therapy,[16] and allowed for human trials to begin.

HUMAN TRIALS WITH SINGLE-AGENT BCNU WAFERS

The initial trials of single-agent BCNU wafers are summarized in **Table 1**.

A phase I to II trial in patients with recurrent glioma identified the 3.85% BCNU wafer as the most effective, based on survival from the time of implantation. The higher-dose group (6.35%) did not have more side effects, but overall survival was lower, possibly because it contained 100% glioblastoma (GB) patients. In the 2 lower-dose cohorts only 60% of patients had GB. The 3.85% wafer was chosen for use in subsequent trials, although there was no apparent difference in toxicity.[17] The phase III trial enrolled 222 patients with recurrent glioma, randomizing them to active or placebo wafers. This trial demonstrated an increased overall survival of 8 weeks ($P = .061$) and led the Food and Drug Administration (FDA) to approve Gliadel (3.85% BCNU wafer) for use in recurrent malignant glioma in 1996.

A phase I safety study of the BCNU wafer in combination with radiation therapy for newly diagnosed glioma was run concurrently with the phase III trial for recurrence. The study demonstrated an increased median survival compared with historical controls, but also showed a higher rate of severe adverse events compared with earlier trials, which included seizures, intracranial hypertension, and neurologic decline in the postoperative period. The phase III trial for newly diagnosed glioma had a lower complication rate than observed in the Phase I trial, but remained concerning. Five percent of patients in the BCNU group had cerebrospinal fluid leaks and 9.1% of patients had intracranial hypertension. Although there was a statistically significant improvement in survival in both the recurrent and up-front trials, it is important to note that patients in the placebo arms did not receive treatment after radiation therapy until they had recurrent tumor Standard practice at the time would likely have followed radiation with chemotherapy. This makes the modest results somewhat difficult to interpret (see **Table 1**).

LIMITATIONS OF BCNU WAFERS IN MALIGNANT GLIOMA

Unlike bevacizumab and oral temozolomide (TMZ), the use of BCNU wafers has not been widely adopted, despite phase III data in its favor. There are several factors that have limited its broader use. A review of patients enrolled at one center in the phase III trial showed that only 25% to 30% of patients with malignant gliomas qualified for the use of BNCU wafer. These patients were younger, with more complete resections and higher performance scores,[24] making the results difficult to generalize to the overall patient population. TMZ, a well-tolerated oral alkylating agent with good penetration of the central nervous system, was being used regularly at around the time the FDA approved Gliadel for up-front therapy in 2003. The Stupp trial, demonstrating increased survival with radiation and concurrent TMZ, was published shortly thereafter, in 2005. Although there has never been a head-to-head trial, the increase in survival using BCNU wafers is similar to radiation with TMZ or PCV (procarbazine, CCNU, vincristine).[25] In a recent retrospective review of BCNU wafers, it also appeared that patients with non–methylated methylguanine methyltransferase (non-MGMT) had shorter survivals.[26] If in the future MGMT status is used to make decisions about first-line therapy, placing BCNU wafers at the time of initial surgery is likely to become less attractive.

Another limitation to the use of BCNU wafers is the complication rate noted after 2003, when use of the wafers expanded beyond controlled trial populations. Centers with early experience using BCNU wafers reported complication rates comprable to those seen in patients who do not receive wafers.[27] However, other centers report adverse events in up to 44% of patients receiving BCNU wafers.[28] Formation of a cyst at the implantation site

Table 1
Human trials using single-agent BCNU wafers

Phase	Reference	Patients	Design	Result	Conclusions
I–II	Brem et al,[17] 1991	21 recurrent malignant glioma	Single-arm, dose escalation	Wafer with 3.85% BCNU (7.7 mg) chosen for phase III; higher dose group had lower survival	Safe and well tolerated without systemic side effects
I	Brem et al,[18] 1995	22 new glioma (21 glioblastoma multiforme)	Single-arm, historical control	Median survival was 42 wk	Safe to use in combination with XRT, but 10/22 patients had an SAE
III	Brem et al,[19] 1995	222 recurrent glioma	Double-blind, placebo-controlled	6-mo survival of 56% vs 47% ($P = .061$) Median survival increased by 8 wk	Marginal change in survival. Placebo patients received no active treatment other than XRT
III	Westphal et al,[20,21] 2003/2006	240 new malignant glioma	Double-blind, placebo-controlled	Median survival 13.8 vs 11.6 mo ($P = .017$)	Effective, but the placebo arm got no treatment other than XRT. Higher rate of cerebral edema, CSF leaks
III	Valtonen et al,[22] 1997	32 new malignant glioma (planned 100)	Double-blind, placebo-controlled	Median survival 58.1 vs 39.9 wk ($P = .012$)	Trial stopped early because of wafer shortage; again, randomized to no active treatment after XRT
I	Olivi et al,[23] 2003	44 recurrent malignant glioma	Single-arm, dose escalation	Wafer with 20% BCNU loading was maximum tolerated dose	Can use higher concentrations of BCNU in implanted wafers

Abbreviations: CSF, cerebrospinal fluid; SAE, severe adverse event; XRT, conventional radiation therapy.

Table 2
Trials of BCNU wafers in combination with other therapy

Reference	Patients	Drug	Design	Results	Conclusions
Weingart et al,[34] 2007	38 recurrent glioma	O6-BG	Phase I	Safe dose of bolus, followed by 7-d infusion	Move to phase II
Quinn et al,[35] 2009	52 recurrent glioblastoma multiforme requiring GTR	O6-BG	Phase II single-arm	82% 6 mo survival (56% historical control); median OS 53 weeks	13.4% infection rate, 19.2% CSF leak. May increase risk of AEs
Gururangan et al,[36] 2001	10 recurrent glioma requiring GTR	Monthly TMZ	Phase I	Safe to use 200 mg/m^2 TMZ in combination	Move to phase II
Limentani et al,[37] 2005	16 new malignant glioma	XRT followed by carboplatin	Phase I	Median progression-free survival 266 days, no grade 3 or 4 AEs	Feasible
Sampath et al,[38] 2005	10 recurrent glioma	Irinotecan	Phase I	Median survival from implant 13.5 mo	Tolerable, possibly more effective than monotherapy
Smith et al,[39] 2008	25 new malignant glioma	GammaKnife within 2 wk of surgery, followed by XRT	Phase I/II	Median Survival 50 wk 2-y survival 22%	Unclear if patients received monthly TMZ; 47% rate of radiation necrosis
Affronti et al,[40] 2009	36 new malignant glioma	XRT+TMZ, then TMZ+rotational chemotherapy	Retrospective review	No statistically significant difference in survival for patients with wafers	Safe and feasible
McGirt et al,[41] 2009	33 new malignant glioma	XRT+TMZ, followed by TMZ	Retrospective review	2-y survival 39% vs 18% if no oral TMZ after Gliadel +XRT	Safe and feasible
Bock et al,[42] 2010	44 new malignant glioma	XRT+TMZ, followed by TMZ	Retrospective review	43% of patients with grade 3 or 4 AEs	Combination may produce more toxicity
Noel et al,[26] 2011	28 new malignant glioma	XRT+TMZ, followed by TMZ	Retrospective review	OS 20.6 (Gliadel) vs 20.8 mo	No improvement in survival
Salvati et al,[43] 2011	32 new malignant glioma	XRT+TMZ, followed by TMZ	Retrospective review	No postsurgical AEs Follow-up median only 6.5 mo	Feasible

Abbreviations: AE, adverse event; GTR, gross total resection; O6-BG, O6-benzylguanine; OS, overall survival; TMZ, temozolomide; XRT, conventional radiation.

may occur in up to 11% of patients and, despite high-dose steroids, may still require surgical intervention.[29] The rate of postcraniotomy infection can be as high as 15% to 28%[30,31] at some major centers. Malignant edema, although less common, can lead to severe neurologic dysfunction and death.[30,32]

COMBINATION TRIALS WITH GLIADEL

Recurrence after treatment with BCNU wafers is nearly universal. Despite local drug delivery, the pattern of recurrence is quite similar to that seen with systemic chemotherapy and radiation therapy; 73% have local recurrence while 27% present with a combination of local and distant recurrence,[33] which has led to several trials combining BCNU wafers with other systemic and local therapies (**Table 2**). O6-benzylguanine (O6-BG) is thought to potentiate the action of BCNU by blocking the activity of a DNA repair enzyme, and seems promising based on phase I/II trials. Although a phase III trial in recurrent glioma has not been opened, O6-BG is being used in trials for newly diagnosed patients (see **Table 2**).

FUTURE DIRECTIONS

Current clinical trials that include BCNU wafers are using them in combination with other agents. An actively recruiting phase II trial is using wafers at the time of surgery, followed by TMZ and bevacizumab concurrently with radiation, then TMZ and bevacizumab concurrently until recurrence. Other local delivery mechanisms are under investigation using BCNU, other chemotherapies, and biological agents. BCNU dissolved in ethanol (DTI-015) has been used in phase I/II trials for recurrent and newly diagnosed glioma.[44,45] Convection-enhanced delivery (a constant positive pressure injection), microcapsule delivery (a diffusion-controlled mechanism), and gels are also being explored in both clinical and preclinical settings.

SUMMARY

Although BCNU wafers are included in the 2011 National Comprehensive Cancer Network guidelines (level 2B), they are just one of the options available for treatment of malignant glioma. Clinical trials support its use in patients with a smaller lesion and good performance status, but whether this is a better option than radiation with concurrent TMZ remains an unanswered question. Recent studies of patients receiving combined therapy suggest there may be a role for BCNU wafers in newly diagnosed glioma, as an addition to radiation and TMZ. Other combinations also appear to be well tolerated. The complications associated with the wafers, such as malignant edema and increased frequency of wound infection, present a barrier to widespread adoption of the technology. In addition, patients who qualify for BCNU wafers are frequently candidates for clinical trials. Up-front use of BCNU wafers can disqualify patients from participating. Future work in this area, using newer delivery mechanisms and combination therapies, shows promise for better drug delivery and overcoming drug resistance.

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