UC Irvine
UC Irvine Previously Published Works

Title

Interstitial chemotherapy with biodegradable BCNU (Gliadel) wafers in the treatment of malignant gliomas.

Permalink

https://escholarship.org/uc/item/7vw099pd

Journal

Therapeutics and Clinical Risk Management, 3(5)

ISSN

1176-6336

Authors

Bota, Daniela A
Desjardins, Annick
Quinn, Jennifer A
et al.

Publication Date

2007-10-01

Copyright Information

Peer reviewed

Interstitial chemotherapy with biodegradable BCNU (Gliadel®) wafers in the treatment of malignant gliomas

Daniela A Bota
Annick Desjardins
Jennifer A Quinn
Mary L Affronti
Henry S Friedman

The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC, USA

Abstract: Malignant gliomas represent the majority of primary brain tumors, and the prognosis of the patients afflicted with these tumors has been historically dismal, with almost uniform progressive neurologic impairment and rapid death. Even with multimodal treatment using surgery, focal radiation, and chemotherapy, no major strides were made until recently. The development of interstitial BCNU wafers (carmustine wafers, Gliadel®) has led to promising results in the treatment of a selected patients with malignant gliomas, as well as with other intracranial malignancies.BCNU is one of the first systemic chemotherapies which had obtained United States Food and Drug Administration (FDA) approval for the treatment of brain tumors. However, systemic use has been hampered by the modest prolongation of survival and by the prolonged myelosuppression and potentially fatal pulmonary toxicity. The development of interstitial therapies with BCNU represented a great step forward, allowing direct delivery to the tumor bed, with virtually no systemic toxicities. Clinical studies of BCNU wafers have showed good efficacy in both newly diagnosed and recurrent gliomas, as well as a possible therapeutic role in other primary or secondary intracranial malignancies. New studies are currently underway trying to improve the efficacy of the BCNU wafers (Gliadel®) by combining them with different systemic chemotherapies. An overview of the current knowledge ranging from the preclinical developments, to the efficacy and safety seen in the clinical trials and in clinical practice following the drug approval to the future avenues of research is therefore timely.

Keywords: BCNU, interstitial therapy, Gliadel® wafers, malignant gliomas

Introduction

Glioblastoma multiforme (GBM) is the most common primary neoplasm of the brain, which affects approximately 10,000 people every year in the United States (Central Brain Tumor Registry of the United States 2004–2005). It is a very aggressive tumor (WHO grade IV), with a historical survival of less the one year, which has changed little over the last two decades (Ohgaki and Kleihues 2005). Multiple attempts have been made to identify effective treatment, leading to the recognition of focal radiotherapy and adjuvant chemotherapy with alkylating agents as modalities which modestly improve patient survival (Selker et al 2002; Stewart 2002; Stupp et al 2005). However, the protective environment of the CNS limits the delivery of the chemotherapy agents inside the brain tumor, with many drugs failing to achieve therapeutic concentrations at the tumor site, even while the systemic levels are at toxic range.

In order to achieve effective local delivery with minimal systemic side-effects different approaches are currently employed, such as administration of therapeutic molecules via intracranially implanted catheters, convection-enhanced drug delivery, or administration through controlled-release polymers (Raza et al 2005). The first of these new agents to be approved by the United States Food and Drug Administration

Correspondence: Henry S Friedman
The Preston Robert Tisch Brain Tumor Center, Duke University Medical Center
Box 3624, Durham, NC 27710, USA
Tel +1 919 684 5301
Fax +1 919 681 1697
Email fried003@mc.duke.edu

(FDA) for the treatment of malignant gliomas is the 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU, carmustine) implant, also known as the Gliadel® (MGI Pharma, Inc.) wafer.

Preclinical data show that the interstitial release of BCNU leads to superior survival when compared with systemic administration in gliosarcoma intracranial models (Tamargo et al 1993), with minimal release of the BCNU in the systemic circulation (Domb et al 1995). Among the numerous polymer matrices studied, polifeprosan 20, a copolymer of 1,3-bis-(p-carboxyphenoxy) propane and sebacic acid in a 20:80 molar ratio, was proven to be the most appropriate for BCNU delivery, due to the fact that it protected the BCNU from hydrolytic degradation before release (Fleming and Saltzman 2002), and was safe in primate brain when given with focal radiation (Brem et al 1994).

In phase 1 and 2 clinical trials the BCNU wafers were well tolerated, with a complication rate acceptable when compared with that of the patients receiving placebo wafers, and demonstrated activity against new and recurrent malignant gliomas (Brem et al 1991, 1995a; Olivi et al 2003). Results of these trials showed that BCNU delivery from the polifeprosan 20 wafers is well tolerated, and has established a safe dose of 7.7 mg of BCNU per wafer (3.85% carmustine loading) (Olivi et al 2003). At this dose, the local side-effects such as brain necrosis and edema are rare, and there is minimal, if any, systemic toxicity (Brem et al 1991, 1995a; Olivi et al 2003).

The BCNU wafers were also evaluated in three randomized phase III studies, the initial one focusing on recurrent malignant gliomas (Brem et al 1995b), and the subsequent two in newly diagnosed patients with malignant gliomas (Valtonen et al 1997; Westphal et al 2003). All three clinical trials demonstrated a statistically significant survival advantage for the patients in the BCNU wafers groups. On the basis of these results, the BCNU wafers received FDA approval for patients with recurrent or newly diagnosed anaplastic astrocytomas and glioblastoma multiforme. This article reviews the mechanism of action of BCNU, the preclinical development of the BCNU wafers for interstitial delivery, and summarizes the results of the clinical trials of BCNU wafers for the treatment of malignant gliomas and other intracranial malignancies.

Background

More then 40 years ago studies carried by the National Cancer Institute led to the development of the initial nitrosurea compounds shown to have activity in animal cancer models (Johnston et al 1963), with the first successful formulation being 1-methyl-3-nitro-1-nitrosoguanidine (Schepartz 1976). The interest in finding more active analogs led to the discovery in 1963 of 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU, carmustine), an agent proven to be highly effective not only in the intraperitoneal L1210 murine leukemia, but also in the treatment of intracerebral L1210. This activity in the intracranial site was felt to be secondary to its ability to cross the blood–brain barrier (Schabel et al 1963). One year later, BCNU was introduced in clinical trials (Loo et al 1966; Weiss and Issell 1982) and was approved by the FDA in March 1977 for the treatment of brain tumors, Hodgkin's disease, and other hematologic malignancies. This led to one of the first effective therapies for human malignant gliomas in clinical trials (Chang et al 1983; Green et al 1983; Selker et al 2002), with a survival advantage of 2 months compared with patients who received radiation alone (Stewart 2002). At the same time, BCNU toxicity secondary to systemic administration became well described, with frequent dose-limiting delayed hematologic toxicity (De Vita et al 1965), non-dose-dependent pulmonary fibrosis (Crittenden et al 1977; Litam et al 1981), and secondary acute leukemia in 5%–10% of the patients (Cohen et al 1976; Michels et al 1985). Further research work also showed that the systemic and intrathecal delivery of BCNU produced penetration for a very short distance (2 mm from the ependymal surface) and started the quest for better delivery systems (Blasberg et al 1975).

Direct administration of BCNU through a catheter inserted in the surgical cavity was initially attempted in 1975, with no clear success, presumably secondary to the short half-life of BCNU in solution (Loo et al 1966) and to the limited delivery to the tumor tissue (Garfield et al 1975).

Biodegradable polymer wafers for the delivery of BCNU in malignant gliomas were developed by Henry Brem and his group, starting in the late 1980s (Yang et al 1989). This delivery system was proven superior to the systemic administration in animal models, and demonstrated limited systemic toxicity (Tamargo et al 1993), providing the rationale for evaluation in patients.

Pharmacology and preclinical data
BCNU mechanism of action, pharmacokinetics, and activity

Though considered to be an alkylating agent, BCNU differs from the other derivatives by having several reaction sites in addition to the carbon–chlorine bond, which are able to interact with a variety of reagents under physiological conditions (Loo et al 1966). Its cytostatic properties are secondary to

its inhibitory effects at multiple levels, such as DNA (Kohn 1977), RNA (Grimmond and Zirvi 1987) and protein synthesis (Penman et al 1976; Weiss and Issell 1982). In vitro, BCNU has shown activity against cell lines derived from numerous malignancies, including leukemia (Schabel 1973), lung cancers, sarcomas, and gliomas (Carter et al 1972).

The main BCNU effect is mediated by its chloroethyl moieties, which can alkylate reactive sites on nucleoproteins (Woolley et al 1976), and interfere with DNA synthesis and repair (Weiss and Issell 1982). DNA cross-linking occurs in two steps: chloroethylation of a nucleophilic site on one strand, and displacement of a chloride ion on the other strand, resulting in formation of an ethyl bridge between the strands, which blocks the DNA unwinding, and consequently DNA and RNA synthesis (Kohn 1977). The high alkylating activity of BCNU is also the cause of its main side-effects, interstitial pneumonitis, due to the DNA injury to the alveolar lining cells (Weiss et al 1981) and suppression of hematopoeisis (Lohrmann et al 1982). Another mechanism of activity is the carbomoylation of nucleoprotein lysine residues, with subsequent decrease in RNA and protein synthesis. The importance of this process in the antitumor effect of BCNU is still debated (Kann 1978).

After both oral and intravenous administration, BCNU has a very short life, with the parent drug not being detectable after 5 minutes (Oliverio 1976), and its active metabolites being detected in urine up to 72 hours after the initial dose. Both the parent drug and its metabolites rapidly enter the cerebrospinal fluid (CSF) (De Vita et al 1967). The preclinical studies also showed wide distribution, with good CSF penetrance (Loo et al 1966), and activity in transplanted gliomas, ependymoblastomas, and astrocytomas (Schabel 1976). However, BCNU penetration inside the brain tissue was just for a very short distance (2 mm from the ependymal surface) (Blasberg et al 1975).

BCNU interstitial delivery with biodegradable matrices

A number of different polymers were studied in order to determine their bio-compatibility and to be able to achieve the graduated, controlled release of BCNU in the tumor tissue. A direct comparison between ethylene-vinyl acetate copolymer and the poly(carboxyphenoxy-propane/sebacic acid) matrices in rats showed that both polymers were well tolerated, and effective in delivering the BCNU, with a significant increase in animal survival (Tamargo et al 1993). The poly(carboxyphenoxy-propane/sebacic acid) matrix was chosen as the foundation for the Gliadel® wafers.

Pharmacological studies showed that the Gliadel® wafers release BCNU in vivo over a period of 21 days, the majority of the drug release taking place in the first 5–7 days (Grossman et al 1992; Domb et al 1995), and degrade completely over a period of 6–8 weeks, with the polymer degradation products being eliminated through the urine (Grossman et al 1992; Wu et al 1994; Dang et al 1996). The BCNU-polifeprosan 20 wafers allowed delivery of BCNU at high concentrations up to 12 mm from the polymer site in animal models (Grossman et al 1992), while distant regions of the brain are exposed only to very low concentrations (Fleming and Saltzman 2002).

Mechanism of resistance

The resistance to BCNU is complex, due to the fact that at least two types of DNA lesions are created: chloroethyl adducts at O^6-guanine and interstrand cross-links (Drablos et al 2004). The repair of the chloroethyl adducts is conducted by O^6-alkylguanine-DNA alkyltransferase (AGT or MGMT). AGT activity has been proven to be a major factor in the resistance to BCNU and to other alkylating agents including methylators, as cells that have a low level of AGT are sensitive to alkylating agents, while cells expressing high levels are resistant (Pegg et al 1995; Friedman et al 1998b; Hegi et al 2004). The administration of O^6-substituted guanines such as O^6-benzylguanine (O^6BG) can effectively deplete the AGT and restore cell sensitivity to BCNU in both cell cultures (Friedman et al 1992) and xenograft models of malignant gliomas (Felker et al 1993).

The repair of the second type of lesions, DNA interstrand cross-links, needs the presence of nucleotide excision repair and homologous recombination factors (McHugh et al 2001), but the contribution of these repair mechanisms to BCNU resistance is not well understood.

Clinical experience with Gliadel® in malignant gliomas
Initial phase I studies
Recurrent malignant gliomas
The initial phase I study to determine the optimal concentration of BCNU was done in patients with recurrent malignant glioma (Brem et al 1991). The study enrolled 21 patients divided into 3 sequential groups to receive up to 8 wafers of increasing BCNU concentrations (1.93%, 3.85%, and 6.35%). All the patients had maximum tumor resection at the time of placement of the BCNU wafers. The three groups had similar demographics, but the first two groups had 60% GBM patients, while the highest dose group contained only GBM patients. All

three concentrations had similar local side-effects, with 13 out of the 21 patients having new areas of contrast enhancement around the resection cavity at least 7 weeks after the surgery and 10 patients out of 21 needed surgeries for decompression and removal of necrotic tissue. No systemic side-effects were noted. The post-implant and overall survival were higher in the two lower-dose groups then in the high-dose group, which can be at least partially explained by the higher percentage of patients with GBM in the third group. In consequence, the 3.85% BCNU was chosen as the standard dose to be used in the phase III clinical trials and marketing.

A second escalation study in recurrent malignant gliomas was conducted by the New Approaches to Brain Tumor Therapy (NABTT) CNS Consortium (Olivi et al 2003). This study enrolled 44 patients with recurrent disease, all of which had received prior external beam radiation. These patients were divided in 5 cohorts to be implanted with wafers containing 6.5%, 10%, 14.5%, 20%, and 28% BCNU concentration per 200 mg wafer. In the 6.5 %, 10%, and 14%, no dose-limiting toxicities were observed, and the adverse events (subdural collection, CSF leak, sepsis, and wound infection) were regarded to be similar to those in the patients subjected to tumor re-resection alone. The 20% dose cohort also had similar side-effects (seizures, brain edema, wound infection, wound drainage, and a bone flap infection). However, three out of the four patients enrolled in the 28% dose cohort developed major brain edema and seizures, and the 20% dose level was confirmed as the maximum tolerated dose. However, at the 20% dose level, the BCNU concentration in the blood reached 27 ng/mL at 4 hours after delivery. No systemic toxicities were included in this study report.

Newly diagnosed malignant gliomas

A phase I trial was also conducted in the newly diagnosed gliomas at the same institutions involved in the initial phase I study for recurrent gliomas (Brem et al 1995a). This trial enrolled 22 patients who received maximum resection, placement of seven to eight wafers impregnated with 3.85% BCNU, and subsequent standard external beam radiation. Ten of the 22 patients experienced severe adverse-effects in the postoperative period, such as seizures, neurologic decline, brain necrosis, infection, and deep venous thrombosis. Nine patients needed a secondary craniotomy after an average of 34 weeks, but 8 had recurrent tumor and only 1 necrosis. The median survival was 42 weeks.

Phase I and III clinical experience

Based on the safety data from the phase I and II clinical trials, and the need for improved treatment in malignant gliomas, a series of phase III clinical trials were conducted.

Recurrent malignant gliomas

The initial phase III study (Brem et al 1995b) enrolled 222 patients with recurrent malignant glioma who had an unilateral single focus of recurrent tumor of at least 1 cm³, a KPS >60%, and no recent treatment with nitrosureas. Patients were implanted with either the carmustine polymer or the placebo polymer disks. The dose of carmustine on the polymer disks was 7.7 mg per wafer (3.85% BCNU). The median survival for the combined pathology (anaplastic astroccytoma and glioblastoma multiforme) was 31 weeks in the carmustine group and 23 weeks in the placebo group (survival advantage of 8 weeks). For the patients diagnosed with glioblastoma multiforme the 6 months survival was 56% in the carmustine group and 47% in the placebo group ($p = 0.061$). The only complication more frequently seen in the treatment group was serious intracranial infection. Based on the results of this study US-FDA approval of Gliadel® for the treatment of recurrent patients was obtained in 1996.

Newly diagnosed malignant gliomas

The first phase III study of carmustine loaded polymers for newly diagnosed patients (Valtonen et al 1997) enrolled 32 newly diagnosed patients (initial enrollment planned for 100 patients) with grade III and IV gliomas. The inclusion criteria required unilateral disease greater than 1 cm³, not crossing the midline, and good performance status. The patients were randomized to receive BCNU or placebo wafers, after which they underwent standard focal beam radiation therapy. No indication of adjuvant treatment was provided. The time from surgery to death was the primary endpoint, with a median survival time of 58.1 weeks for BCNU vs 39.9 for placebo, with a survival advantage of 18 weeks ($p = 0.012$). The adverse effects were comparable between these two groups, and included wound infection, septic inflammation with meningismus, CSF leukocytosis with hydrocephalus, deep venous thrombosis with pulmonary thromboembolism, pneumonia, visual disturbances, and hemiparesis.

A larger phase III study to confirm the previous data enrolled 240 patients from 38 centers in 14 countries (Westphal et al 2003). The patients were again randomized to be implanted with BCNU vs placebo wafers, followed by focal radiation, while adjuvant systemic chemotherapy was explicitly prohibited until the time of tumor recurrence. The patient follow-up reported in this study was between 12 and 30 months. The median survival in the intent-to-treat group (grade III and IV tumors) was 13.9 months for the patients receiving BCNU wafers vs 11.6 months for the placebo group ($p = 0.03$). The GBM subgroup multivariate analysis

showed that BCNU wafers prolonged survival in the treatment group, after correction for prognosis factors (p = 0.04), with a risk reduction of 31% (95% CI, 3%–51%). More CSF leaks and increased intracranial pressure secondary to mass effect and edema were seen in the BCNU-wafer-treated group. It is important to mention that this study had targeted a selected population, as a retrospective review of the patients enrolled from the Edinburgh center showed that only 25% of the patients with malignant glioma could be enrolled in the trial, and that they were younger, had better performance status, and were more likely to have tumor resection and postoperative radiotherapy (Whittle et al 2003).

A long-term report (56 months follow-up period) including data on the patients still alive at the time of publication of the phase III study confirmed a median survival of 13.8 months vs 11.6 months (p = 0.017) in favor of the BCNU-wafer-treated group, and a continuous survival advantage at 1, 2, and 3 years (Westphal et al 2006). The report of the pattern of recurrence in a subgroup of 24 patients from the Westphal study showed a time to progression of 165 days for the patients in the BCNU wafers group vs 101 days for the placebo group (p = 0.023) (Giese et al 2004). All the patients receiving BCNU wafers eventually had recurrent tumor, with 73% of the patients having recurrent tumor adjacent to the resection cavity, and 27% having both local and distal recurrences.

A meta-analysis combining two phase III clinical trials for newly diagnosed patients (Valtonen et al 1997; Westphal et al 2003) has also been reported (Meldorf et al 2003). The meta-analysis included all the patients diagnosed with GBM, and reported a median survival for the Gliadel® group of 13.1 months vs 10.9 months for the placebo group (p = 0.031), and a hazard ratio of 0.71 (p = 0.019) at the multivariant analysis, which translates in a 29% reduction in the risk of dying. The results of this meta-analysis led to the FDA approval of Gliadel® for newly diagnosed high grade glioma patients in 2003.

Complications

A number of complications related to the Gliadel® wafers were identified during the phase III clinical trials, but the rate was similar to that in patients receiving placebo wafers (Valtonen et al 1997; Westphal et al 2003). However, in clinical practice following the drug approval, more treatment-related complications were identified, as the treatment was extended also to patients who were not eligible in the initial studies.

The rate of postcraniotomy surgical infection after BCNU wafer placement was reported to be as high as 28%, and is correlated with inadequate antibiotic prophylaxis (McGovern et al 2003). Extensive cerebral edema was also reported after Gliadel® placement, and led to severe neurologic compromise and death (Weber and Goebel 2005). Another cause of severe toxicity and death with Gliadel® wafers recently reported is obstructing hydrocephalus, and the authors of the case-report concluded that a large opening of the ventricle during surgery might be considered a contraindication for wafer placement (Gallego et al 2007).

Local treatment effects, such as pericavity necrosis are also commonly seen, affecting 11% of all patients, and 33% of the patients undergoing re-operation for radiological progression, which it makes difficult to differentiate between tumor recurrence and treatment effect based on non-invasive studies (Kleinberg et al 2004). Other observations following Gliadel® implantation include the formation of tumor bed cysts with new neurologic symptoms secondary to mass effect. This complication has been addressed successfully with either high dose steroids or surgical decompression depending on the degree of mass effect (McGirt et al 2002).

Overcoming resistance – combination trials

Due to the clear survival advantage in a well defined group of patients with new and recurrent malignant gliomas, new strategies were developed in order to augment the therapeutic effect of the BCNU wafers by decreasing the tumor resistance to alkylating agents mediated by AGT or by combining the BCNU wafers with either systemic chemotherapeutic agents such as temozolomide, carboplatin, PCV, and irinotecan or other interstitial therapies such as interleukin-2, iodine-125 seeds, GliaSite® (Cytyc Corp.), and radiosurgery (Ashby and Ryken 2006).

Gliadel® and O^{6}Benzylguanine (O^{6}BG)

The initial work in animal models showed that O^{6}BG can potentiate the activity of carmustine wafers by inhibiting the activity of AGT, a DNA repair enzyme involved in tumor resistance to alkylating agents including BCNU, and prolong animal survival (Rhines et al 2000). The initial trial of O^{6}BG in patients with brain tumors demonstrated suppression of AGT activity when O^{6}BG was administered at a dose of 120 mg/m^2 18 hours before surgery (Friedman et al 1998a). Built on this, a phase I trial of Gliadel® combined with O^{6}BG has demonstrated that the combination is well tolerated when O^{6}BG is administred as a 120 mg/m^2 bolus 1 hour before surgery, followed by continuous infusion at 30 mg/m^2/day for up to 7 days (Weingart et al 2007). The phase II clinical

trial of Gliadel® plus O⁶BG in recurrent glioblastoma multi-forme patients from our institution (Quinn et al 2007) used a 120 mg/m² bolus over 1 hour administered after surgery, and on day 3 and 5 simultaneously with a 5-day infusion at 30 mg/m²/day. Preliminary results indicated a 80% 6-month survival and 47 weeks median survival, which is significantly better compared with 56% 6-month survival and 31 weeks median survival in the original Brem study. The adverse effects were similar to those described with Gliadel® alone (Quinn et al 2007).

Combination treatment with systemic chemotherapy

Gliadel® and temozolomide were shown in separate studies to prolong patient's survival, leading to a phase I study to determine the optimal dose of temozolomide to be used in patients with recurrent gliomas who had prior placement of Gliadel® wafers. Patients tolerated doses up to 200 mg/m² for 5 days given every 4 weeks, with only 1 patient developing grade III thrombocytopenia, and 2 out of 10 patients had no tumor recurrence after 1 year (Gururangan et al 2001). A phase II multicenter clinical trial is currently underway for patients with newly diagnosed malignant gliomas (LaRocca et al 2006). The patients enrolled had resection and Gliadel® insertion, followed by focal beam radiation with concomitant daily temozolomide (at 75 mg/m²), followed by monthly temozolomide (5-day regimen, at 200 mg/m²). At the last report, 33 patients were enrolled, with a median follow-up of 8.1 months. The median survival is 18.5 months, and the median progression-free survival is 6.4 months.

A second phase I study combined Gliadel® wafer implantation with immediate postoperative carboplatin followed by radiation therapy in patients with newly diagnosed malignant gliomas. Carboplatin dose was calculated based on Calvert formula, where the dose of carboplatin (mg) = target area under the carboplatin concentration curve vs time curve (AUC) × glomerular filtration rate + 25. The maximum tolerated dose for carboplatin which was administered on either day 3 or 4 after surgery corresponded to an AUC of 6. No toxicities were seen (Limentani et al 2005).

The combination of Gliadel® and PVC (procarbazine, lomustine, and vincristine) chemotherapy in newly diagnosed patients with malignant glioma was explored in the context of a phase I/II clinical trial (LaRocca et al 2005). Though a small study (9 patients enrolled), the combination seems to be tolerated, and possibly effective.

Our group has conducted a retrospective study to determine if Gliadel® wafer insertion at the time of initial surgery benefited patients receiving radiation therapy with concurrent temozolomide, followed by rotational multi-agent chemotherapy (temozolomide, CCNU, CPT-11) (Rich et al 2007). In this study, a difference in survival was found between the patients that had Gliadel® wavers vs those that had surgery alone.

Finally, in recurrent patients with glioblastoma multiforme, the toxicity and efficacy of the combination of Gliadel® and intravenous irinotecan was reported (Sampath et al 2005a). In the 10 patients enrolled, the combination was well tolerated and possibly more effective then monotherapy.

Combination treatment with local chemotherapy

The combination of Gliadel® and permanent I-125 Seeds was addressed in 4 different clinical trials enrolling recurrent malignant glioma patients (Foltz et al 2001; Tozer et al 2003; Darakchiev et al 2004; Zamorano et al 2005). The combination was safe, and the major complication was radiation necrosis (up to 24% of the patients). The largest of these studies (Darakchiev et al 2004) enrolled 34 patients with recurrent glioblastoma, and reported a progression-free survival of 47 weeks, and overall survival of 73 weeks, which compares favorably with the published data on Gliadel® monotherapy (Brem et al 1995b).

Consecutive use of brachytherapy (Gliasite®) and Gliadel® was studied in a phase I/II study which enrolled 27 patients with recurrent glioblastoma (Sampath et al 2005b). The overall median survival was 27 weeks, and the complications were rare, but included 1 death (intracranial hemorrhage) and 4 thrombotic events (DVT).

Only animal data are available at this time evaluating the combination of BCNU wafers with local administration of interleukin-2 (IL-2). In the rodent model, the animals that received an intracranial implant of microspheres containing IL-2, followed 5 days later by BCNU wafers showed superior survival compared with the animals that received either one of the two drugs alone or the placebo implants (Rhines et al 2003).

Other tumors
Pituitary adenomas, craniopharingiomas, and esthesioblastoma

The results of a phase I feasibility study from University of Virginia show that Gliadel® is a reasonable option in the treatment of non-glial intracranial tumors such as pituitary adenomas and craniopharyngiomas. Among the 10 patients

enrolled in this study, 7 were still alive after a mean follow-up of 19 months, with 4 patients free of recurrent tumor, and 2 with stable disease (Laws et al 2003). No side-effects such as CSF leaks were observed in this population, though more than half the patients have received either stereotactic radiosurgery or conventional focal radiation to the tumor bed.

A case report was also published about the use of carmustine wafers in the treatment of esthesioblastomas, with good local control and minimum complications (Park et al 2006). More research needs to be done in order to be able to conclude that this treatment is efficacious in the treatment of this rare tumor.

Metastatic brain tumors

Animal studies from Brem's group show that Gliadel® in combination with radiation is effective against the four metastatic tumor models tested in the initial study: lung carcinoma, renal cell carcinoma, colon carcinoma and melanoma (Ewend et al 1996), as well as in a model of breast carcinoma (Ewend et al 1998). A newly published phase II study reports on the safety and efficacy of Gliadel® wafers followed by whole-brain radiation for the treatment of single brain metastasis (Ewend et al 2007). This treatment achieved superior local control, with zero local recurrences and a rate of distal brain relapse of 16%, similar to other studies of brain metastasis (Patchell et al 1990, 1998). Therapy was well tolerated, with 3 severe side-effects such as seizures and respiratory compromise, and 7 mild or moderate adverse effects (nausea, fever, constipation, and eye pain). The median survival was 33 weeks, with 33% survival at 1 year, and 25% at 2 years.

Summary and conclusion

BCNU polymeric wafers represent an innovative way of delivering chemotherapy directly to the intracerebral high-grade tumors, with no systemic toxicity. Building on the known activity of BCNU as alkylating agent in malignant gliomas, it allows for sequential drug release in a constant and safe manner in the surrounding brain tissue. This method is very well tolerated, with minimal local toxicity.

Clinical trials using Gliadel® have shown that it is a valid option in a selected group of patients with malignant gliomas (good performance status, only one relatively small lesion), in both the new diagnosed and recurrent settings. Recent studies are suggesting that the activity of the BCNU wafers can be improved by administration of agents that overcome resistance to BCNU (such as O^6-BG), and the results of combination trials with other therapeutic modalities appear promising. More data need to be accumulated in

order to have a clear understanding of the role of Gliadel® in the treatment of other intracranial neoplasms, as well as intracranial metastatic disease.

The complications of using the Gliadel® seem to be comparable with those of craniotomy alone, but increased difficulty with wound healing, and rare and potential fatal incidents of malignant brain edema, as well as of chemical meningitis followed by obstructive hydrocephalus, have been reported. Therefore, the survival benefits of Gliadel® placement should be balanced by the clinician with the concern for possible toxicity.

The limitations of the BCNU wafers are directly related to the limited penetrance of BCNU, as most of the tumors recur locally, at a short distance from the wafers. Therefore, it is critical to evaluate valid systemic treatments, which can both address the local and the distant brain involvement, and which can be safely used in this setting. A number of promising multimodal therapies are currently progressing through clinical trials, based on the good safety profile already demonstrated in the combinations studies of different systemic chemotherapeutic agents such as temozolomide, carboplatin, PCV, and carboplatin in patients that have received Gliadel® (Ashby and Ryken 2006).

In conclusion, the unique properties of the Gliadel®, its lack of systemic side-effects, and its documented safety and efficacy justify its use in malignant gliomas, and its potential applications in other intracranial tumors. Large-scale trials addressing ways to overcome local resistance to BCNU, as well as multi-agent chemotherapy combinations, are currently in different stages. Further work needs to focus in developing better local delivery systems, with improved penetrance in the brain tissue, as well in addressing the multifactorial mechanisms of BCNU resistance, and in attempting the interstitial delivery of improved chemotherapeutic agents.

References

Ashby LS, Ryken TC. 2006. Management of malignant glioma: steady progress with multimodal approaches. *Neurosurg Focus,* 20:E3.

Blasberg RG, Patlak C, Fenstermacher JD. 1975. Intrathecal chemotherapy: brain tissue profiles after ventriculocisternal perfusion. *J Pharmacol Exp Ther,* 195:73–83.

Brem H, Ewend MG, Piantadosi S, et al. 1995a. The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trial. *J Neurooncol,* 26:111–23.

Brem H, Mahaley MS Jr, Vick NA, et al. 1991. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. *J Neurosurg,* 74:441–6.

Brem H, Piantadosi S, Burger PC, et al. 1995b. Placebo-controllefd trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet,* 345:1008–12.

Brem H, Tamargo RJ, Olivi A, et al. 1994. Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. *J Neurosurg,* 80:283–90.

Carter SK, Schabel FM Jr, Broder LE, et al. 1972. 1,3-bis2-chloroethyl.-1-nitrosourea bcnu. and other nitrosoureas in cancer treatment: a review. *Adv Cancer Res,* 16:273–332.

Central Brain Tumor Registry of the United States. 2004–2005. Primary Brain Tumors in the United States. Statistical Report 1997–2001. Central Brain Tumor Registry of the United States.

Chang CH, Horton J, Schoenfeld D, et al. 1983. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study. *Cancer,* 52:997–1007.

Cohen RJ, Wiernik PH, Walker MD, et al. 1976. Acute nonlymphocytic leukemia associated with nitrosourea chemotherapy: report of two cases. *Cancer Treat Rep,* 60:1257–61.

Crittenden D, Tranum BL, Haut A, et al. 1977. Pulmonary fibrosis after prolonged therapy with 1,3-bis 2-chloroethyl.-1-nitrosourea. *Chest,* 72:372–3.

Dang W, Daviau T, Brem, H. 1996. Morphological characterization of polyanhydride biodegradable implant gliadel during in vitro and in vivo erosion using scanning electron microscopy. *Pharm Res,* 13:683–91.

Darakchiev BJ, Albright R, Breneman JC. et al. 2004. Prolonged survival in patients with recurrent glioblastoma multiforme treated by resection with implantation of permanent I-125 seeds and BCNU-impregnated wafers. [abstract]. AANS Meeting 2004; Orlando, FL, USA.

De Vita VT, Carbone PP, Owens AH Jr, et al. 1965. Clinical trials with 1,3-bis2-chloroethyl.-1-nitrosourea, NSC-409962. *Cancer Res,* 25:1876–81.

De Vita VT, Denham C, Davidson JD, et al. 1967. The physiological disposition of the carcinostatic 1,3-bis2-chloroethyl.-1-nitrosourea BCNU. in man and animals. *Clin Pharmacol Ther,* 8:566–77.

Domb AJ, Rock M, Perkin C, et al. 1995. Excretion of a radiolabelled anticancer biodegradable polymeric implant from the rabbit brain. *Biomaterials,* 16:1069–72.

Drablos F, Feyzi E, Aas PA, et al. 2004. Alkylation damage in DNA and RNA – repair mechanisms and medical significance. *DNA Repair Amst,* 3:1389–407.

Ewend MG, Brem S, Gilbert M, et al. 2007. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer* Res, 13:3637–41.

Ewend MG, Sampath P, Williams JA, et al. 1998. Local delivery of chemotherapy prolongs survival in experimental brain metastases from breast carcinoma. *Neurosurgery,* 43:1185–93.

Ewend MG, Williams JA, Tabassi K, et al. 1996. Local delivery of chemotherapy and concurrent external beam radiotherapy prolongs survival in metastatic brain tumor models. *Cancer Res,* 56:217–23.

Felker GM, Friedman HS, Dolan ME, et al. 1993. Treatment of subcutaneous and intracranial brain tumor xenografts with O6-benzylguanine and 1,3-bis2-chloroethyl.-1-nitrosourea. *Cancer Chemother Pharmacol,* 32:71–6.

Fleming AB, Saltzman WM. 2002. Pharmacokinetics of the carmustine implant. *Clin Pharmacokinet,* 41:03–19.

Foltz GD, Spence A, Stelzer K, et al. 2001. Combined treatment of recurrent glioblastoma with gliadel wafers and iodine-125 seeds. Annual Meeting of American Association of Neurological Surgeons, San Diego, CA.

Friedman HS, Dolan ME, Moschel RC, et al. 1992. Enhancement of nitrosourea activity in medulloblastoma and glioblastoma multiforme. *J Natl Cancer Inst,* 84:926–31.

Friedman HS, Kokkinakis DM, Pluda J, et al. 1998a. Phase I trial of O6-benzylguanine for patients undergoing surgery for malignant glioma. *J Clin Oncol,* 16:570–5.

Friedman HS, McLendon RE, Kerby T, et al. 1998b. DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. *J Clin Oncol,* 16:851–7.

Gallego JM, Barcia JA, Barcia-Marino C. 2007. Fatal outcome related to carmustine implants in glioblastoma multiforme. *Acta Neurochir Wien,* 149:61–5.

Garfield J, Dayan AD, Weller RO. 1975. Postoperative intracavitary chemotherapy of malignant supratentorial astrocytomas using BCNU. *Clin Oncol,* 1:13–22.

Giese A, Kucinski T, Knopp U, et al. 2004. Pattern of recurrence following local chemotherapy with biodegradable carmustine BCNU. implants in patients with glioblastoma. *J Neuro Oncol,* 66:51–60.

Green SB, Byar DP, Walker MD, et al. 1983. Comparisons of carmustine, procarbazine, and high-dose methylprednisolone as additions to surgery and radiotherapy for the treatment of malignant glioma. *Cancer Treat Rep,* 67:21–32.

Grimmond HE, Zirvi KA. 1987. Biochemical analysis of the effects of 1,3-bis2-chloroethyl.-1-nitrosourea on the growth of a human melanoma cell line. *Cancer Lett,* 36:31–7.

Grossman SA, Reinhard C, Colvin OM, et al. 1992. The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. *J Neurosurg,* 76:640–7.

Gururangan S, Cokgor L, Rich JN, et al. 2001. Phase I study of Gliadel wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. *Neuro Oncol,* 3:246–50.

Hegi ME, Diserens AC, Godard S, et al. 2004. Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. *Clin Cancer Res,* 10:1871–4.

Johnston TP, McCaleb GS, Montgomery JA. 1963. The synthesis of antineoplastic agents. xxxii. N-nitrosoureas. I. *J Med Chem,* 6:669–81.

Kann HE Jr. 1978. Comparison of biochemical and biological effects of four nitrosoureas with differing carbamoylating activities. *Cancer Res,* 38:2363–6.

Kleinberg LR, Weingart J, Burger P, et al. 2004. Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest,* 22:1–9.

Kohn KW. 1977. Interstrand cross-linking of DNA by 1,3-bis2-chloroethyl.-1-nitrosourea and other 1-2-haloethyl.-1-nitrosoureas. *Cancer Res,* 37:1450–4.

Larocca R, Glisson S, Hargis J, et al. 2005. High-grade glioma treated with surgery; carmustine wafer; postoperative radiation; and procarbazine, lomustine, and vincristine chemotherapy. *Neurosurgery Quarterly,* 15:167–71.

Larocca R, Hodes J, Villanueva W, et al. 2006. A phase II study of radiation with concomitant and then sequential temozolomide TMZ. in patients with newly diagnosed supratentorial high-grade malignant glioma who have undergone surgery with carmustine BCNU. Wafer insertion. *Neuro Oncol,* 8:445.

Laws ER Jr, Morris AM, Maartens N. 2003. Gliadel for pituitary adenomas and craniopharyngiomas. *Neurosurgery,* 53:255–69; discussion 259–60.

Limentani SA, Asher A, Heafner M, et al. 2005. A phase I trial of surgery, Gliadel wafer implantation, and immediate postoperative carboplatin in combination with radiation therapy for primary anaplastic astrocytoma or glioblastoma multiforme. *J Neuro Oncol,* 72:241–4.

Litam JP, Dail DH, Spitzer G, et al. 1981. Early pulmonary toxicity after administration of high-dose BCNU. *Cancer Treat Rep,* 65:39–44.

Lohrmann HP, Lepp KA, Schreml W. 1982. 5-Fluorouracil, 1,3-bis2-chloroethyl.-1-nitrosourea, and 1-2-chloroethyl.-3-4-methylcyclohexyl.-1-nitrosourea: effect on the human granulopoietic system. *J Natl Cancer Inst,* 68:541–7.

Loo TL, Dion RL, Dixon RL. et al. 1966. The antitumor agent, 1,3-bis2-chloroethyl.-1-nitrosourea. *J Pharm Sci,* 55:492–7.

McGirt MJ, Villavicencio AT, Bulsara KR, et al. 2002. Management of tumor bed cysts after chemotherapeutic wafer implantation. Report of four cases. *J Neurosurg,* 96:941–5.

McGovern PC, Lautenbach E, Brennan PJ, et al. 2003. Risk factors for postcraniotomy surgical site infection after 1,3-bis 2-chloroethyl.-1-nitrosourea Gliadel. wafer placement. *Clin Infect Dis,* 36:759–65.

McHugh PJ, Spanswick VJ, Hartley JA. 2001. Repair of DNA interstrand crosslinks: molecular mechanisms and clinical relevance. *Lancet Oncol*, 2:483–90.

Meldorf MG, Riddle V, Agarwal S, et al. 2003. Long-term efficacy of the Gliadel wafer in patients with glioblastoma multiforme. Annual Meeting of American Association of Neurological Surgeons, San Diego, CA.

Michels SD, McKenna RW, Arthur DC, et al. 1985. Therapy-related acute myeloid leukemia and myelodysplastic syndrome: a clinical and morphologic study of 65 cases. *Blood*, 65:1364–72.

Ohgaki H, Kleihues P. 2005. Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. *J Neuropathol Exp Neurol*, 64:479–89.

Oliverio VT. 1976. Pharmacology of the nitrosoureas: an overview. *Cancer Treat Rep*, 60:703–7.

Olivi A, Grossman SA, Tatter S, et al. 2003. Dose escalation of carmustine in surgically implanted polymers in patients with recurrent malignant glioma: a new approach to brain tumor therapy CNS Consortium trial. *J Clin Oncol*, 21:1845–9.

Park MC, Weaver CE Jr, Donahue JE, et al. 2006. Intracavitary chemotherapy Gliadel. for recurrent esthesioneuroblastoma: case report and review of the literature. *J Neuro Oncol*, 77:47–51.

Patchell RA, Tibbs PA, Regine WF, et al. 1998. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA*, 280:1485–9.

Patchell RA, Tibbs PA, Walsh JW, et al. 1990. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*, 322:494–500.

Pegg AE, Dolan ME, Moschel RC. 1995. Structure, function, and inhibition of O^6-alkylguanine-DNA alkyltransferase. *Prog Nucleic Acid Res Mol Biol*, 51:167–223.

Penman M, Huffman R, Kumar A. 1976. Regulation of ribosomal RNA synthesis and processing during inhibition of protein synthesis by 1,3-bis2-chloroethyl.-1-nitrosourea. *Biochemistry*, 15:2661–8.

Quinn JA, Vredenburgh JJ, Rich JN, et al. 2007. Phase II trial of Gliadel plus O^6-benzylguanine O^6-BG. for patients with recurrent glioblastoma. 43rd ASCO Annual Meeting.

Raza SM, Pradilla G, Legnani FG, et al. 2005. Local delivery of antineoplastic agents by controlled-release polymers for the treatment of malignant brain tumours. *Expert Opin Biol Ther*, 5:477–94.

Rhines LD, Sampath P, Dimeco F, et al. 2003. Local immunotherapy with interleukin-2 delivered from biodegradable polymer microspheres combined with interstitial chemotherapy: a novel treatment for experimental malignant glioma. *Neurosurgery*, 52:872–9; discussion 879–80.

Rhines LD, Sampath P, Dolan ME, et al. 2000. O^6-benzylguanine potentiates the antitumor effect of locally delivered carmustine against an intracranial rat glioma. *Cancer Res*, 60:6307–10.

Rich JN, Affronti ML, Day JM, et al. 2007. Overall survival of primary glioblastoma GBM patients receiving carmustine BCNU. Wafers followed by radiation and concurrent temozolomide plus rotational multi-agent chemotherapy. *J Clin Oncol, 2007 ASCO Annual Meeting Proceedings*. In press.

Sampath P, Sungarian A, Alderson L, et al. 2005a. BCNU-impregnated wafers Gliadel. plus irinotecan Camptosar. in combination treatment for patients with reccurent glioblastoma multiforme. [abstract] Annual Meeting of the CNS 2005; New Orleans, LA, USA.

Sampath P, Weaver CE Jr, Alderson L, et al. 2005b. Consecutive use of brachytherapy gliaside. and intratumoral chemotherapy gliadel. for recurrent glioblastoma: A phase I/II study with independent clinical review. Annual Meeting of American Association of Neurological Surgeons, Boston, MA.

Schabel FM Jr, Johnston TP, McCaleb GS, et al. 1963. Experimental evaluation of potential anticancer agents VIII. Effects of certain nitrosoureas on intracerebral L1210 leukemia. *Cancer Res*, 23:725–33.

Schabel FM Jr. 1973. Historical development and future promise of the nitrosoureas as anticancer agents. *Cancer Chemother Rep 3*, 4:3–6.

Schabel FM Jr. 1976. Nitrosoureas: a review of experimental antitumor activity. *Cancer Treat Rep*, 60:665–98.

Schepartz SA. 1976. Early history and development of the nitrosoureas. *Cancer Treat Rep*, 60:647–9.

Selker RG, Shapiro WR, Burger P, et al. 2002. The Brain Tumor Cooperative Group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery*, 51:343–55; discussion 355–7.

Stewart LA. 2002. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet*, 359:1011–8.

Stupp R, Mason WP, Van Den Bent MJ, et al. 2005. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*, 352:987–96.

Tamargo RJ, Myseros JS, Epstein JI, et al. 1993. Interstitial chemotherapy of the 9L gliosarcoma: controlled release polymers for drug delivery in the brain. *Cancer Res*, 53:329–33.

Tozer K, Silbergeld DL, Rostomily RC, et al. 2003. Concomitant use of Gliadel and permanent low-activity I-125 seed implants for recurrent malignant glioma. Annual Meeting of American Association of Neurological Surgeons, Denver, CO.

Valtonen S, Timonen U, Toivanen P, et al. 1997. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. *Neurosurgery*, 41:44–8; discussion 48–9.

Weber EL, Goebel EA. 2005. Cerebral edema associated with Gliadel wafers: two case studies. *Neuro Oncol*, 7:84–9.

Weingart J, Grossman SA, Carson KA, et al. 2007. Phase I trial of polifeprosan 20 with carmustine implant plus continuous infusion of intravenous O^6-benzylguanine in adults with recurrent malignant glioma: new approaches to brain tumor therapy CNS consortium trial. *J Clin Oncol*, 25:399–404.

Weiss RB, Issell BF. 1982. The nitrosoureas: carmustine BCNU. and lomustine CCNU. *Cancer Treat Rev*, 9:313–30.

Weiss RB, Poster DS, Penta JS. 1981. The nitrosoureas and pulmonary toxicity. *Cancer Treat Rev*, 8:111–25.

Westphal M, Hilt DC, Bortey E, et al. 2003. A phase 3 trial of local chemotherapy with biodegradable carmustine BCNU. wafers Gliadel wafers. in patients with primary malignant glioma. *Neuro Oncol*, 5:79–88.

Westphal M, Ram Z, Riddle V, et al. 2006. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir Wien*, 148:269–75; discussion 275.

Whittle IR, Lyles S, Walker M. 2003. Gliadel therapy given for first resection of malignant glioma: a single centre study of the potential use of Gliadel. *Br J Neurosurg*, 17:352–4.

Woolley PV, Dion RL, Kohn KW, et al. 1976. Binding of 1-2-chloroethyl.-3-cyclohexyl-1-nitrosourea to L1210 cell nuclear proteins. *Cancer Res*, 36:1470–4.

Wu MP, Tamada JA, Brem H, et al. 1994. In vivo versus in vitro degradation of controlled release polymers for intracranial surgical therapy. *J Biomed Mater Res*, 28:387–95.

Yang MB, Tamargo RJ, Brem H. 1989. Controlled delivery of 1,3-bis2-chloroethyl.-1-nitrosourea from ethylene-vinyl acetate copolymer. *Cancer Res*, 49:5103–7.

Zamorano L, Li Q, Levin K, et al. 2005. Brachytherapy with I-125 permanent implant combined with sequential Gliadel in the treatment of GBM: A novel approach.[abstract] AANS Meeting 2005; New Orleans, LA, USA.