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REVIEW

Polifeprosan 20, 3.85% carmustine slow-release wafer in malignant glioma: evidence for role in era of standard adjuvant temozolomide

This article was published in the following Dove Press journal:
Core Evidence
25 October 2012
Number of times this article has been viewed

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Abstract: The Polifeprosan 20 with carmustine (BCNU, bis-chloroethylnitrosourea, Gliadel®) polymer implant wafer is a biodegradable compound containing 3.85% carmustine which slowly degrades to release carmustine and protects it from exposure to water with resultant hydrolysis until the time of release. The carmustine implant wafer was demonstrated to improve survival in blinded placebo-controlled trials in selected patients with newly diagnosed or recurrent malignant glioma, with little increased risk of adverse events. Based on these trials and other supporting data, US and European regulatory authorities granted approval for its use in recurrent and newly diagnosed malignant glioma, and it remains the only approved local treatment. The preclinical and clinical data suggest that it is optimally utilized primarily in the proportion of patients who may have total or near total removal of gross tumor. The aim of this work was to review the evidence for the use of carmustine implants in the management of malignant astrocytoma (World Health Organization grades III and IV), including newly diagnosed and recurrent disease, especially in the setting of a standard of care that has changed since the randomized trials were completed. Therapy has evolved such that patients now generally receive temozolomide chemotherapy during and after radiotherapy treatment. For patients undergoing repeat resection for malignant glioma, a randomized, blinded, placebo-controlled trial demonstrated a median survival for 110 patients who received carmustine polymers of 31 weeks compared with 23 weeks for 122 patients who only received placebo polymers. The benefit achieved statistical significance only on analysis adjusting for prognostic factors rather than for the randomized groups as a whole (hazard ratio = 0.67, $P = 0.006$). A blinded, placebo-controlled trial has also been performed for carmustine implant placement in newly diagnosed patients prior to standard radiotherapy. Median survival was improved from 11.6 to 13.9 months ($P = 0.03$), with a 29% reduction in the risk of death. When patients with glioblastoma multiforme alone were analyzed, the median survival improved from 11.4 to 13.5 months, but this improvement was not statistically significant. When a Cox's proportional hazard model was utilized to account for other potential prognostic factors, there was a significant 31% reduction in the risk of death ($P = 0.04$) in this subgroup. Data from other small reports support these results and confirm that the incidence of adverse events does not appear to be increased meaningfully. Given the poor prognosis without possibility of cure, these benefits from a treatment with a favorable safety profile were considered meaningful. There is randomized evidence to support the use of carmustine wafers placed during resection of recurrent disease. Therefore, although there is limited specific evidence, this treatment is likely to be efficacious in an environment when nearly all patients receive temozolomide as part of initial management. Given that half of the patients in the randomized trial assessing the value of carmustine implants in recurrent disease had received prior chemotherapy, it is likely that this remains a valuable treatment at the time of repeat resection, even after temozolomide. There are data from multiple reports to support safety. Although there is randomized evidence to support the use of this therapy in newly diagnosed

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patients who will receive radiotherapy alone, it is now standard to administer both adjuvant temozolomide and radiotherapy. There are survival outcome reports for small cohorts of patients receiving temozolomide with radiotherapy, but this information is not sufficient to support firm recommendations. Based on the rationale and evidence of safety, this approach appears to be a reasonable option as more information is acquired. Available data support the safety of using carmustine wafers in this circumstance, although special attention to surgical guidelines for implanting the wafers is warranted.

Keywords: carmustine, Polifeprosan 20, malignant glioma

Summary

Outcome measure	Evidence	Implications
Disease specific scientific evidence	BCNU is known to be active. Local failure is predominant mode of failure. Blood brain barrier can otherwise prevent adequate drug delivery. Preclinical studies confirm goal of localized drug delivery can be achieved. In mammalian studies 1 Slow release occurs 2 Leads to high localized drug concentrations for days 3 Little toxicity or safety issues identified 4 Safe with radiation.	An agent known to be active in malignant glioma, when administered intravenously, was selected for study. This technology may be useful in delivering active drugs that have not been clinically useful because they do not cross the blood brain barrier when administered intravenously.
Patient Oriented Evidence • In recurrent malignant glioma	Blinded placebo controlled randomized data demonstrates benefit in comparison with placebo wafers. Although benefit is modest, there is little toxicity or patient burden. Benefit statistically significant on adjusted analysis only. Safety confirmed in smaller retrospective and prospective reports.	Survival outcome is significantly, although modestly, improved with little burden or risk to the patient.
• In initial management of malignant glioma, with radiation	Blinded placebo controlled randomized data demonstrates benefit in comparison with placebo wafers. Survival benefit, with limited toxicity, appears similar compared to results of other treatments that are used in this disease which continues to have a poor prognosis.	Survival outcome is significantly, although modestly, improved with little burden or risk to the patient.
• In initial management of malignant glioma, with radiation and temozolomide	Small series suggest safety. Limited evidence about efficacy from small series. Considered an appropriate option.	It is probable that there is a benefit based on uncontrolled studies and studies in related clinical situations with glioblastoma, but this has not been definitively demonstrated.
Economic Evidence	Limited analysis. Unclear that cost meets per quality adjusted life year was within general standards of the British National Health service, but use permitted within licensed indications. Considered appropriate and approved by US and European regulatory agencies as a result of supporting randomized data, limited options shown to be effective, favorable risk/toxicity profile, and potential value of modest improvements in setting of poor prognosis.	This option has been considered appropriate based on the demonstrated benefit, costs and burdens of other commonly used treatments for this disease, and lack of superior alternatives.
Other Issues	There may be significant opportunity to use the underlying polymer technology to deliver other therapies. The value in other intracranial malignant diseases such as brain metastasis may exist, but has not been assessed in large prospective studies or randomized trials.	Future study using this technology to deliver other drugs is warranted.

Introduction

Carmustine (BCNU, bis-chloroethylnitrosourea, Gliadel®) wafers, in the commercially available formulation (Polifeprosan 20, 3.85% carmustine), have been demonstrated in randomized trials to improve outcome when used either as multimodality initial therapy in patients with newly diagnosed malignant glioma[1,2] or as an adjunct to surgery for recurrence.[3] Although the benefits were modest, the improvement was considered to be meaningful in a disease with an exceptionally poor prognosis and for which few other options have been proven to be effective. In addition, the toxicity profile, with attention to special surgical techniques, was quite favorable, resulting in minimal patient burden. Since the completion of these randomized trials demonstrating the value of carmustine wafers, temozolomide has been shown to induce responses in recurrent high-grade glioma and to improve median and relatively longer-term survival[4,5] when used in the initial management of newly diagnosed patients. Therefore, it is useful to re-evaluate the role of carmustine implants and the applicability of the supporting evidence in light of this new development that has altered the standard of care for the initial management of malignant glioma.

Despite much study and effort, high-grade gliomas of the brain have remained challenging to treat effectively. The first advance in standard management resulted from a landmark randomized trial published in 1978[6,7] which demonstrated that radiotherapy improved median survival in patients with high-grade glioma, even though survival beyond 12–18 months remained quite poor. These studies also suggested that carmustine chemotherapy, thought to be active for glioma[8,9] and to penetrate the blood-brain barrier, may improve the possibility of relatively long-term survival for 12–18 months, but this benefit was not persistent in the longer term, nor did it achieve statistical significance. In addition, in the setting of recurrent disease, systemically administered carmustine was found to be useful for inducing a generally short-term response or stabilization in a proportion of patients with recurrent malignant glioma, as did some other agents, such as procarbazine, vincristine, and lomustine. The lack of substantial success in the treatment of this disease potentially relates to the biology of the tumor which may result in resistance to standard therapeutic approaches, the infiltrative properties which make resection with truly negative margins in the brain impossible, the limits to the amount of radiation that can be safely given to the entire area at risk, and limited penetrance of systemically administered drugs due to the blood-brain barrier. After radiotherapy was found to be efficacious in a randomized trial, the next therapy shown to improve survival in such trials in this disease was the carmustine implant in patients with recurrent disease in 1995[3] and newly diagnosed patients in 2003.[1,2]

Because of the poor outcome of this disease, there was and continues to be great interest in developing new therapeutic approaches. One potential approach to improving outcome that has long been investigated is enhancing drug delivery by overcoming the limitation created by the blood-brain barrier.[10–14] This is the rationale behind the use of carmustine wafers, which are placed directly into the resection cavity. Approaches have included osmotic disruption of the blood-brain barrier, intra-arterial administration of drugs at high concentration directly to the area of risk, and direct administration to the brain. The latter approach is particularly attractive because it not only overcomes the impact of the blood-brain barrier, but may also limit systemic toxicity and allow delivery of higher concentrations of drug to the localized region of highest risk than would be possible even if the blood-brain barrier were nonexistent. Such local therapeutic approaches are of particular interest in this disease because the main pattern of early failure is primarily at or adjacent to the initial tumor location, leading directly to symptoms and ultimately death, and distant metastasis outside the central nervous system remains a remote possibility. Potential administration methods may include direct injection, placement of infusion catheters, convection-enhanced delivery, and placement of slow-release polymers. Of the approaches tested thus far, only placement of slow-release carmustine polymer implants has been demonstrated in randomized trials to improve survival at any point in the course of the illness.

The randomized trials testing carmustine wafers provided core evidence that this approach was efficacious in providing a modest yet real and meaningful improvement in survival in appropriately selected patients, with minimal toxicity and less patient time commitment and burden.[1–3] Although the diffusion of this intervention into routine practice has not been studied, its use has clearly varied between different neurosurgeons and care teams. Wafer implantation is only suitable for patients who are able to have at least a near gross total resection to create a cavity to hold the wafers and with only minimal gross residual tumor, such that it is likely to be covered by a high concentration of carmustine. In addition, the benefits have been most clear in analysis that adjusts for prognostic factors, rather than in simple unadjusted comparisons of randomized groups. In this setting, where patients are randomized prior to craniotomy, it is not possible to know in advance and stratify for extent of resection, final pathologic grade, or postoperative condition

and course, as is the case in trials testing adjuvant systemic therapies. When selecting patients for this therapy, it should be noted that an unplanned subgroup analysis[15] showed that a significant survival benefit could only be demonstrated for patients with greater than 90% resection, in keeping with the known drug distribution.

Demonstration of activity for temozolomide[4,5] and its incorporation into routine clinical practice has raised new questions about optimal use of carmustine implant therapy. It is highly likely that carmustine implants remain an important option for those who have recurrent disease after prior therapy, even in the current environment where most would have received prior therapy with temozolomide, an alkylating agent. Half of the patients in the randomized trial demonstrating the benefits of carmustine wafers in the treatment of recurrent disease had actually received prior chemotherapy, and thus it is highly likely that the results of this trial remain valid now that most patients will have been treated with temozolomide.

The current optimal role of carmustine implants at the time of initial surgery is more controversial in the absence of randomized data or large prospective series utilizing carmustine implants, radiotherapy, and temozolomide in combination. First of all, it is unclear if temozolomide or a carmustine wafer implant is significantly better than the other as a single agent combined with radiotherapy as the outcomes have not been directly compared. Limited evidence exists from several small studies suggesting that carmustine implants used at the time of initial resection are safe in this new clinical context where temozolomide is to be given along with and subsequent to radiotherapy, and at least raises the question of whether the addition of a carmustine implant may improve outcome even when temozolomide is utilized.[16–31] The accumulation of new evidence on the role of carmustine implants in the initial management of malignant glioma has been hindered by the fact that patients with such wafer placement have been excluded from most trials testing other new therapies because of concern about unpredictable toxicity and difficulties in interpreting results. This factor may also reduce the use of carmustine implant wafers in initial management because patients and/or physicians may wish to preserve the option to access experimental therapies. In our practice, we do continue to offer the choice of this combined approach in selected surgically resectable patients after careful discussion of the alternatives. The disease-specific scientific evidence and patient-specific evidence for the use of Polifeprosan 20 carmustine implants is summarized in Table 1 and discussed in more detail below.

Disease-specific scientific evidence

The Polifeprosan wafer was selected as a potentially appropriate means to deliver carmustine chemotherapy by controlled release after direct implantation of the wafers, because it supports gradual release and is hydroponic, thereby protecting carmustine from exposure to water which would result in hydrolysis and deactivation.[28,32–34] Carmustine was selected as an appropriate agent because it has well known efficacy in malignant glioma. Local therapy has unique potential to be beneficial in this disease, where the blood-brain barrier can be an obstacle to delivery of many drugs.

The wafer is a copolymer of 1,3-bis-(*p*-carboxyphenoxy) propane (CPP) and sebacic acid in a 20:80 ratio.[28,35–38] This compound was selected because it supports slow release and protects the carmustine from inactivation by exposure to water until it is released. Two-phase degradation of the polymer results in release of carmustine. In the first phase, upon exposure to the aqueous environment of tissues, the bonds of the copolymer are hydrolyzed over a period of approximately ten hours. The bonds involving sebacic acid to sebacic acid or to CPP appear to degrade rapidly, whereas CPP-CPP bonds in the polymer degrade more slowly. The result is gradual degradation from the surface inwards, protecting the carmustine in the interior from the aqueous environment. After initial degradation of the polymer bonds, there follows a period of erosion which originates at the surface layer, and carmustine release continues. The physical process of wafer degradation from the surface inwards has been confirmed by electron microscopy.[29,39]

Because evaluation of drug and polymer concentrations in the brain cannot be performed in human clinical trials, the available data originate from in vivo mammalian studies. Much of these data were accumulated in parallel with clinical development of the product in humans, and does confirm that the goal of delivering BCNU at a high localized concentration is achieved. A study undertaken to explore the kinetics of wafer degradation and carmustine release[27] from implanted wafers in a rabbit model using a polymer containing radiolabeled sebacic acid, CPP, or carmustine, demonstrated that only 10% of sebacic acid remained in place after a week. Interestingly, the water-insoluble CPP remained, with little excreted in the first 7–9 days, but with increasing excretion thereafter, which was thought to be

Table 1 Significant evidence: Polifeprosan 20 with carmustine polymer implant wafers

Disease-specific scientific evidence	Carmustine is known to be active
	Local failure is predominant mode of failure
	Blood-brain barrier can otherwise prevent adequate drug delivery
	Preclinical studies confirm goal of localized drug delivery can be achieved in mammalian studies • Slow release occurs • Leads to high localized drug concentrations for days • Little toxicity or safety issues identified • Safe with radiation
Patient-oriented evidence	Blinded, placebo-controlled, randomized data demonstrate benefit in comparison with placebo wafers
In recurrent malignant glioma	Although benefit is modest, there is little toxicity or patient burden
	Benefit statistically significant on adjusted analysis only
	Safety confirmed in smaller retrospective and prospective reports
In initial management of malignant glioma, with radiation	Blinded, placebo-controlled, randomized data demonstrate benefit in comparison with placebo wafers
	Survival benefit, with limited toxicity, appears similar compared with results of other treatments that are used in this disease which continues to have a poor prognosis
In initial management of malignant glioma, with radiation and temozolomide	Small series suggest safety
	Limited evidence about efficacy from small series
	Considered an appropriate option
Economic evidence	Limited analysis
	Unclear that cost meets per quality-adjusted life-year was within general standards of the British National Health Service, but use permitted within licensed indications
	Considered appropriate and approved by US and European regulatory agencies as a result of supporting randomized data, limited options shown to be effective, favorable risk/toxicity profile, and potential value of modest improvements in setting of poor prognosis
Other issues	There may be significant opportunity to use the underlying polymer technology to deliver other therapies
	Value in other intracranial malignant diseases such as brain metastasis may exist, but has not been assessed in large prospective studies or randomized trials

facilitated by the ultimate fragmentation and disintegration of the implant over time. After 3 days, approximately 40% of the carmustine still remained undelivered in the polymer, whereas by the end of a week very little could be detected, confirming the predicted gradual release.

The actual distribution of the drug in the brain has been measured in several mammalian species, and has been found to vary. The maximal dose, as would be expected, is at the polymer/tissue interface. For example, in a rabbit model,[40] the distribution of radiolabeled carmustine was assessed with 2.5%, 5%, and 10% loading of wafers and with direct injection. Comparison groups were treated with radiolabeled inulin-containing wafers and with direct injection of radiolabeled carmustine. Three days after implantation, 30%–50% of the brain volume demonstrated the presence of radioactive carmustine, whereas by 7 days, this had fallen to 5%–18% of the brain volume, with the proportions being higher where polymer loading was stronger. Three days after implantation, significant concentrations (defined as at least 10% of the concentration at the tissue/polymer interface) of carmustine were detected at a radius of 10–12 mm, with an average concentration of 3, 6, and 8 mM for the three loadings of the polymer, respectively. It may be of great importance that a significantly larger volume may actually be exposed to active concentrations, which may be 14–15 μM.[41] Evidence of inflammation was seen on histologic examination at 3 days in animals receiving carmustine wafers but not inulin-containing wafers, suggesting a response to the drug and not the wafer itself. The observed inflammation generally improved at later sacrifice points on days 7–21. After direct injection, carmustine was observed to be widely distributed in the brain in the first few hours, then rapidly cleared, with little remaining by 24 hours. Levels of radiolabeled inulin, a larger stable molecule, remained high for a longer period of time, consistent with the hypothesis that a larger molecule with limited penetrance of the blood-brain barrier would be "trapped" and therefore persist longer and diffuse further. Although the specifics did vary, similar results were observed in a rat model.[42]

In larger primate experiments using the Cynomolgus monkey,[43,44] carmustine was detected after wafer placement, even in distant areas of the brain, potentially due to re-entry into brain tissue after this lipophilic agent has penetrated into the cerebrospinal fluid or intracranial blood. Significant concentrations of carmustine in the cerebrospinal fluid were indeed confirmed. Because carmustine administered by the polymer maintains drug concentrations for a long period of time compared with standard intravenous administration, the authors used the area under the curve (AUC, concentration over time) as a metric to compare the polymer with intravenous administration of carmustine as a means of delivering drug to brain tissue. Standard intravenous administration was estimated to result generally in a four-fold smaller AUC in distant areas of the brain compared with wafer placement, with 25–1200-fold less at the polymer/brain interface. It should be recognized that the clinical implications of the AUC as well as the peak concentration of carmustine are not well studied, but this observation can be considered concrete evidence that this therapeutic approach had a potential impact on a relevant volume of brain tissue. Preclinical findings in a rat 9L glioma model provide some evidence that slow-release delivery may be superior, with prolonged survival when Polifeprosan 20 wafers were used as a delivery method compared with a similar direct injection of carmustine into tumor tissue.[45]

Thus, the disease-specific scientific evidence supported clinical development of this therapy in this specific formulation, and in general could support use of this technology to deliver other agents at high concentrations beyond the blood–brain barrier. The pattern of failure with current clinical management, even with inclusion of temozolomide, continues to be primarily localized, and potentially amenable to modification by local drug delivery which also may have the benefit of limited systemic exposure and toxicity.

Patient-specific evidence for carmustine implant in recurrent disease

A Phase I study of recurrent malignant glioma[46] undergoing resection was initiated, based on the then available data demonstrating the safety of carmustine implants in mammalian models, benefit in a rat 9 L glioma model, and clinical need. Dose escalation proceeded through three carmustine concentrations in the wafer, ie, 1.93%, 3.85%, and 6.35%, with median post-implant survival times of 65, 64, and 32 weeks, respectively. Although this was a Phase I study and not designed to assess comparative survival outcome, and there was indeed an imbalance towards a higher proportion of confirmed glioblastoma multiforme at the highest dose level, the 3.85% dose was selected for further clinical evaluation based partially on this observation. All of the dose levels were tolerable, and systemic toxicities were not encountered with the wafer-administered chemotherapy.

In the blinded, placebo-controlled Phase III trial that followed,[47] 222 patients with recurrent malignant brain tumors from 27 medical centers and requiring reoperation were randomly assigned to receive surgically implanted biodegradable polymer discs with or without 3.85% carmustine wafers. Patients were required to have a single, unilateral, resectable contrast-enhancing lesion >1 cm in size, a recommendation for surgery regardless of polymer placement, and Karnofsky performance score ≥ 60. Approximately 80% of the enrolled patients had $>75\%$ resection of tumor. Sixty-five percent had glioblastoma as the final pathology at the time of reoperation.

Although there was no difference in survival between the randomized groups on unadjusted analysis, median survival of 110 patients who received carmustine polymers was 31 weeks compared with 23 weeks for 122 patients who received only placebo polymers (hazard ratio = 0.67, $P = 0.006$, after accounting for the effects of prognostic factors). Among patients with confirmed glioblastoma (grade IV), 6-month survival in those treated with carmustine polymer discs was greater than in those treated with placebo (64% versus 44%, $P = 0.02$). No significant systemic or intracranial toxicity was encountered. However, some concern has been expressed about benefit only being demonstrated after adjustment for prognostic factors, based upon the primary overall comparison of the randomized groups.[48,49] Nevertheless, these benefits were considered meaningful, and US Food and Drug Administration approval was granted in 1996 for this indication.

Additional prospective data are also available from the control arm of a multi-institutional trial in recurrent glioblastoma which included randomization between carmustine wafer placement and convection-enhanced delivery of IL13-PE38QQR. The median survival of 93 control patients treated by Polifeprosan 20 with carmustine 3.85% was 35.3 weeks (8.8 months), which was similar to that in the experimental arm. Adverse events were considered similar to those expected after craniotomy alone in this group.[50] This randomized trial also provided strong evidence for the safety of utilizing carmustine implants. The important toxicities are summarized in Table 2. It is important to note that the randomized trials compared carmustine-impregnated wafers

with placebo wafers, but not with similar surgery without any wafer implantation. Supportive retrospective data discussed below comparing risks with carmustine wafer implantation and craniotomy alone provided further support for the impression that this approach in newly diagnosed and recurrent patients does not appear to enhance the risks of surgery meaningfully.

Afterwards, the issue of carmustine concentration was revisited in a multi-institutional dose-escalation trial[51] carried out by the New Approaches to Brain Tumor Therapy Consortium funded by the National Cancer Institute. The Phase I trial that motivated initial development of the carmustine 3.85%-loaded polymer did not convincingly identify this as the maximum tolerated dose, raising the question of whether a further improvement in outcome would be possible utilizing a higher concentration of drug, should this prove to be safe. Polymer loading in this follow-up study included carmustine concentrations of 6.5%, 10%, 14.5%, 20%, and 28%. This study was motivated by the idea, confirmed in mammalian studies, that higher loading concentrations would result in higher administered carmustine adjacent to the wafer implants and at a distance in the brain. Intracranial complications involving edema and/or wound healing occurred in three of four patients treated with the 28% loading, but ultimately 20 patients were accrued at the 20% loading to confirm this as an appropriate dosing for further study. Although serum carmustine was actually detectable above the 6.5% loading, the concentration was 500 times lower than concentrations known to cause systemic toxicity. Unfortunately, although a larger trial to determine whether 20% loading would lead to superior efficacy was considered, it did not occur, so this question remains unexplored, and higher-concentration wafers are not commercially available.

Patient-specific evidence for carmustine implant in newly diagnosed patients

There was even greater interest in improving the initial management of newly diagnosed patients where the potential positive impact of an effective therapy may be greatest. In preparation for clinical trials, a primate study[52] was done to assess safety by clinical, imaging, and pathologic follow-up of cranial radiotherapy administered along with carmustine implantation. Eighteen Cynomolgus monkeys were randomly assigned to a control group, a group implanted with a blank polymer, a group implanted with a carmustine polymer, or a cohort with a carmustine polymer in the left brain and a blank placebo polymer in the right brain with follow-up cranial radiotherapy at 60 Gy (2 Gy/day) to the whole brain. Except for the expected postoperative complications, the animals were not observed to have neurologic events. For the animals with a polymer implant and without irradiation, imaging and pathologic follow-up suggested an inflammatory response with transient edema, and pathologic evidence of a thin rim of chronic inflammation through the 72 days of postoperative follow-up. In the group receiving radiotherapy, one animal sacrificed 72 days after radiation had a necrotic reaction around the carmustine impregnated polymer, not observed adjacent to the blank polymer, whereas in another animal no such reaction was observed at sacrifice on day 196 after radiotherapy. This was considered to demonstrate sufficient safety to proceed with human studies.

After a 22-patient Phase I trial provided initial evidence that the Polifeprosan 20 with carmustine implant followed by standard radiotherapy is a safe approach in humans,[53] a Phase III randomized trial was initiated in Norway and Finland.[54] Unfortunately, although the intention was to enroll 100 patients, an interruption in the carmustine wafer supply necessitated discontinuation after 32 patients were randomized. When the results were analyzed, median survival for the enrolled patients was improved from 40 weeks to 58 weeks ($P = 0.012$). In this relatively small trial, there was an imbalance, with more favorable grade III histology patients in the control arm, but when the glioblastoma multiforme subset was analyzed separately, the results remained positive, with median survival improved from 40 to 53 weeks ($P = 0.008$)

Table 2A Complications with carmustine implants in recurrent disease

Therapy	n	Seizures	Edema	Healing	Infection
Randomized trial, repeat surgery for recurrence[3]					
Carmustine implants	110	36%	4%	14%	3.6%
Placebo wafer	112	29%	1%	5%	0.95%
JHU retrospective report of complications, repeat resection at recurrence[60]					
Carmustine implants	122	NR	NR	0	4.9
Craniotomy alone	278	NR	NR	0.7	3.5

Abbreviation: JHU, Johns Hopkins University.

Table 2B Common adverse events after surgery and wafer placement, newly diagnosed patients

Therapy	n	Seizures	Edema	Healing	Infection
Prospective randomized trial, carmustine implants or placebo wafers[1]					
Carmustine implants	120	33%	22%	16%	5%
Placebo	120	38%	19%	12%	6%
JHU retrospective report of complications, primary resection[60]					
Carmustine implants	166	NR	NR	1.2%	1.2%
Craniotomy alone	447	NR	NR	0.2%	0.7%

Abbreviation: JHU, Johns Hopkins University.

Afterwards, a more definitive 230-patient,[1,2] placebo-controlled, blinded international trial was sponsored by Guilford Pharmaceuticals in which patients were randomized to undergo surgical resection with active or placebo wafer placement, followed by standard radiotherapy, with the objective of determining whether there was a survival benefit. The randomized groups were well matched in respect to age, performance status, and grade III versus grade IV histology. Systemic chemotherapy was not given until the time of recurrence, as was the standard of care at the time. The study was designed with adequate power to detect an 18% improvement in one-year survival. Median survival was improved from 11.6 months to 13.9 months ($P = 0.03$), with a 29% reduction in the risk of death. When the glioblastoma multiforme patients alone were analyzed, median survival improved from 11.4 months to 13.5 months, but this improvement was not statistically significant. When a Cox's proportional hazard model was utilized to account for other potential prognostic factors, a significant 31% reduction in the risk of death ($P = 0.04$) was found in this subgroup.

At the request of the British National Health Service,[15] an unplanned subgroup analysis was performed that reportedly demonstrated a significant survival benefit in the population with >90% resection of gross tumor but not in those with partial resection. The recommendation was made that this is an appropriate therapy under that circumstance based on these clinical data and the scientific evidence existing about distribution of the drug. The analysis of the implant provided by the manufacturer demonstrated that, for this subgroup (n = 111), there was a mean and median overall survival gain of 4.2 months and 2.15 months, respectively (unstratified log-rank analysis $P = 0.0061$).

In contrast, progression-free survival was 5.9 months in both arms, based on radiographic (25% increase in largest cross-sectional area, new lesion) or clinical criteria, raising the question of whether there actually was a substantial benefit in tumor control to support the observed survival benefit. This observation, which is related to progression-free survival, is likely not to be meaningful contrary evidence because survival was improved and there continues to be controversy even until now as to the utility of progression as an endpoint after radiotherapy in malignant glioma. The weakness of this endpoint results from the difficulty in distinguishing between tumor-related and treatment-related clinical and imaging changes, and this may make this endpoint quite unreliable, with survival potentially being the only definitive endpoint. In particular, in the case of patients treated with radiotherapy and carmustine implantation, our experience at Johns Hopkins University suggested that imaging changes that are considered to be most consistent with recurrence can have uncertain implications. In a report of 45 patients treated with carmustine implantation followed by radiotherapy,[55] five of 15 patients (33%, ie, 11% of all treated patients) taken to the operating room for presumed operable local recurrence were found to have a pure treatment effect or necrosis with no active glioma. Moreover, it is now well documented that, even with radiation and systemic temozolomide, there is a significant incidence of treatment effects which are difficult to distinguish radiographically from tumor tissue and are termed "pseudoprogression".[56–59] With this knowledge, caution is recommended in determining recurrence after radiotherapy (whether or not the patient has also received polymer therapy and/or systemic chemotherapy), and studies are underway to develop techniques to better distinguish treatment effects from true tumor recurrence.

Other study endpoints suggested a symptomatic or quality of life benefit.[1] The primary functional endpoint was decline in performance status, and there was a significant improvement in median time to decline from 10.4 months to 11.9 months, with a one-year deterioration-free rate of 48% versus 39% ($P = 0.05$), respectively. A statistically significant benefit was also demonstrated for ten of 11 other individual neuroperformance and neurologic examination elements assessed. Although this did not include rigorous quality of life assessment, it does provide evidence of delayed deterioration in quality of life.

The toxicity observed in both arms of this randomized trial was acceptable. Neurologic adverse events, including seizures, neurologic deficits, and operative complications, were similar in both groups, as were postoperative complications, except for cerebrospinal fluid leak (5% versus 0.8%), without an increase in infections. Added attention to the use of a watertight dural seal is now considered especially important in reducing the risk of cerebrospinal fluid leak. Beyond this, an additional poorly defined event of late intracranial hypertension (generally more than 6 months after surgery) was also more frequent at 9.1% versus 1.7%; of uncertain etiology, this could be related to the circumstances of tumor recurrence as much as to long-term effects, and has not been reported in other series. Other major events included seizures, which occurred in 23% of patients with carmustine wafer implantation versus 20% with placebo, and brain edema (23% versus 20%, respectively), which is similar to what would be expected from surgery alone.

Significant additional supporting evidence of safety comes from a large single-institution report from Johns Hopkins University[60] of operative complications in 288 patients receiving the carmustine implant (166 newly diagnosed, 122 for recurrence) and in 725 pts having craniotomy without any polymer for malignant glioma. These data provide important information about safety that supplements the randomized data where both the carmustine groups and the placebo groups had wafers implanted, but did not contain groups with craniotomy alone. In this large retrospective analysis, patients who underwent carmustine implantation versus craniotomy had similar incidences of perioperative infection at the surgical site (2.8% versus 1.8%, $P = 0.33$), cerebrospinal fluid leak (2.8% versus 1.8%, $P = 0.33$), meningitis (0.3% versus 0.3%, $P = 1.00$), incisional wound healing difficulty (0.7% versus 0.4%, $P = 0.63$), symptomatic malignant edema (2.1% versus 2.3%, $P = 1.00$), seizures at 3 months (14.6% versus 15.7%, $P = 0.65$), deep-vein thrombosis (6.3% versus 5.2%, $P = 0.53$), and pulmonary embolism (4.9% versus 3.7%, $P = 0.41$). For the complications of wound healing and infection, thought to represent a higher risk for repeat resection after recurrence, the data were separately reported for the population having carmustine implantation at initial surgery and for those having it during a subsequent surgery for recurrence, and are presented in Table 2. There has not been an observation of hematologic toxicity potentially related to carmustine released from the wafers in any clinical context.

It should be noted that the supporting retrospective data above are from a high-volume craniotomy center with experience in carmustine implantation. Some single-institution trials have reported complications, but these reports are difficult to evaluate because the series are often small, and it has also been noted that, over time, knowledge has developed about procedures for optimal placement of the polymers. Giese et al[61] has published recommendations based on the early experience with polymer implants, emphasizing the following: attention to sufficient preoperative and postoperative anticonvulsants and dexamethasone; watertight dural closure; limit potential for contamination of dural closure from carmustine by irrigation and do not use instruments in contact with carmustine for dural closure; prophylactic intraoperative and postoperative antibiotics; attention to bone flap and soft tissue closure; irrigation of extradural wound with saline in case there has been contamination by carmustine; and a cautious dexamethasone taper. In addition, a significant connection between the surgical cavity and the ventricular system has long been considered to create a risk of obstructive hydrocephalus should a polymer or polymer fragment enter the cerebrospinal fluid space. Over time, more information has been obtained about the spectrum of "normal" imaging findings which may occur after carmustine implantation,[62,63] which may further improve the clinical management of these patients.

Carmustine implant wafers were approved by the US Food and Drug Administration as part of the management of newly diagnosed patients, along with postoperative radiotherapy, in 2003 and by the European Union in 2004. As a point of comparison, the randomized landmark Brain Tumor Study Group trial, reported back in 1978,[6,7] confirmed the value of radiotherapy in improving median survival, and also demonstrated that the addition of intravenous carmustine did not improve median survival, but did lead to a statistically nonsignificant improvement at one year and a survival of 18 months. This small benefit led to frequent use of this treatment as a standard option in the US, even though two-year survival remained negligible. In contrast, Polifeprosan 20 carmustine wafers have been demonstrated to have a survival benefit extending several years for some patients, Moreover, while only rarely resulting in significant toxicity, systemic administration of carmustine chemotherapy results in a significant risk of thrombocytopenia (<90,000 in approximately 25% of patients, and less than 50,000 in 6%–7%) along with a seemingly less substantial survival benefit.[6] After radiation therapy was confirmed to be beneficial in 1978, the next therapy shown to be helpful in improving survival in the initial management of malignant glioma in a well powered randomized trial was indeed this trial using carmustine wafers, and reported 25 years later.

Carmustine implants in newly diagnosed patients in era of temozolomide

When Polifeprosan 20 carmustine implant wafers were first developed, carmustine was the standard systemic chemotherapy option, and the value of administration in addition to radiotherapy was unclear, given the limited benefit. Temozolomide was approved for use in the United States in newly diagnosed glioblastoma in 2005, and became a standard part of therapy, especially because longer-term follow-up[5] suggested not only a modest but significant improvement in median survival, but also a very meaningful if somewhat limited improvement in the previously negligible possibility of 3-5 year survival. That occurred after radiotherapy alone as adjuvant therapy. At this point, the benefit of using carmustine implants in addition to temozolomide and whether temozolomide significantly improves outcome once carmustine implants have been placed, is less clear.

It is important to consider that survival with carmustine implantation and adjuvant temozolomide in newly diagnosed patients have not been directly compared, and either may be appropriate when used alone in selected patients. The advantages of temozolomide include appropriateness, regardless of the extent of resection, and ability to obtain final pathology results prior to decision-making and actual administration. With carmustine implantation, actual discussion with the patient and provision of consent must occur at a difficult time before the patient has had a concrete diagnosis of malignant glioma and under the time pressure of a need for surgery, given that the treatment would be administered based on intraoperative findings and diagnosis. The advantages of carmustine implantation include limited local toxicity, absence of systemic toxicity, and no need for the commitment involved in repeated administration, as is required with systemic therapies. Survival results for each therapy from the critical randomized trials are summarized in Table 3. Although variable patient selection makes direct comparison fraught with potential bias, examination of the data does raise the question of whether the outcome from each of these therapies alone could be substantially similar. The most striking differences in the patient populations are that the carmustine polymer is appropriately placed after a major resection has been achieved, whereas many temozolomide patients have had only a biopsy or limited resection. Another potentially important difference in the patient populations that may in this case bias against the carmustine implant group is that the implant patients were enrolled before surgery, and included patients who may not have later been

Table 3 Outcome of randomized trials assessing adjuvant use of carmustine implants or temozolomide compared with control adjuvant radiation arms

Control arms	Control arms (RT)				Experimental arms (RT + carmustine implant or RT and TMZ)			
Study	n	Medium survival	Two-year survival	Three-year survival	n	Median (months)	Two-year survival	Two-year survival
Westphal (placebo wafer and RT)[18]*	120 (Placebo wafer and RT)	11.6 m	8.3%	1.7%	120 (BCNU wafer and RT)	13.8	15.8%	9%
EORTC: (control, RT alone) (584 Stupp, R. 2009; 603 Stupp, R. 2001)	286 (RT alone)	12.1 m	10.9%	4.4%	287 (RT and TMZ)	14.6	27%	16%
EORTC: biopsy-only subgroup	45	7.8 m	4.6%	4.6%	48	9.4	10.4%	7.8%
EORTC: partial resect subgroup	128	11.7 m	9.4%	3.7%	126	13.5	23.7%	14.3%
EORTC: complete resect subgroup	113	14.2 m	15.0%	5.3%	113	18.8	38.4%	21.4%

Notes: *Results based on extent of resection not available for polymer study. Most would have had substantial or total debulking of gross disease based on intraoperative assessment.
Abbreviations: BCNU, carmustine; EORTC, European Organisation for Research and Treatment of Cancer; RT, radiotherapy; TMZ, temozolomide.

eligible for temozolomide as a result of new deficits, age, or poor recovery. Finally, a higher proportion of patients in the carmustine implant trials would have had grade III astrocytoma for the same reason, because treatment decisions were made based on frozen section without the benefit of definitive analysis of the pathology specimens, and this is thought to reflect the reality of clinical use of this agent, that would exist both in clinical trials and in routine use. However, it is interesting that the results for the control surgery plus placebo wafer and radiation arm are similar to that achieved in the radiation alone control arm of the European Organisation for Research and Treatment of Cancer trial of temozolomide, thus failing to provide support for the hypothesis that the patients in these particular trials had an inherently different prognosis (Table 3). In any event, carmustine implantation alone may be an appropriate consideration for patients who are not good candidates for temozolomide, including some elderly patients.[59]

It is quite reasonable to recommend, based on the current limited evidence and the scientific rationale, that standard therapy with temozolomide/radiation proceed after carmustine implantation in appropriate candidates, with the possibility that there will be further improvements in outcome when these approaches are combined. There is a significant scientific rationale to support the hypothesis that there might be a benefit to the use of carmustine wafers in the setting of adjuvant temozolomide and radiotherapy for glioblastoma. Because the molecular mechanisms of action of these drugs differ, there are clearly patients who respond to one agent while being resistant to another, and polymer-based therapy provides a high concentration of drug in the highest-risk area of the margin around the resection bed, which remains the common area of recurrence. However, true synergy is unlikely because the carmustine concentrations in the brain are likely to be low by the time adjuvant temozolomide begins 3–4 weeks later. In contrast, there is still the potential for benefit from the "temporal synergy" resulting from immediate treatment of the tumor, beginning at the time of surgery, whereas there is generally at least a 3–4-week delay until the start of adjuvant temozolomide and radiotherapy. Prospective and retrospective single-institution experiences support the safety of using temozolomide after placement of carmustine wafers for recurrent disease, but do not provide convincing evidence about whether or not efficacy is enhanced. A dose-escalation trial tested the safety of carmustine implants in recurrent disease along with escalation of the dose of temozolomide given orally on days 1–5 of 28-day cycles. There were no dose-limiting toxicities at 100 mg/m^2 and 150 mg/m^2 per day, and one third of the patients at the full dose of 200 mg/m^2/day had grade III toxicity, leading to the selection of the latter as the maximum tolerated dose,[64] which matches the dose generally utilized when temozolomide is given in recurrent disease without a polymer implant. Survival outcome when these therapies are combined has been the subject of multiple small reports, as summarized in Table 4. There has been no evidence of increased systemic toxicity nor of increased surgical complications. A randomized trial would be required to confirm that there is a survival benefit when a carmustine implant is part of therapy along with temozolomide, given the potentially significant selection biases and heterogenous prognostic factors that may obscure differences in therapeutic outcome. In the absence of core randomized data, decisions must be made about combined use of these freely available therapies based on the existing preclinical and clinical evidence, which suggests that safety is not substantially compromised and that there may be a survival benefit. More data are clearly needed.

The outcome for patients treated with adjuvant temozolomide and radiotherapy, with and without the wafer implant, has been directly compared in several small retrospective reports, a type of analysis that may only provide weak evidence. Noel et al[30] reported a comparison of 28 patients who had carmustine implantation with 37 patients who did not. There was no clinically or statistically significant difference with or without carmustine implants, with a median overall survival of 20.6 months and 20.8 months, respectively, and 12-month and 24-month overall survival rates of 78.6% and 40.9% and 78.4% and 33.3%, respectively, with and without carmustine wafer placement. McGirt et al[23,65] reported that with carmustine implant + radiotherapy + temozolomide, median survival was 20.7 months and two-year survival was 36%, whereas median survival with temozolomide without

Table 4 Survival outcome with placement of carmustine implants, followed by radiotherapy and temozolomide

Study	n	Median survival (months)	Two years	GBM
Pan et al[19]	21	17	NR	21/21
Noel et al[30]	28	20.6	41%	20/28
La Rocca and Mehdorn[31]	41	19.7	31%	40/41
Affronti et al[24]	36	22	47%	Unknown
Bock et al[25]	44	12.7	58% (1-year)	All GBM
McGirt et al[23,65]	33	21.3	39%	All GBM
Menie et al[21]	43	20	NR	Unknown

Note: These results may be assessed in context of results with radiation alone and radiation with temozolomide contained in Table 3.
Abbreviation: GBM, glioblastoma multiforme.

wafer implant was 14.7 months ($P < 0.001$). However, 60% of the wafer patients and only 30% of temozolomide patients had a gross total resection. When confined to the smaller subgroup, including only those who had a total resection, median survival was 21.5 months versus 19.8 months ($P = 0.30$) Given the nature of these reports, the limited patient numbers, and the unknown prognostic factors in the setting of modest potential benefit, it is not possible to reach firm conclusions about the benefit of adding carmustine implants to the current standard combined modality therapy for newly diagnosed patients, although for the present it remains an appropriate choice based on the rationale of combining these approved therapies and documentation of safety.

Economic evidence

Economic assessment has been limited. Conclusions about the economic impact of this treatment would require extensive and complex information about life extension, quality of life, cost, impact on cost of later therapy or care, and costs related to any alternatives that may have been used. Even when the analysis is done, the appropriateness of a treatment may also vary, based on the approach or the "willingness to pay" monetary level customary in the health care system of different nations.

Analysis has been done by the Cochrane Collaboration as well as the National Institute for Health and Clinical Excellence of the British National Health Service.[15,48,49,66] The value of this therapy in recurrent disease was questioned based on the observation that there was no statistically significant improvement in survival for the randomized groups, but only after adjustment for prognostic factors. In newly diagnosed patients, the analysis suggested that the cost would exceed the willingness to pay within the United Kingdom by 30,000 pounds per quality-adjusted life-year at that time. Interestingly, the role of adjuvant temozolomide in newly diagnosed patients was also considered in the British National Health Service analysis, and a similar conclusion was reached about that therapy. The document does state that the conclusion may vary based on assumptions, and that the conclusion should be interpreted according to individual circumstances by practitioners with awareness of the poor prognosis and lack of many other potentially effective options. Therefore, in the analysis completed by the National Health Service in 2007 and reviewed in 2010, guidance was issued that temozolomide was an appropriate choice in newly diagnosed glioblastoma and that carmustine implantation was appropriate when ≥90% of the tumor was resected. Specifically, it was concluded that no recommendation could be made on the sequential use of both therapies on the basis of the available evidence. A re-evaluation including any new evidence is planned for 2015.

Wafer technology: missed and future opportunities

The evidence, while it demonstrates that this particular commercially available pharmaceutical preparation is efficacious in the circumstances described here, also demonstrates the potential of an underlying gradual release polymer that may not yet be fully exploited. As discussed, a clinical trial has demonstrated that the loading of carmustine may potentially be increased, while maintaining safety, with possible improvement in carmustine distribution and outcome. Unfortunately, the potential benefits of increased polymer loading on outcome have not been tested with an approach that would provide evidence sufficient to advance the clinical use of this technology further.

There may also be a greater benefit from exploring the use of other chemotherapeutic agents with this delivery system. Carmustine was certainly quite appropriate to select for initial study because it had known activity in malignant glioma. However, part of the usefulness of systemic carmustine may result from its ability to penetrate the blood-brain barrier, whereas that may be a limitation with a direct delivery approach such as this because it can also quickly exit through the blood-brain barrier[28,67] and not be retained in the brain as it diffuses a greater distance. Other drugs may in fact be more biologically active in high-grade glioma, and yet have not succeeded in clinical trials of systemic administration because they are not reaching the tumor. Modeling based on these clinical observations does confirm that carmustine may not be the optimal drug for delivery by this method precisely because it penetrates the blood-brain barrier and therefore may be removed before penetrating deeply or persisting for a prolonged period of time. This was confirmed in mammalian studies using a wafer containing inulin, a large molecule that has less potential to cross the blood-brain barrier, and does indeed persist longer and penetrate more deeply as predicted. Therefore, there may be other agents with potentially significant efficacy, especially if they are directly administered to the area of risk, but which have not yet been demonstrated to be efficacious because the blood-brain barrier is not penetrated by drugs administered systemically.[68] The feasibility of slow-release Polifeprosan 20 polymer preparations containing other drugs has been confirmed in preclinical models with paclitaxel,[69] 5-iodo-2V deoxyuridine,[70,71] temozolomide,[68] taxotere,[72] camptothecin,[73,74] tiripazamine,[75] and other agents.

In humans, there have also been preliminary data obtained to assess the safety of agents given systemically along with wafer therapy, but these studies were not sufficient for meaningful assessment of efficacy. For example, O^6-benzylguanine was given perioperatively along with carmustine wafer implantation for resection of recurrent high-grade glioma[76] in a prospective Phase I study. This agent inhibits O^6-alkylguanine DNA alkyltransferase, known to repair carmustine as well as temozolomide alkylation, and is therefore thought to have potential as a chemosensitizer. A 52-patient Phase II study using this approach showed a median survival of 50 weeks, and the one-year and two-year overall survival rates were 47% and 10%, respectively, suggesting possible benefit. A Phase I dose-escalation study has provided evidence that carboplatin can be safely administered with radiotherapy after carmustine wafer placement, even when administration begins as early as postoperative days 3–4.[77] There has been limited evaluation of post-implantation CPT-11 in recurrent disease.[78] A Phase I/II trial explored intensifying radiotherapy by adding 12 Gy gamma knife radiosurgery within two weeks after surgery, with a 50-week median survival but the expected increased risk of radionecrosis.[79] There continue to be ongoing initial trials utilizing Gliadel wafers with regimens of adjuvant bevacizumab, radiotherapy, and standard-dose[80] and dose-dense[81] temozolomide. No agent, including temozolomide, has been tested in a robust fashion for efficacy when given along with Polifeprosan 20 carmustine polymer implantation. Sufficient safety evidence exists to allow utilization of temozolomide along with Polifeprosan 20, 3.85% carmustine implant in routine practice as discussed here. In that these polymer implants have not been demonstrated to enhance the toxicity of systemic agents, investigation for synergy in treating tumor tissue would be quite warranted, should new active systemic agents be identified.

Finally, the use of this technology for other indications within the central nervous system has not been fully explored. Prevention of postoperative recurrence of resected brain metastasis is an appropriate potential indication because local recurrence is common and the tumor tends to penetrate much less deeply than glioma. A multi-institutional trial[82] demonstrated that 0/25 patients had tumor bed recurrence when carmustine implants were utilized followed by whole brain radiotherapy. However, the baseline standard management of brain metastasis is also changing, and focal or stereotactic radiotherapy instead of whole brain radiotherapy has been increasingly utilized. It would be meaningful to determine whether carmustine implantation alone is a viable alternative to radiosurgery in preventing tumor bed recurrence.

Summary of current evidence

Carmustine implants have been demonstrated in a randomized trial to improve survival and function after repeat resection of recurrent high-grade glioma, and this observation remains applicable today. Even though the changes in standard management now result in a population previously treated with temozolomide, there is no evidence that the potential activity of carmustine will be reduced, and the randomized trial that demonstrated a benefit included a substantial proportion of patients who had received prior chemotherapy. An added advantage is that it can improve the outcome without effort, toxicity, or the time commitment of systemic chemotherapy from the patient perspective. In the situation of a patient with suspected high-grade glioma about to undergo surgery, it may be necessary for the patient to engage in complex preoperative decision-making about the various options with a relatively short time interval and without full prior confirmation of the diagnosis.

Carmustine implants improve survival, as shown in a randomized trial, when used along with standard radiotherapy in the adjuvant treatment of newly diagnosed malignant glioma, but its benefits along with now standard adjuvant combined temozolomide plus radiation have not been assessed in a randomized or even a prospective Phase II trial. Study has been limited because patients treated with standard carmustine implants are generally excluded from other experimental trials which would have provided more prospective data. Based on the limited reports available and the scientific rationale for combined benefit, it is reasonable to continue to utilize carmustine implants in appropriately selected patients with $>90\%$ resection, and to follow with a standard regimen of adjuvant temozolomide along with radiation. Only a randomized trial, which is not presently planned, can meaningfully define the appropriate combination of these therapies.

Carmustine wafer implantation appears to be safe and does not appear to increase surgical complications meaningfully, with regard to special procedures, or to result in systemic toxicity. Guidelines for an optimal surgical approach to placement of carmustine implant polymers have been developed based on the initial experience and have been published. There is no evidence that carmustine implants enhance systemic toxicity. From a patient perspective, the possibility of some improvement in survival with this grave illness is attractive, using a treatment that involves little increase in effort, toxicity, or risk. A disadvantage

from the patient perspective is that, in the management of newly diagnosed patients, it often limits eligibility for other experimental trials that may be of interest, and the therapeutic options must be considered and decided on by the patient prior to surgical confirmation of the diagnosis.

A concluding important point may be that this body of investigation could be viewed as not only providing specific evidence for a therapy for brain malignancy, but also providing core evidence for a technology that may be used for direct gradual release of chemotherapy and that may still be utilized to deliver other drugs or for other indications.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol*. 2003;5(2):79–88.
2. Westphal M, Ram Z, Riddle V, Hilt D, Bortey E, Executive Committee of the Gliadel Study Group. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)*. 2006;148(3):269–275.
3. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The polymer-brain tumor treatment group. *Lancet*. 1995;345(8956):1008–1012.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
5. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459–466.
6. Walker MD, Alexander E Jr, Hunt WE, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial. *J Neurosurg*. 1978;49(3):333–343.
7. Walker MD, Green SB, Byar DP, et al. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *N Engl J Med*. 1980;303(23):1323–1329.
8. Burger PC. Malignant astrocytic neoplasms: classification, pathologic anatomy, and response to treatment. *Semin Oncol*. 1986;13(1):16–26.
9. Nieder C, Grosu AL, Molls M. A comparison of treatment results for recurrent malignant gliomas. *Cancer Treat Rev*. 2000;26(6):397–409.
10. Patel MM, Goyal BR, Bhadada SV, Bhatt JS, Amin AF. Getting into the brain: approaches to enhance brain drug delivery. *CNS Drugs*. 2009;23(1):35–58.
11. Buonerba C, Di Lorenzo G, Marinelli A, et al. A comprehensive outlook on intracerebral therapy of malignant gliomas. *Crit Rev Oncol Hematol*. 2011;80(1):54–68.
12. Burkhardt JK, Riina HA, Shin BJ, Moliterno JA, Hofstetter CP, Boockvar JA. Intra-arterial chemotherapy for malignant gliomas: a critical analysis. *Interv Neuroradiol*. 2011;17(3):286–295.
13. Kesari S. Understanding glioblastoma tumor biology: the potential to improve current diagnosis and treatments. *Semin Oncol*. 2011;38 Suppl 4:S2–S10.
14. Buonerba C, Di Lorenzo G, Marinelli A, et al. A comprehensive outlook on intracerebral therapy of malignant gliomas. *Crit Rev Oncol Hematol*. 2011;80(1):54–68.
15. National Institute for Health and Clinical Excellence. Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma. Available from: www.nice.org.uk/TA121. Accessed March 18, 2012.
16. Salvati M, D'elia A, Frati A, Brogna C, Santoro A, Delfini R. Safety and feasibility of the adjunct of local chemotherapy with biodegradable carmustine (BCNU) wafers to the standard multimodal approach to high grade gliomas at first diagnosis. *J Neurosurg Sci*. 2011;55(1):1–6.
17. Salmaggi A, Duri S, Silvani A, et al. Loco-regional treatments in first-diagnosis glioblastoma: literature review on association between Stupp protocol and Gliadel. *Neurol Sci*. 2011;32 Suppl 2:S241–S245.
18. Perry J, Chambers A, Spithoff K, Laperriere N. Gliadel wafers in the treatment of malignant glioma: a systematic review. *Curr Oncol*. 2007;14(5):189–194.
19. Pan E, Mitchell SB, Tsai JS. A retrospective study of the safety of BCNU wafers with concurrent temozolomide and radiotherapy and adjuvant temozolomide for newly diagnosed glioblastoma patients. *J Neurooncol*. 2008;88(3):353–357.
20. Noel G, Schott R, Froelich S, et al. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior Gliadel implantation (carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2012;82(2):749–755.
21. Menei P, Metellus P, Parot-Schinkel E, et al. Biodegradable carmustine wafers (Gliadel) alone or in combination with chemoradiotherapy: the French experience. *Ann Surg Oncol*. 2010;17(7):1740–1746.
22. McGirt MJ, Than KD, Weingart JD, et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. *J Neurosurg*. 2009;110(3):583–588.
23. McGirt MJ, Brem H. Carmustine wafers (gliadel) plus concomitant temozolomide therapy after resection of malignant astrocytoma: growing evidence for safety and efficacy. *Ann Surg Oncol*. 2010;17(7):1729–1731.
24. Affronti ML, Heery CR, Herndon JE II, et al. Overall survival of newly diagnosed glioblastoma patients receiving carmustine wafers followed by radiation and concurrent temozolomide plus rotational multiagent chemotherapy. *Cancer*. 2009;115(15):3501–3511.
25. Bock HC, Puchner MJ, Lohmann F, et al. First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: a multicenter experience. *Neurosurg Rev*. 2010;33(4):441–449.
26. Dixit S, Hingorani M, Achawal S, Scott I. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without previous Gliadel implantation (carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2011;81(5):1593.
27. Domb AJ, Rock M, Perkin C, Yipchuck G, Broxup B, Villemure JG. Excretion of a radiolabelled anticancer biodegradable polymeric implant from the rabbit brain. *Biomaterials*. 1995;16(14):1069–1072.
28. Fleming AB, Saltzman WM. Pharmacokinetics of the carmustine implant. *Clin Pharmacokinet*. 2002;41(6):403–419.
29. Gopferich A. Erosion of composite polymer matrices. *Biomaterials*. 1997;18(5):397–403.
30. Noel G, Schott R, Froelich S, et al. Retrospective comparison of chemoradiotherapy followed by adjuvant chemotherapy, with or without prior Gliadel implantation (carmustine) after initial surgery in patients with newly diagnosed high-grade gliomas. *Int J Radiat Oncol Biol Phys*. 2012;82(2):749–755.
31. La Rocca RV, Mehdorn HM. Localized BCNU chemotherapy and the multimodal management of malignant glioma. *Curr Med Res Opin*. 2009;25(1):149–160.
32. Domb AJ, Israel ZH, Elmalak O, Teomim D, Bentolila A. Preparation and characterization of carmustine-loaded polyanhydride wafers for treating brain tumors. *Pharm Res*. 1999;16(5):762–765.
33. Domb AJ, Rock M, Schwartz J, et al. Metabolic disposition and elimination studies of a radiolabelled biodegradable polymeric implant in the rat brain. *Biomaterials*. 1994;15(9):681–688.

34. Domb A. Gliadel – a preparation for the supplementary treatment of brain cancer. *Harefuah*. 1999;137(3–4):127–131.
35. Brown LR, Wei CL, Langer R. In vivo and in vitro release of macromolecules from polymeric drug delivery systems. *J Pharm Sci*. 1983;72(10):1181–1185.
36. Domb A, Maniar M, Bogdansky S, Chasin M. Drug delivery to the brain using polymers. *Crit Rev Ther Drug Carrier Syst*. 1991;8(1):1–17.
37. Laurencin C, Domb A, Morris C, et al. Poly(anhydride) administration in high doses in vivo: studies of biocompatibility and toxicology. *J Biomed Mater Res*. 1990;24(11):1463–1481.
38. Lin SH, Kleinberg LR. Carmustine wafers: localized delivery of chemotherapeutic agents in CNS malignancies. *Expert Rev Anticancer Ther*. 2008;8(3):343–359.
39. Dang W, Daviau T, Brem H. Morphological characterization of polyanhydride biodegradable implant gliadel during in vitro and in vivo erosion using scanning electron microscopy. *Pharm Res*. 1996;13(5):683–691.
40. Grossman SA, Reinhard C, Colvin OM, et al. The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers. *J Neurosurg*. 1992;76(4):640–647.
41. Hunter KJ, Deen DF, Pellarin M, Marton LJ. Effect of alpha-difluoromethylornithine on 1,3-bis(2-chloroethyl)-1-nitrosourea and cis-diamminedichloroplatinum(II) cytotoxicity, DNA interstrand cross-linking, and growth in human brain tumor cell lines in vitro. *Cancer Res*. 1990;50(9):2769–2772.
42. Fung LK, Shin M, Tyler B, Brem H, Saltzman WM. Chemotherapeutic drugs released from polymers: distribution of 1,3-bis(2-chloroethyl)-1-nitrosourea in the rat brain. *Pharm Res*. 1996;13(5):671–682.
43. Fleming AB, Saltzman WM. Pharmacokinetics of the carmustine implant. *Clin Pharmacokinet*. 2002;41(6):403–419.
44. Fung LK, Ewend MG, Sills A, et al. Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain. *Cancer Res*. 1998;58(4):672–684.
45. Buahin KG, Brem H. Interstitial chemotherapy of experimental brain tumors: comparison of intratumoral injection versus polymeric controlled release. *J Neurooncol*. 1995;26(2):103–110.
46. Brem H, Mahaley MS Jr, Vick NA, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. *J Neurosurg*. 1991;74(3):441–446.
47. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-Brain Tumor Treatment Group. *Lancet*. 1995;345(8956):1008–1012.
48. Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K. Chemotherapy wafers for high grade glioma. *Cochrane Database Syst Rev*. 2011;3:CD007294.
49. Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K. Chemotherapeutic wafers for high grade glioma. *Cochrane Database Syst Rev*. 2008;3:CD007294.
50. Kunwar S, Chang S, Westphal M, et al. Phase III randomized trial of CED of IL13-PE38QQR vs gliadel wafers for recurrent glioblastoma. *Neuro Oncol*. 2010;12(8):871–881.
51. Olivi A, Grossman SA, Tatter S, et al. Dose escalation of carmustine in surgically implanted polymers in patients with recurrent malignant glioma: a new approaches to brain tumor therapy CNS Consortium Trial. *J Clin Oncol*. 2003;21(9):1845–1849.
52. Brem H, Tamargo RJ, Olivi A, et al. Biodegradable polymers for controlled delivery of chemotherapy with and without radiation therapy in the monkey brain. *J Neurosurg*. 1994;80(2):283–290.
53. Brem H, Ewend MG, Piantadosi S, Greenhoot J, Burger PC, Sisti M. 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*. 1995;26(2):111–123.
54. Valtonen S, Timonen U, Toivanen P, et al. Interstitial chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. *Neurosurgery*. 1997;41(1):44–48.
55. Kleinberg LR, Weingart J, Burger P, et al. Clinical course and pathologic findings after Gliadel and radiotherapy for newly diagnosed malignant glioma: implications for patient management. *Cancer Invest*. 2004;22(1):1–9.
56. Gunjur A, Lau E, Taouk Y, Ryan G. Early post-treatment pseudoprogression amongst glioblastoma multiforme patients treated with radiotherapy and temozolomide: a retrospective analysis. *J Med Imaging Radiat Oncol*. 2011;55(6):603–610.
57. Chamberlain MC. Pseudoprogression in glioblastoma. *J Clin Oncol*. 2008;26(26):4359.
58. Sanghera P, Rampling R, Haylock B, et al. The concepts, diagnosis and management of early imaging changes after therapy for glioblastomas. *Clin Oncol (R Coll Radiol)*. 2012;24(3):216–227.
59. Chaichana KL, Zaidi H, Pendleton C, et al. The efficacy of carmustine wafers for older patients with glioblastoma multiforme: prolonging survival. *Neurol Res*. 2011;33(7):759–764.
60. Attenello FJ, Mukherjee D, Datoo G, et al. Use of Gliadel (BCNU) wafer in the surgical treatment of malignant glioma: a 10-year institutional experience. *Ann Surg Oncol*. 2008;15(10):2887–2893.
61. Giese A, Bock HC, Kantelhardt SR, Rohde V. Risk management in the treatment of malignant gliomas with BCNU wafer implants. *Cen Eur Neurosurg*. 2010;71(4):199–206.
62. Colen RR, Zinn PO, Hazany S, et al. Magnetic resonance imaging appearance and changes on intracavitary Gliadel wafer placement: a pilot study. *World J Radiol*. 2011;3(11):266–272.
63. Hammoud DA, Belden CJ, Ho AC, et al. The surgical bed after BCNU polymer wafer placement for recurrent glioma: serial assessment on CT and MR imaging. *AJR Am J Roentgenol*. 2003;180(5):1469–1475.
64. Gururangan S, Cokgor L, Rich JN, et al. Phase I study of gliadel wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. *Neuro Oncol*. 2001;3(4):246–250.
65. McGirt MJ, Than KD, Weingart JD, et al. Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of glioblastoma multiforme. *J Neurosurg*. 2009;110(3):583–588.
66. Garside R, Pitt M, Anderson R, et al. The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(45):iii–iv, ix–221.
67. Arifin DY, Lee KY, Wang CH, Smith KA. Role of convective flow in carmustine delivery to a brain tumor. *Pharm Res*. 2009;26(10):2289–2302.
68. Brem S, Tyler B, Li K, et al. Local delivery of temozolomide by biodegradable polymers is superior to oral administration in a rodent glioma model. *Cancer Chemother Pharmacol*. 2007;60(5):643–650.
69. Walter KA, Cahan MA, Gur A, et al. Interstitial taxol delivered from a biodegradable polymer implant against experimental malignant glioma. *Cancer Res*. 1994;54(8):2207–2212.
70. Williams JA, Dillehay LE, Tabassi K, Sipos E, Fahlman C, Brem H. Implantable biodegradable polymers for IUdR radiosensitization of experimental human malignant glioma. *J Neurooncol*. 1997;32(3):181–192.
71. Yuan X, Dillehay LE, Williams JR, Williams JA. Synthetic, implantable polymers for IUdR radiosensitization of experimental human malignant glioma. *Cancer Biother Radiopharm*. 1999;14(3):187–202.
72. Sampath P, Rhines LD, DiMeco F, Tyler BM, Park MC, Brem H. Interstitial docetaxel (Taxotere), carmustine and combined interstitial therapy: a novel treatment for experimental malignant glioma. *J Neurooncol*. 2006;80(1):9–17.
73. Storm PB, Moriarity JL, Tyler B, Burger PC, Brem H, Weingart J. Polymer delivery of camptothecin against 9 L gliosarcoma: release, distribution, and efficacy. *J Neurooncol*. 2002;56(3):209–217.
74. Weingart JD, Thompson RC, Tyler B, Colvin OM, Brem H. Local delivery of the topoisomerase I inhibitor camptothecin sodium prolongs survival in the rat intracranial 9 L gliosarcoma model. *Int J Cancer*. 1995;62(5):605–609.
75. Yuan X, Tabassi K, Williams JA. Implantable polymers for tirapazamine treatments of experimental intracranial malignant glioma. *Radiat Oncol Investig*. 1999;7(4):218–230.

76. Weingart J, Grossman SA, Carson KA, et al. Phase I trial of polifeprosan 20 with carmustine implant plus continuous infusion of intravenous O6-benzylguanine in adults with recurrent malignant glioma: new approaches to brain tumor therapy CNS Consortium Trial. *J Clin Oncol*. 2007;25(4):399–404.
77. Limentani SA, Asher A, Heafner M, Kim JW, Fraser R. 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 Neurooncol*. 2005;72(3):241–244.
78. Cohen L, Cokgor I, Kerby T, Rich J, Stewart E. Phase I trials of gliadel plus CPT-11 or temodal (temozolomide). *Proceedings of the American Society of Clinical Oncology*. 1999:573.
79. Smith KA, Ashby LS, Gonzalez LF, et al. Prospective trial of gross-total resection with Gliadel wafers followed by early postoperative gamma knife radiosurgery and conformal fractionated radiotherapy as the initial treatment for patients with radiographically suspected, newly diagnosed glioblastoma multiforme. *J Neurosurg*. 2008;Suppl 109:106–117.
80. National Cancer Institute. NCT01186406: Gliadel, XRT, temodar, avastin followed by avastin, temodar for newly diagnosed glioblastoma multiforme (GBM). Available from: http://www.cancer.gov/clinicaltrials. Accessed March 18, 2012.
81. NCT00660621: A Phase II study of Gliadel, concomitant temozolomide and radiation, followed by dose dense therapy with temozolomide plus bevacizumab for newly diagnosed malignant high grade glioma. Available from: www.cancer.gov/clinicaltrials. Accessed March 18, 2012.
82. Ewend MG, Brem S, Gilbert M, et al. Treatment of single brain metastasis with resection, intracavity carmustine polymer wafers, and radiation therapy is safe and provides excellent local control. *Clin Cancer Res*. 2007;13(12):3637–3641.