

## Gliadel for brain metastasis

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### Abstract

With therapies for systemic malignancy improving, life expectancy for cancer patients is becoming increasingly dependent on control of brain metastatic disease. Despite improvements in surgical and radiotherapy modalities for control of brain metastasis, the prognosis for patients with brain metastases is poor. The development of controlled release polymers has led to novel new therapies for malignant brain tumors consisting of direct surgical delivery of chemotherapy agents to the tumor bed and sustained chemotherapy release over a prolonged period of time. Although there is a large body of literature in support of BCNU polymer wafer for primary brain malignancy and experimental brain metastases, clinical studies evaluating the BCNU polymer wafer for brain metastatic disease are relatively sparse. In this review, we discuss the role of the BCNU polymer wafer for brain metastasis focusing specifically on rationale for use of locally delivered sustained release polymers, history of the BCNU polymer wafer, and emerging studies examining the role of the BCNU polymer wafer for metastatic brain tumors.

**Key Words:** Brain tumor, brain metastasis, BCNU polymer wafer, gliadel chemotherapy, local delivery

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## INTRODUCTION

The development of controlled release polymers has led to novel new therapies for malignant brain tumors consisting of direct surgical delivery of chemotherapy agents to the tumor bed and sustained chemotherapy release over a prolonged period of time. The BCNU polymer wafer has been used clinically for several years and was Food and Drug Administration (FDA)-approved for use in patients with malignant glioma in 1996.<sup>[34]</sup> Numerous clinical studies have emerged examining the role of BCNU polymer wafers for management of primary malignant brain tumors.<sup>[5,7,55,56]</sup> Although there is a large

body of literature in support of BCNU polymer wafer for primary brain malignancy, clinical studies evaluating the BCNU polymer wafer for brain metastatic disease are relatively sparse.<sup>[15]</sup> With therapies for systemic malignancy improving, life expectancy for cancer patients is becoming increasingly dependent on control of brain metastatic disease.<sup>[3,20]</sup> Thus, there is a need to develop new treatment options for cerebral metastases, and given the increasing acceptance of BCNU chemotherapy wafers in primary brain tumors, the role of similar local drug delivery strategies for brain metastasis has generated renewed enthusiasm.<sup>[15-17,21,30,36,44]</sup> In this review, we will discuss the role of the BCNU polymer wafer for brain metastasis

focusing specifically on rationale for use of locally delivered sustained release polymers, history of the BCNU polymer wafer, and emerging studies examining the role of the BCNU polymer wafer for metastatic brain tumors.

## **RATIONALE FOR USE OF BIS-CHLOROETHYLNITROSOUREA POLYMER WAFERS FOR BRAIN METASTASES**

### **Clinical rationale**

Cerebral metastasis is a common result of systemic malignancy and a primary cause of morbidity and mortality for cancer patients.<sup>[35,45]</sup> Up to 30% of patients with systemic malignancy develop symptomatic intracranial metastasis, which corresponds to more than 100,000 patients a year in the United States alone.<sup>[24,49]</sup> While many types of cancer can spread to the brain, lung cancer, breast cancer, and melanoma account for the majority of cases (67-80%).<sup>[18,22,37]</sup> The incidence of cerebral metastatic disease is expected to increase in coming years due to several factors. First, the occurrence of cerebral metastasis is known to increase exponentially as a function of age.<sup>[12]</sup> Therefore, with the overall gain in life expectancy over the past decades, the incidence and prevalence of cerebral metastatic disease is expected to increase substantially.<sup>[49]</sup> Second, advances in neuroimaging techniques have led to an increase in the diagnosis of cerebral metastasis.<sup>[35]</sup> Third, advancements in systemic chemotherapy, hormonal therapy, and radiotherapy have improved systemic control of malignancy, leading to a greater propensity for cancer relapse presenting as central nervous system (CNS) metastatic disease in spite of apparent systemic control.<sup>[3,49,51,53]</sup> The growing significance of cerebral metastatic disease to the neurosurgeon is manifest in the dramatic increase in neurosurgical resections performed for cerebral metastasis in the US from 3900 resections in 1988 to over 7000 resections in 2000.<sup>[3]</sup>

Despite significant advances in cancer therapies leading to improved systemic control, a large number of patients with cerebral metastatic disease die from intracranial progression in the setting of good systemic control.<sup>[10,14]</sup> The blood-brain barrier (BBB) prevents many effective systemic treatments from taking effect in the brain.<sup>[13,14]</sup> Consequently, the brain provides a sanctuary for malignancy in the setting of otherwise effective systemic control. For example, in breast cancer patients, trastuzumab has increased response rates, lengthened time to progression, and increased overall survival, but is commonly associated with CNS relapse.<sup>[14]</sup> In bio-chemotherapy for metastatic melanoma, up to one-third of patients who exhibited complete response to therapy later had relapse in the CNS, and no patients with CNS disease prior to therapy had remission of disease in the CNS.<sup>[38]</sup>

With the incidence of cerebral metastatic disease increasing and control of systemic malignancy improving despite often-uncontrolled intracranial spread, optimizing management of metastatic brain tumors is a great priority. The current mainstay of therapy consists of some combination of surgical resection, whole brain radiation therapy, and stereotactic radiosurgery.<sup>[49]</sup> Unfortunately, the failure rate for these treatments is high. For a single metastases treated with surgical resection and postoperative radiation, local recurrence is as high as 40% and distant CNS recurrence is as high as 21%.<sup>[39-41]</sup> Local recurrence occurs as a result of tumor spread beyond the immediate surgical resection cavity. Even in the setting of gross total resection, local recurrence can still occur from these microscopic infiltrative cells.<sup>[41]</sup>

### **Mechanistic rationale**

Tumors respond to chemotherapy as a result of sensitivity of tumor cells to administered chemotherapy and the ability to deliver therapeutic concentrations of the chemotherapeutic agent to the tumor.<sup>[11]</sup> Drug delivery to the CNS is determined by lipophilicity, ionization state, molecular weight, and transport across the BBB.<sup>[9]</sup> Because of their high molecular weight and low lipophilicity, many of the drugs effective against systemic malignancy and their concomitant brain metastases do not effectively cross the BBB.<sup>[13]</sup> This barrier is one of the most significant obstacles to treating metastatic brain tumors with conventional chemotherapies. There is some local disruption of the BBB by brain metastasis, which is demonstrated by contrast-enhancement on postcontrast magnetic resonance imaging (MRI).<sup>[4,31]</sup> This allows for transport of a variable amount of certain chemotherapeutics across the BBB dependent on the degree of BBB disruption.<sup>[31,59]</sup> Microdialysis catheters and surgical tissue sampling have demonstrated variable concentrations of chemotherapeutic drugs within tumor with this BBB disruption.<sup>[59]</sup> Studies also demonstrate different levels of multidrug-resistance genes in brain metastatic tumor samples compared with systemic primary tumor, suggesting varied exposure to chemotherapeutic drugs in the CNS.<sup>[13,19]</sup> Steroids and antiangiogenic agents can restore BBB function, making tumor-induced BBB disruption even less reliable as a mechanism of chemotherapeutic drug delivery.<sup>[25,42,52]</sup> These facts suggest that within the region of tumor-induced BBB disruption, there is variable and unreliable exposure to chemotherapeutic drugs. Additionally, there is significant microscopic tumor spread and micrometastases that extends well beyond the margins of BBB disruption.<sup>[57]</sup>

The overall chemosensitivity of metastatic brain tumors is a function of both inherent chemosensitivity and acquired chemoresistance. Inherent chemosensitivity is determined primarily by tumor histology, which determines the cytologic structure and function of the tumor and ultimately determines cell response. For example,

small cell lung cancer (SCLC) is considered one of the most chemosensitive histologies, whereas melanoma is considered minimally chemosensitive.<sup>[11]</sup> Indirectly, tumor size, tumor heterogeneity, and surrounding microenvironment (ischemia, hypoxia, and pH) may influence both tumor sensitivity and BBB permeability.<sup>[1,11,13]</sup> When considering chemotherapy for brain metastasis, agents with efficacy for the primary systemic lesion are presumed to be most effective against brain metastasis.<sup>[19]</sup> However, brain metastases occurring subsequent to chemotherapy for systemic disease often develop chemoresistance to the previously used chemotherapy.<sup>[11]</sup> Clinical studies suggest that patients with brain metastases without prior exposure to chemotherapy have better response rates compared with patients with prior chemotherapy exposure.<sup>[28,33]</sup>

Because of these limitations to standard systemically administered chemotherapeutics, there has been a clinical need to explore novel alternatives, such as the BCNU polymer wafer. Surgically delivered local chemotherapeutics such as the BCNU polymer wafer bypass the BBB completely, which allows for therapeutic concentrations of chemotherapeutic to be delivered directly to the tumor bed and surrounding tissues. Locally delivered polymer chemotherapy agents do not directly address the issue of tumor sensitivity and chemoresistance, but if more chemotherapies are developed for surgical delivery via a sustained release polymer, it could enhance the repertoire and effectiveness of chemotherapy options for CNS metastases that normally do not cross the BBB.

## History of the BCNU polymer wafer

### Development

In 1976, Langer and Folkman developed a polymer specialized for the sustained release of macromolecules using ethylene vinyl acetate (EVAc).<sup>[27]</sup> The biocompatibility of this compound was subsequently tested and confirmed in both rabbit and rodent models.<sup>[26,47,48,58]</sup> Because the EVAc copolymer is nonbiodegradable, it was never approved for human clinical use in the brain. In 1985, Leong *et al.* developed a new biodegradable polyanhydride named poly[bis(p-carboxyphenoxy)] propane-sebacic acid (PCPP: SA) that enabled sustained release of macromolecules.<sup>[29]</sup> This polyanhydride is considered a model for optimal drug carrier molecule for several reasons: First, it is biodegradable and allows constant-rate drug delivery; second, it is extremely hydrophobic, which provides a strong protection mechanism for the drug it carries; and lastly, the composition of the polymer can be easily modified to fine tune the rate of breakdown and concomitant drug delivery. For these reasons, PCPP: SA was chosen as the carrier polymer for the BCNU polymer wafer.

In 1993, Tamargo *et al.* reported the first use of BCNU-embedded polymer wafers in a rat model of 9L gliosarcoma.<sup>[47]</sup> In this study, they compared intraperitoneal administration of BCNU with both EVAc and PCPP: SA BCNU embedded wafers. The results showed a 2- to 3-fold increase in survival and stunted tumor growth for rats that underwent placement of BCNU embedded wafers. Subsequent studies examined the pharmacokinetics of BCNU polymer wafers. Using the EVAc polymer in the rat brain, drug concentrations peaked at 4 hours and remained elevated through 1 week following implantation.<sup>[58]</sup> In another study, the BCNU implantation using a PCPP: SA polymer wafer was compared with direct injection of BCNU into tumor.<sup>[23]</sup> With BCNU polymer implantation, therapeutic BCNU concentrations were maintained at up to 10 mm from the tumor site between 3 and 10 days following implantation. In contrast, with direct BCNU injection, therapeutic concentrations peaked within hours of injection and dropped below therapeutic levels rapidly. Studies in nonhuman primates demonstrated safety of BCNU polymer wafers with radiation therapy, which eventually lead to human clinical trials.<sup>[8]</sup>

### *The BCNU polymer wafer and primary brain malignancy*

To date, numerous clinical trials have been performed to evaluate the safety and efficacy of the BCNU polymer wafer for treatment of glioma both alone and in combination with other therapies.<sup>[5,7,32,54,56]</sup> These trials have examined BCNU polymer wafers both for recurrent glioma and first-line therapy. In initial placebo-controlled studies, the BCNU polymer wafer was associated with an increase in median survival from 5.4 to 7.2 months in patients undergoing surgery for recurrent glioblastoma multiforme (GBM).<sup>[7]</sup> For patients with implantation at initial resection for GBM, survival was reported at 13.4 months for BCNU polymer wafer-treated patients and 9.2 months for placebo wafer-treated patients.<sup>[50]</sup> The evidence for survival benefit and safety of the BCNU polymer wafer was augmented by subsequent phase 3 clinical trials<sup>[56]</sup> and retrospective reviews reporting similar results.<sup>[2]</sup> These promising results led to FDA approval of BCNU polymer wafer implantation for malignant glioma in 1996.

### The BCNU polymer wafer and brain metastases

Despite the promising results of BCNU polymer wafers in treatment of malignant glioma and the obvious mechanistic advantages of local administration of chemotherapy for metastatic brain tumors, studies evaluating the use of the BCNU polymer wafer against metastatic brain tumors are limited both in experimental animal research and human clinical trials.

### *Animal studies*

In 1996, Ewend *et al.* published the first experimental use of the BCNU polymer wafer with external beam

radiotherapy in various animal models of metastatic brain tumor.<sup>[17]</sup> Murine models of lung carcinoma, renal cell carcinoma, colon carcinoma, and melanoma were tested. The BCNU polymer wafer alone prolonged survival in the melanoma and renal cell carcinoma models. When used in combination with radiotherapy, the BCNU polymer wafer prolonged survival in all cancer models tested.<sup>[16,17]</sup> Use of radiotherapy alone was not as effective as when used in conjunction with the BCNU polymer wafer. These promising results lead the way for future studies in humans with metastatic brain tumors.

#### *Human clinical trials*

In 2007, Ewend *et al.* reported their experience on the BCNU polymer wafer for treatment of solitary brain metastasis in conjunction with radiation therapy.<sup>[15]</sup> In this report, 25 patients with solitary brain metastasis from various primary malignancies underwent craniotomy for tumor resection and placement of BCNU polymer wafers followed by whole-brain radiotherapy. This was a three-institutional feasibility study, and there was no comparison group. The median survival was 33 weeks with 33% of patients surviving past 1 year and 25% of patients surviving past 2 years. Interestingly, there was no local recurrence observed at a median follow-up period of over 36 weeks, but four patients did develop recurrence elsewhere in the brain. Two patients developed seizures, but there were no wound complications, suggesting that use of the BCNU polymer wafer was safe in this patient population.

Other preliminary studies of the BCNU polymer wafer for brain metastases have been presented as abstracts at various meetings.<sup>[21,36,44]</sup> Collectively, these reports studied over 100 patients who underwent surgical resection of brain metastasis with placement of BCNU polymer wafers as adjuvant therapy, followed by radiotherapy regimens. The cumulative follow-up for these patients is unavailable, but only two local recurrences were reported. In general, these abstracts suggest that the use of the BCNU polymer wafer is safe for patients with brain metastasis; reported complications included two patients who developed seizures, two with postoperative wound complications, and one with respiratory distress. These abstract results mirror the results of the work by Ewend *et al.* suggesting that the BCNU polymer wafer is well-tolerated in brain metastasis patients and may decrease local disease recurrence.<sup>[15]</sup> However, the intraoperative administration of BCNU polymer wafers as local chemotherapy for brain metastasis remains a treatment option that requires additional clinical inquiry before its more widespread application. In the authors' experience, BCNU polymer wafers have been implanted during repeat surgery in select patients who had stable systemic disease, excellent performance status, and whose brain metastases demonstrated repeated recurrences despite aggressive surgical resection, whole

brain radiotherapy, and radiosurgery. In order to broaden the application of biodegradable chemotherapy polymers for brain metastasis, more rigorous, multi-institutional, and prospective trials with appropriate control groups are necessary to adequately assess safety and effectiveness in a larger patient cohort with brain metastasis.

## CONCLUSION

Despite ample evidence demonstrating safety and efficacy of the BCNU polymer wafer for malignant glioma, research evaluating its use for metastatic brain tumor is relatively limited. Preliminary studies in both animal models and humans suggest that use of the BCNU polymer wafer is safe and may decrease local recurrence in metastatic brain tumors. Although in animal models there is a reported survival benefit with BCNU polymer wafer treatment,<sup>[16,17]</sup> data demonstrating this in humans are not yet available. Currently, BCNU is the only chemotherapy clinically available in a sustained-released polymer wafer for surgical implantation in patients, but future work may lead to the availability of more effective chemotherapy agents and local delivery technology to improve the clinical outcome of patients with brain metastasis.<sup>[6,43,46]</sup> In its present form, BCNU polymer wafers may serve as an alternate treatment option for adjuvant chemotherapy in specific clinical situations where single or oligo-brain metastases remain recalcitrant to standard surgical and radiotherapy modalities.

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