Published in final edited form as:

J Radiat Oncol. 2015 September ; 4(3): 235–241. doi:10.1007/s13566-015-0210-y.

Outcome of Adult Brain Tumor Consortium (ABTC) prospective dose-finding trials of I-125 balloon brachytherapy in high-grade gliomas: challenges in clinical trial design and technology development when MRI treatment effect and recurrence appear similar

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Abstract

Objectives—The aim of this study is to define the maximal safe radiation dose to guide further study of the GliaSite balloon brachytherapy (GSBT) system in untreated newly diagnosed glioblastoma (NEW-GBM) and recurrent high-grade glioma (REC-HGG). GSBT is a balloon placed in the resection cavity and later filled through a subcutaneous port with liquid I-125 Iotrex, providing radiation doses that diminish uniformly with distance from the balloon surface.

Methods—The Adult Brain Tumor Consortium initiated prospective dose-finding studies to determine maximum tolerated dose in NEW-GBM treated before standard RT or after surgery for REC-HGG. Patients were inevaluable if there was progression before the 90-day posttreatment toxicity evaluation point.

Results—Ten NEW-GBM patients had the balloon placed, and 2/10 reached the 90 day timepoint. Five REC-HGG enrolled and two were assessable at the 90-day evaluation endpoint. Imaging progression occurred before 90-day evaluation in 7/12 treated patients. The trials were closed as too few patients were assessable to allow dose escalation, although no dose-limiting

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Ethical standards statement All human and animal studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

Conflict of interest The authors declare that they have no competing interests.

toxicities (DLTs) were observed. Median survival from treatment was 15.3 months (95 % CI 7.1–23.6) for NEW-GBM and 12.8 months (95 % CI 4.2–20.9) for REC-HGG.

Conclusion—These trials failed to determine a maximum tolerated dose (MTD) for further testing as early imaging changes, presumed to be progression, were common and interfered with the assessment of treatment-related toxicity. The survival outcomes in these and other related studies, although based on small populations, suggest that GSBT may be worthy of further study using clinical and survival endpoints, rather than standard imaging results. The implications for local therapy development are discussed.

Keywords

Glioblastoma; Radiotherapy; Brachytherapy; I-125; Glioma

Introduction

GliaSite balloon brachytherapy (Fig 1) (Proxima Therapeutics, Inc., Alpharetta, GA and Isoray Medical, Inc., Richland, WA) using I-125 Iotrex liquid radioisotope was designed as a novel and technically accessible method of delivering local radiotherapy at a high dose with a predictable dose distribution [1–4]. This generated interest in determining optimal patient selection, doses, and combinations with systemic therapies [3]. GliaSite balloon brachytherapy (GSBT) uses a balloon catheter intracavitary system as a spherically shaped volumetric radiation source (4–35 ml) designed to fill the tumor resection cavity, allowing the dose to be precisely defined and easily reproduced. The Adult Brain Tumor Consortium (ABTC, formerly NABTT: New Approached to Brain Therapy Consortium) had previously demonstrated the safety of the GliaSite brachytherapy (GSBT) catheter device [4], and dose-finding trials were initiated. However, the delivery system became unavailable in 2008 with the results not yet reported and was reintroduced in 2012.

Radiation therapy remains the single most effective adjuvant modality in the management of glioblastoma multiforme (GBM). However, even with aggressive surgery, radiation, and chemotherapy, virtually all patients recur and die of their disease. Furthermore, 90 % of recurrences are located within 2 cm of the enhancing edge of the original tumor [5–8]. Once recurrence is demonstrated, median survival times are limited, even with optimum therapy. Since the main pattern of failure is local, an improvement in local control could result in improved survival. Management of local disease may be enhanced by escalation of radiation treatment, either at the time of initial therapy or by administering additional radiation at the time of recurrence. Unfortunately, the imaging consequences of increasing the dose of radiotherapy may appear radiologically and clinically identical to tumor growth. This makes it very difficult to know if radiographic changes with or without clinical worsening are from progressive growth of the brain tumor or represent treatment-related toxicities to the brain.

ABTC therefore launched two trials in an attempt to determine the maximum tolerated dose (MTD) of GSBT followed by conventional external beam radiation therapy (EBRT) in newly diagnosed GBM (NABTT 2105) and as a single treatment modality (NABTT 2106) in patients with recurrent GBM. We now present the results of the two initial prospective

ABTC (formerly NABTT) studies of this device to aid in the design of future trials and encourage further study.

Methods

This study was approved by the Cancer Therapy Evaluation Program at the National Cancer Institute and by the institutional review board of each participating institution, which included the Cleveland Clinic, Emory University, Henry Ford Hospital, Johns Hopkins University, the University of Pennsylvania, and Wake Forest University. Informed consent was obtained from all participants. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Eligibility criteria

Eligibility criteria for newly diagnosed patients

To be eligible for this protocol, patients were required to be ≥ 18 years of age, have a preoperatively suspected and postoperatively confirmed supratentorial grade IV astrocytoma (glioblastoma multiforme), be a candidate for maximal surgical resection of the tumor mass, and have residual enhancing tumor within the expected brachytherapy treatment volume. Furthermore, the resection could not be expected to result in a new permanent neurologic deficit. In addition, a Karnofsky performance score of ≥60, a mini mental state exam (MMSE) score ≥ 15, and normal hematologic and renal functions (absolute neutrophil count of ≥ 1500/mm³, platelets ≥ 100,000/mm³, creatinine ≤ 1.7 mg/dl, and BUN with normal limits) were required. Patients had to sign an Institutional Review Board (IRB) approved written informed consent form prior to registration on study as well as a presurgical and a postsurgical consent before receiving study brachytherapy.

Eligibility criteria for recurrent high-grade glioma patients

Patients were eligible for this study if they were ≥ 18 years, had a Karnofsky performance score of ≥60 at screening, had a mini mental state exam (MMSE) score of ≥ 15, had a previously diagnosed histologically proven malignant glioma (anaplastic astrocytoma, anaplastic oligodendroglioma, or glioblastoma multiforme) with unifocal disease, which was progressive or recurrent following radiation therapy with or without chemotherapy, and were candidates for maximal surgical resection of the tumor mass. Any expected residual enhancing tumor had to be within the expected brachytherapy treatment volume. Resection could not be expected to result in a new permanent neurologic deficit. In addition, patients had to have previously received definitive (≥ 5000 cGy) external beam radiation therapy, had to be greater than 3 months from completing radiation therapy, and had normal hematologic and renal function. Patients had to have recovered from toxicity of prior therapy. An interval of at least 3 months had to have elapsed since the completion of the most recent course of radiation therapy while at least 3 weeks had to have elapsed since the completion of a non-nitrosourea-containing chemotherapy regimen or at least 6 weeks since the completion of a nitrosourea-containing chemotherapy regimen. Patients had to have signed an Institutional Review Board (IRB) approved written informed consent form prior to registration on study.

Patients were ineligible if they had two or more separate foci of contrast-enhancing tumor extending beyond the expected brachytherapy prescription volume on the preoperative MRI, enhancing tumor crossing >1 cm beyond the midline on the preoperative MRI, radiographically apparent leptomeningeal spread and/or ventricular invasion outside the anticipated radiation treatment volume or marked edema on the preoperative MRI scan (or CT for those patients who were ineligible for MRI) with significant shift that was not anticipated to be corrected by the tumor resection surgery. Patients with medical illnesses which would preclude protocol treatment, those with other concomitant malignancies, and those who were pregnant or breast-feeding were also excluded. Finally, patients who planned to receive other antineoplastic therapy within 90 days of the completion of brachytherapy were excluded.

Treatment plan

Patients with newly diagnosed glioblastoma (NEW-GBM) were scheduled to undergo surgery with placement of the GliaSite balloon. Brachytherapy was to begin 3 to 21 days following surgery. Standard external brain radiation therapy (EBRT), 60 Gy in 30 fractions, followed within 30 days of the brachytherapy and not more than 60 days from the time of resection. The brachytherapy doses were as outlined below. Imaging was performed preoperatively, within 48–72 h postoperatively with the balloon inflated, at the end of EBRT, every 2 months for 1 year following completion of EBRT, and as clinically indicated thereafter. Glucocorticoids were administered as clinically indicated. Dose-limiting toxicities were defined as grade 3 to 4 neurologic, headache, nausea vomiting, or an unresolved CSF leak within 3 months of brachytherapy, radiation necrosis requiring craniotomy within 3 months of completion of brachytherapy, or any fatal events. Patients were removed from the protocol when there was clinical or radiologic evidence of progressive disease, when the patient started another treatment, or at any time that the patient desired to withdraw. An acceptable incidence of dose-limiting toxicities in this patient population was considered 20 % which was to be assessed 90 days following the completion of EBRT. Patients who came off study for imaging progression or death unrelated to treatment earlier than 90 days were considered unevaluable and replaced, unless they had experienced a dose-limiting toxicity (DLT). The anticipated cohort size was five patients with an expansion at the maximum tolerated dose (MTD) to ten patients.

Dose escalation

For patients with NEW-GBM, the starting dose for brachy-therapy was 70 Gy prescribed at 1 cm from the balloon surface cavity. This was to be escalated and de-escalated using traditional dose-escalating methods. The MTD was defined as the dose level that would result in DLTs in two of ten treated patients or 10 Gy below the dose level that would result in 2/5 DLTs. A DLT was defined as NCI CTC 2.0 grade three or four toxicity that had not resolved within 1 month of onset or 3 months from end of protocol radiotherapy (whichever was longer), any grade 5 toxicity, or radiation necrosis requiring craniotomy within 3 months from completion of brachytherapy. Progressive disease (PD) was defined as progressive neurologic abnormalities not explained by causes unrelated to tumor progression, >25 % increase in the volume of enhancing tumor, or new enhancement on MRI.

For patients with REC-HGG, the GliaSite balloon was placed at surgery and it was loaded with radioisotope 5–7 days postoperatively. The cohort sizes, follow-up schedules, and determination of dose-limiting toxicities were identical to those in the newly diagnosed population. However, the initial dose prescribed was 80 Gy rather than the 70 Gy proposed in the NEW-GBM patients who were also receiving EBRT.

Results

NABTT 2105: newly diagnosed patients

A total of ten NEW-GBM patients were enrolled on protocol 2105 at the initial dose step. The median patient age was 57 years (27–68), median KPS was 90 (60–100), median balloon size was 3 cm (2–4), median GSBT dose was 70 Gy at 1 cm depth (53–70), median dwell time was 95 h (92–165), and median delivered radioactivity was 365 mCi (195–419). Even when ten patients who were accrued as inevaluable patients were replaced, eight of ten did not reach the 90-day evaluation timepoint. Five had radiographic changes presumed to represent recurrence within 90 days of the end of radiotherapy (brachytherapy plus EBRT) (median 32 days, during treatment—83 days), one died of a pulmonary embolism, one was removed from study to receive another therapy, and one patient was accidentally underdosed.

Although dose-limiting toxicities as defined above were not noted in any patient, it became increasingly clear during the conduct of this trial that we could not determine whether the progressive contrast enhancement observed following brachytherapy was the result of the local radiation or tumor progression. Although the protocol would have allowed continued accrual and dose escalations with an assumption that increasing posttreatment enhancement represented progressive disease, the investigators realized that determination of a reliable MTD would not be possible in this setting and the trial was therefore closed to further accrual.

Nine patients have died and one was lost follow-up. The median overall survival of patients treated on this trial was 15.3 months (95 % CI 7.1–23.6) (Fig 2). Patients who had no residual disease seen on postoperative imaging had a median survival time of 20.2 months, whereas those who had residual disease survived a median of 9.1 months ($p=0.0584$). No dose-limiting toxicities were observed.

NABTT 2106: Recurrent high-grade glioma

For patients with REC-HGG, a total of five patients received the GliaSite balloon and radioisotope. The median age of these patients was 56 years (43–67). The median KPS was 90 (60–100). Three patients had a diagnosis of GBM (WHO IV), 1 had AA (WHO III), and 1 had AO (WHO III). The median number of cycles of previous chemotherapy was 3 (1–6). The median previous external beam radiation therapy dose was 60 Gy (56–63). The median balloon size was 3.0 cm (2.0–4.0). All patients received a dose of 80 Gy at 1 cm. The median dwell time was 116 h (115–168). The median delivered radioactivity was 429 mCi (237–661). No additional external beam radiotherapy was administered. One patient was taken off study prior to the evaluation endpoint to start another therapy.

The same issues described above for NEW-GBM were noted relating to new contrast enhancement that could be related to therapy or progressive disease. As a result, this trial was also closed to accrual without determining an MTD. No DLT was encountered. One patient was removed for imaging progression at 81 days. The patient taken off study to start a new treatment had a PR. Of the remaining three evaluable patients, imaging progression was observed 4.0 and 4.2 months after brachytherapy. All patients died at the time of the database being closed. The median survival for this patient population was 12.8 months (95 % CI 4.2–20.9) (Fig 2). Patients without residual disease survived 16.4 months, whereas those with residual disease survived 10.9 months (NS). There were no instances of dose-limiting toxicity.

Discussion

The GliSite balloon is an FDA-approved device designed to provide brachytherapy following resection to patients with newly diagnosed or recurrent high-grade gliomas. These phase I dose escalation trials were designed to determine safe doses of brachytherapy that could be administered to patients with NEW-GBM and REC-HGG and to estimate the effect of this on survival. However, high doses of local radiation [9–11] appear to disturb the integrity of the blood-brain barrier resulting in MRI scans which reveal increased contrast enhancement, peritumoral edema, and mass effect that is indistinguishable from tumor progression. In situations such as this, when the toxicities of therapy mimic tumor progression, it becomes impossible to accurately assess the extent of treatment-related toxicities or to conduct meaningful dose escalation studies using an imaging endpoint. As a result of this observation, these studies were terminated and the answers to the questions which were posed remain unanswered. Further study did not proceed as the device was no longer available in 2008, but manufacture has resumed in 2012.

Various strategies to focally escalate radiation therapy dose to visible tumor have been attempted in phase III studies, notably stereotactic radiosurgery [12] and standard catheter brachytherapy implant [13]. Neither has yielded a significant improvement in survival or local control. These trials included patients with substantial gross residual contrast-enhancing tumor, whereas the GliSite device is optimally used for patients with minimal or microscopic residual disease adjacent to a resection cavity. For example, RTOG 0023 [14], a preliminary study of accelerated radiotherapy using weekly stereotactic conformal boosts for GBM, did not suggest a survival benefit for the overall population, but patients who had undergone a gross total resection showed a trend towards improved median survival (17 vs. 12 months).

GliSite brachytherapy may be of benefit based on advantageous radiation dosimetry, even though radioactive seed brachytherapy was never convincingly demonstrated to improve outcome. With this balloon brachytherapy system, there is predictable deposition of dose through the entire treatment volume [3], decreasing uniformly with distance from the balloon surface (Fig 3). With the use of radioiodine or iridium seeds, there are hot spots of high radiation adjacent to each seed creating a risk of necrosis and radiotherapy cold spots that exist between seeds creating a risk of early treatment failure [15]. Radiosurgery, an alternative means of dose escalation, is targeted at contrast-enhancing tumor with minimal

dose delivered to adjacent brain which may harbor subclinical disease. GBST is well suited to treatment of potential microscopic disease as the implant is within a cavity created by maximal resection and dose is delivered to surrounding tissue whether it harbors grossly visible tumor or microscopic disease.

Although these were GSBT dose-finding studies not intended to measure survival outcome, survival results were assessed as a safety precaution as there was potential that radiation-induced injury might result in premature death. This limited survival data suggests that this treatment may have been active and is worthy of further study. The median survival was 15.3 months for NEW-GBM patients and 12.8 months for recurrent disease similar to other reports using this device [4, 16–19] (Table 1), although well-powered prospective trial has not occurred. Temozolomide chemotherapy, now standard in the management of newly diagnosed glioblastoma, was not utilized. In the trial demonstrating the value of temozolomide, median survival of newly diagnosed patients was improved from 12.1 to 14.6 months, but gross total resection was not required. Similar populations of patients to those enrolled in our studies, newly diagnosed or REC-HGG undergoing gross total or near total resection, comprised the control groups of randomized clinical trial testing a different local therapy (polifeprosan with carmustine wafers). NEW-GBM treated with standard radiation alone on the control arm had a median survival of 11.6 months [20, 21], and resected REC-HGG had a survival of 5.3 months [22].

Subsequent to the conduct of these studies, other reports of outcome with the GliaSite device have demonstrated the pitfalls of using imaging endpoints. An analysis of outcome for 20 patients treated with GliaSite brachytherapy for recurrent disease at Johns Hopkins confirmed the observation that imaging changes, including substantially increased contrast enhancement, are not correlated with survival and may therefore represent benign treatment-related effects rather than progressive tumor for some patients [16]. Eighty percent had an imaging confirmed gross total resection, and routine MRIs through 3 months of follow-up were assessed. Patients observed to develop a maximal T1-weighted enhancement thickness >1 cm actually had a median survival of 13.6 months, and those with T1-weighted lesions <1 cm had an inferior median survival of 8.5 months ($p=.014$). In another report with GliaSite brachytherapy [23], 5/8 patients had progressive contrast enhancement after GliaSite balloon brachytherapy. In one patient, this resolved; in two patients, pathology confirmed treatment effect/necrosis; and tumor was confirmed for two patients. MRI spectroscopy did not reliably correlate with outcome. It is now understood that imaging progression resulting from treatment effects (pseudoprogression) can be observed even with the use of standard radiotherapy, especially along with systemic temozolomide [11, 24–26]. For these reasons, we do not consider imaging progression an appropriate endpoint for the evaluation of outcome of this device.

The experience developing GliaSite may be contrasted with the successful development of polifeprosan 20 with carmustine wafers as an FDA-approved local therapy utilized in a similar population, including patients with NEW-GBM or recurrent high-grade REC-HGG glioma suitable for gross total or near total resection. Importantly, the dose-finding and safety studies as well as the efficacy trials for the use of BCNU wafers included only clinical and survival but not imaging endpoints [20–22, 27–29]. In fact, it was later learned that with

this intensified local therapy imaging, evidence of progression frequently was an effect of this treatment as well [30], and considering imaging changes themselves as toxicity or progression may have thus hindered development of this therapy. Nevertheless, randomized trials of carmustine wafer therapy proceeded demonstrating a median survival for 110 patients with REC-HGG who received carmustine polymers of 7.2 months compared with 5.3 months for 122 patients who only received placebo polymers [22]. For NEW-GBM patients, median survival was improved from 11.6 to 13.9 months ($p=0.03$) with wafer therapy [20, 21].

Thus, we believe that clinical events and survival should be the important endpoints, rather than imaging findings, used in early evaluation of novel therapeutic strategies that include radiotherapy. Although selection factors may influence survival outcome, large databases now exist that allow results to be assessed in the context of historical controls including similar subgroups of patients such that unexpectedly poor results may raise safety concerns in early testing and good outcome may prompt phase II testing regardless of imaging assessment of response and control. Ultimately, better imaging techniques may more reliably distinguish recurrence from treatment effects. Techniques under consideration include PET, MRI spectroscopy, rCBV MRI, and other novel approaches.

Conclusion

These ABTC trials of the GliaSite brachytherapy device failed to determine an MTD dose for further testing as there was presumed to be a high incidence of early progression that prevented assessment of treatment-related toxicity. Therefore, ABTC abandoned development of a line of investigation including not only use of this device as a single therapeutic modality but also combining this method of administering radiotherapy with other systemic or locally infused agents. However, the favorable survival outcomes in these and other studies, although based on small populations, suggest this therapy may be beneficial and worthy of further study to optimize use and dosing. A manufacturer-sponsored study to determine the safety and dose of GliaSite brachytherapy in patients with NEW-GBM treated with the EORTC regimen of radiation therapy and temozolomide closed in early 2008 when the treatment balloon became unavailable. Planning is now underway to conduct a similar study as well as trials combining this biologically different and continuous radiation dosing with systemic agents.

Future study will be based on a new cesium-131-based liquid preparation designed for use in the GliaSite system. An advantage, in comparison with I-125, is reduced radiation safety risk, as should the balloon rupture the isotope will not be retained in a patient's thyroid gland and the shorter half-life allows in faster decontamination should a spill occur. Another potential advantage is a higher energy than I-125 (30.4 vs. 28.5 KeV), resulting in less dose at the balloon-brain interface required to provide the planned dose at the desired depth into the brain.

Acknowledgments

Funding This study was funded by the National Cancer Institute Grants CA62-475 and CA137443 and by Proxima Therapeutics, Alpharetta, GA.

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Fig. 1. GliaSite brachytherapy balloon implanted in the brain (image courtesy of Isoray Medical, Inc.)

Fig. 2.
Overall survival NABTT 2105 and 2106 (NDGBM and RGBM)

Fig. 3.
Depiction of dose falloff beyond surface of a 3-cm diameter GliaSite brachytherapy balloon
(image courtesy of Isoray Medical, Inc.)

Table 1

Survival results for GliSite therapy for recurrent high-grade glioma

Recurrent high-grade glioma	Number	Median survival (months)
Tatter [4]	21	12.7
Chan [17]	17	9
Gobitti [19]	15	13
Gabayan [18, 19]	95	9 (GBM) 11 (anaplastic astrocytoma)
Current series	4	12.8
Newly diagnosed glioma		
Welsh [31]	20	11.4
Current series	9	15.3