Superselective intraarterial cerebral infusion of bevacizumab: a revival of interventional neuro-oncology for malignant glioma

Howard A. Riina, Justin F. Fraser, Sherese Fralin, Jared Knopman, Ronald J. Scheff and John A. Boockvar* 1

1Weill Cornell Brain Tumor Center, Department of Neurosurgery, Weill Cornell Medical College of Cornell University, New York, NY

*Corresponding to: John A. Boockvar, MD Associate Professor of Neurological Surgery Co-Director, Weill Cornell Brain Tumor Center Department of Neurological Surgery, Weill Medical College of Cornell University 510 E 70th Street, NY, New York 10021. Telephone: 212-746-5575. E-mail: jab2029@med.cornell.edu

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INTRODUCTION

Glioblastoma multiforme (GBM) and anaplastic astrocytoma (AA) comprise the primary high-grade brain tumors in adults. Exhibiting the most aggressive behavior among brain tumors, these neoplasms kill up to 15,000 Americans a year, with a median overall survival durations of only 12-15 months for GBM, and 3-4 years for AA, from the initial diagnosis, despite multimodal treatment approaches. These cancers invariably recur despite up-front therapy, which consists of surgical resection, radiation and temozolomide (Temodar) chemotherapy. The current standard initial care for GBM is surgical debulking followed by radiation therapy and concurrent temozolomide, followed by maintenance temozolomide. Until recently, there was no standard treatment for recurrent disease. Patients with recurrent GBM usually are offered immunotherapy with bevacizumab either alone or in combination with Irinotecan (CPT-11) intravenously. Recent studies incorporating bevacizumab in the recurrent disease setting have demonstrated up to 50% 6-month progression free survival (PFS), a dramatic improvement from previous data (see below). Despite this success, all patients ultimately require another salvage therapy or succumb to their disease. Improvements either in the delivery of bevacizumab or a better understanding of its CNS penetration is needed to effectively enhance its efficacy in this fatal disease. Because SIACI has the potential to achieve high first pass delivery of Bevacizumab to the tumor, we expect
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improved response rates in our patients to this active
drug. Our Institutional Review Board (IRB)-approved
research protocol is primarily designed to determine the
safety of bevacizumab administered using SIACI in
patients with recurrent high-grade glioma. As this is the
first reported use of selective microcatheter delivery of
a targeted agent to a brain tumor this report will detail
the technical aspects of the delivery method including
dosages of the administered drugs. If proven safe by
larger Phase I clinical trials, this novel delivery method
may alter the way our therapies are given to patients
with GBM.

MATERIALS AND METHODS

Case History

A 52 year old male who presented with left hand
numbness, seizures and memory deficit, was found to
have an enhancing right parietal brain tumor (Figure
1A). In February, 2009 he underwent a right parietal
stereotactic biopsy at an outside facility followed by
a craniotomy and gross total resection of the brain
tumor at our institution by the senior author (JAB)
(Figure 1B). Pathology came back as Glioblastoma
Multiforme, WHO Grade IV. He started radiation
and Temodar in March, 2009. Following completion of
radiation, a repeat MRI in May, 2009 showed new
marginal perioperative enhancement that most likely
reflected postoperative changes. Increasing nodular
enhancement in the right periatrrial white matter and
new nodular enhancement at the posterosuperior mar-
gin of the resection cavity were suspicious for recurrent
neoplasm. Confluent right parietal and right periatrrial
perioperative T2 hyperintensity with extension into
the splenium the corpus callosum most likely reflected
vasogenic edema and/or nonenhancing infiltrative neo-
plasm. At this time he denied any seizure activity. The
patient started maintenance Temodar.

Follow-up MRI performed in July, 2009 showed a
minimal interval increase in previously noted nodular
enhancement within the right periatrrial white matter
abutting the subependyma of the right atrium and nodu-
lar enhancement at the posterosuperior margin of the
resection cavity. In addition, there was subependymal/
leptomeningeal nodular enhancement along the frontal
horns and right temporal horn, most consistent with new
leptomeningeal/CSF seeding of neoplasm and progressive
disease. The patient denied any seizure activity, but
reported worsening headaches. After informed consent
was obtained from the patient, he received superselective
intraarterial (IA) Mannitol and Bevacizumab on
August 11, 2009 (see below), and was discharged the
following day without complication. Post procedure CT
scan of the head showed no hemorrhage or worsening
edema.

An MRI performed in September 2009, three weeks
following the selective intraarterial Mannitol and Beva-
cizumab administration, showed interval improvement
in the appearance of the gadolinium enhancement
in the right parietal resection cavity where intraarte-
rial Bevacizumab was targeted (Figure 2). He began
receiving biweekly intravenous Bevacizumab and
CPT-11 (Irinotecan) 4 weeks following the IA Avastin
administration.

Technical aspects of the Superselective
Intraarterial Procedure

The common femoral artery was accessed with a
19 guage needle which was exchanged for a 6 French
Sheath. A 6 French guider catheter was then advanced
into the right internal carotid artery. Biplane angiogra-
phy over the cranium from a right ICA injection dem-
onstrated the right middle cerebral arterial branches
supplying the tumor (Figure 3A). After administering
intravenous weight-based heparin, a microcatheter was
advanced over a microwire into a distal branch off the
inferior trunk of the right MCA bifurcation. Selective
biplane angiography through the microcatheter from

Figure 1. The patient presented after stereotactic
needle biopsy at an outside hospital of an enhancing
right parietal multifocal lesion on post contrast T1 axial
(A) and sagittal (B) MRI images. The patient underwent
a gross total resection confirmed on postoperative axial
(C) and sagittal (D) T1 post-contrast imaging.
Figure 2. The patient underwent SIACI of unlabeled Avastin for recurrent GBM. A. Sagittal post contrast MRI showing tumor recurrence (yellow arrow). B. Superselective microcatheter delivery up until craniotomy site. C. Contrast injection of superselective catheter. D. Sagittal, coronal and axial post contrast images prior to a single dose of Intraarterial Avastin (2mg/kg). E. The same images of the tumor 3-weeks after a single superselective Intraarterial intracerebral injection (SIACI) showing diminished enhancement of gadolinium in the tumor.

Figure 3. A. Lateral angiography through the right ICA demonstrates a distal superior branch from the inferior division of the right MCA providing blood circulation to the resection cavity and recurrent tumor (yellow arrow). B. Superselective angiography through the superior/medial branch of the inferior division of the right MCA demonstrates anterograde flow to the underlying tumor cavity. C. Lateral angiogram through the right ICA after superselective infusion of mannitol/Bevacizumab through the right MCA demonstrates increased vascular blush and hyperemia within the underlying tumor cavity as compared to phase-comparative pre-infusion angiogram.
DISCUSSION

Bevacizumab is a monoclonal antibody (mAb) which binds to vascular endothelial growth factor (VEGF). It blocks the formation of new blood vessels in tumors, but also affects existing vasculature. Bevacizumab reduces brain tumor edema, "normalizes" tumor blood vessels, and is an effective antitumor agent alone or in combination with chemotherapy. In patients with GBM, the expression of VEGF is associated with a poor prognosis. Several mAbs to VEGF have inhibited the growth of GBM in vitro and in vivo(1). Within the last year, intravenous bevacizumab, as a single agent or in combination with irinotecan, has become a standard frontline therapy for recurrent GBM. In a recent phase II trial, bevacizumab, randomized with or without concurrent irinotecan chemotherapy, was administered to 167 patients with recurrent GBM. Primary endpoints of the study, assessed by MR imaging, were 6-month PFS and response rate (≥50% decrease in tumor size). Median durations of treatment were 16 weeks with bevacizumab alone and 22 weeks with bevacizumab plus irinotecan. Treatment with both agents yielded a 6-month PFS of about 50%, compared with historic rates of 15% in patients with GBM(2). The 1-year overall survival with bevacizumab and irinotecan was superior to historical controls: 37% versus 21%, respectively. There was some toxicity associated with treatment including infections, venous-thromboembolic events, and wound healing complications -- occurring in 9.5%, 2.4%, and 3.6% of patients, respectively(3-7). A 46.4% rate of Grade 3 or higher toxicity was seen in patients receiving bevacizumab alone(8). These data demonstrate that bevacizumab is active in recurrent GBM, and the FDA recently approved IV bevacizumab for use in this setting. It is clear, however, that current response rates can be improved and toxicity with systemic delivery avoided with selective delivery techniques such as put forth in this proposal.

The substantial pharmacologic advantage of intraarterial cerebral delivery compared with intravenous cerebral chemotherapy has been proven in animal models of glioma as well as in clinical studies(9). Compared with intravenous injection, superselective injection of 99mTc-HMPAO (Ceretec®) into human cerebral arteries (the middle, anterior, and posterior) achieved a concentration of radiotracer in brain tissue 50 times higher than with IV injection(10). In other clinical studies of cerebral chemotherapy, the concentration delivered to the tumor by using intraarterial injection versus intravenous administration of chemotherapeutic agents was five times higher with hydrosoluble drugs and up to 50 times higher with liposoluble drugs. Because of this pharmacologic advantage, intraarterial chemotherapy for brain gliomas has been performed for more than 20 years with the aim of improving the limited efficacy of intravenous chemotherapy by overcoming the obstacles to drug delivery (11-14). Furthermore, intraarterial chemotherapy results in a more localized delivery than does intravenous administration; this is well-suited for treatment of primary brain malignancies, as these tumors rarely metastasize and as most recurrences are local. Intraarterial chemotherapy, however, is still controversial, because clinical results have suggested but not proved superior efficacy-toxicity profile. In a study of 113 patients using intraarterial (via the internal carotid injection) carboplatin, 5.3% had asymptomatic complications, 8.0% had transient neurological complications and 2.6% had permanent minor complications and 2.6% had major permanent complications(9). No studies to date have evaluated the safety or efficacy of a targeted therapeutic like bevacizumab that is delivered via selective intra-arterial infusion to human brain tumors. Bevacizumab is well suited for delivery to the brain tumors using SIACI because of its ability to selectively target tumor tissue and because of toxicity associated with the systemic mode of delivery.

The delivery of chemotherapy to the liver via selective hepatic artery catheterization is a standard approach in the treatment of hepatocellular carcinoma and cholangiocarcinoma(15), with the advantages of higher chemotherapy exposure to the tumor over a longer period of time and minimization of systemic toxicity. These advantages lead to high response rates, where 35-83% of patients will have an objective radiologic response. In several randomized trials of patients with unresectable colon cancer, intraarterial delivery of therapy has been compared to systemic therapy or to no therapy at all. A meta-analysis of multiple randomized trials demonstrated an improvement in response rate from 14-41% and a 27% relative survival advantage (P = 0.0009)(15). These studies show that intra-arterial infusion of chemotherapeutic agents to other organ systems is a feasible and tolerable treatment approach to
improve outcome in patients with locally advanced cancers without distant metastasis.

When considering a broad approach to the treatment of malignant brain tumors, the blood-brain barrier (BBB) is identified as an important obstacle to the delivery of antineoplastic agents. It is with that understanding that the osmotic BBB disruption technique was developed (16-21). This technique has been performed in conjunction with chemotherapy infusion since 1981, and preclinical and clinical studies have clearly established that this approach significantly increases the delivery of antineoplastic agents to the tumor (21-24). In particular, the BBB results in very low permeability to large biomolecules such as antibodies like bevacizumab. Previous work has shown that BBB disruption (BBBD) prior to the delivery of drugs improves the efficacy of a tumor specific mAb. Intraarterial infusion of mannitol (25%; 3-10ml/s for 30seconds) in order to achieve osmotic disruption of the cerebral circulation has been well described (18, 25). Neuweit et al. performed 3498 BBBD procedures of the internal carotid artery using the same dose in conjunction with alkylating agent chemotherapy infusions in 405 patients. There was no associated risk of intracerebral hemorrhage, seizure or stroke. Finally, BBBD may enhance drug efficacy in the CNS. Fortin et al. used BBBD in some patients receiving intraarterial chemotherapy for intracranial tumors. Among the 20 patients treated for GBM with intra-arterial carboplatin, median survival from diagnosis for those in whom BBBD was used prior to chemotherapy infusion was 154 weeks, while it was 90 weeks for those in whom it was not utilized (26). In this report, we show that BBBD disruption prior to the delivery of bevacizumab using SIACI is technically feasible. This brief hyperemia allows for increased exposure of mAb to the tumor VEGF targets. Future studies using radio labeled tracers such as $^{64}$Cu-DOTA-Bevacizumab will allow us to precisely determine CNS distribution of drug after selective delivery.

CONCLUSION

In order to overcome the blood brain barrier (BBB) and limit systemic toxicity of IV Bevacizumab, we have devised a Phase I protocol to transiently break down the BBB with intraarterial (IA) Mannitol and to selectively deliver Bevacizumab via superselective intraarterial cerebral infusion (SIACI). This report describes the technical aspects of the procedure and its associated benefits and risks. This novel delivery method may significantly impact the way our therapies are given to patients with GBM.

REFERENCES


