Superselective Intra-Arterial Cerebral Infusion of Novel Agents After Blood–Brain Disruption for the Treatment of Recurrent Glioblastoma Multiforme: A Technical Case Series

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KEYWORDS

• Glioblastoma multiforme • Intra-arterial chemotherapy
• Bevacizumab • Cetuximab • Temozolomide

Every year approximately 12,000 cases of glioblastoma multiforme (GBM) are newly diagnosed in the United States,[1] constituting the most common primary brain tumor. GBM carries a grim prognosis with a 2-year survival rate after diagnosis of approximately 26.5%,[2,3] even with a multidisciplinary treatment including surgical resection followed by radiation therapy and concomitant temozolomide.[4] Once the tumor recurs, patients are treated with several chemotherapeutic agents, such as bevacizumab and irinotecan, which have been shown to improve progression-free survival and overall survival.[5] Because treatment effects are modest and nothing to date has been shown to extend life satisfactorily, there is a great need for novel therapeutics. Several novel therapeutic modalities are under study and development, including immunotherapies involving tumor vaccines[6] and selective intra-arterial (IA) delivery of chemotherapeutics.[7]

Application of IA delivery of chemotherapeutics to treat malignant gliomas was introduced into clinical practice decades ago with the IA infusion of carmustine by an intracarotid approach.[8] These early studies showed no survival difference between IA and intravenous administration and even revealed a high complication rate, such as white matter necrosis or blindness in patients treated with the IA approach, which most likely occurred as a result of unselective catheter use and direct infusion of toxic agents.[9–11] Recently, however, modern specialized microcatheters are better able to selectively deliver drugs to distal tumor vessels to enhance local drug delivery.[12,13] At our institution, we use specialized microcatheters for superselective infusion of bevacizumab, cetuximab, and temozolomide. Our phase I trial revealed that the use of IA bevacizumab after blood–brain barrier disruption (BBBD) for recurrent GBM is safe and well tolerated.[7]

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Neurosurg Clin N Am 23 (2012) 323–329
doi:10.1016/j.nec.2012.01.008

Here, we present a technical case series of patients who received IA delivery of bevacizumab, cetuximab, or temozolamide after BBBD with mannitol. We describe the technical aspects of the procedure and the hospital course and 1-month imaging. All patients were included in an Institutional Review Board–approved phase I clinical trial to determine safety and tolerability. These data support the rationale to export the results to larger studies to evaluate the efficacy of this modality.

ILLUSTRATIVE CASES

Case One: BBBD/IA Bevacizumab

History and examination

The patient is a 52-year-old woman, who presented after subtotal resection of a right temporal lobe GBM in June 2009 at a community hospital followed by 2 months of radiation therapy and temozolamide chemotherapy. Chemotherapy was complicated by a hematologic toxicity including thrombocytopenia and neutropenia. In January 2010, there was evidence of tumor progression on magnetic resonance imaging (MRI). The subinsular enhancing component increased in size, whereas the right temporal lesion remained stable (**Fig. 1**A). Because of her history of neutropenia, additional temozolomide therapy was not recommended, and the patient entered our phase I trial for IA infusion of bevacizumab after BBBD with mannitol in February 2010.

IA treatment: technical description

After obtaining consent, the patient was placed in the supine position in the angiography suite under general anesthesia. The right common femoral artery was found by palpation, and a 19-gauge single-wall needle was inserted into this artery. We replaced the needle with a 6F catheter sheath connected to continuous heparin saline flush. Then, a 5F Torcon catheter was advanced into the right common carotid artery over a 0.035-in angled guidewire. A right common and internal carotid artery angiogram were performed to ensure anterograde flow. Intravenous heparin was then administered after measurement of a baseline activated clotting time (ACT). An Excelsior SL 10 microcatheter angled 45 degrees was then advanced into the right M1 segment over a Synchro 2 soft microwire. After removal of the microwire, 10 mL of 25% mannitol solution was infused for 2 minutes (see **Fig. 1**B). Then, we infused 13 mg/kg of bevacizumab in 36 mL of saline for 36 minutes; postinfusion angiogram excluded arterial vessel damage.

Immediate postoperative course

Postoperative hospital course was unremarkable and immediate follow-up MRI demonstrated a decreased in size in the heterogenous enhancement of the right temporofrontal mass and decreased F-18 fluorodeoxyglucose (FDG) uptake on positron emission tomography scan in the same area (see **Fig. 1**A).

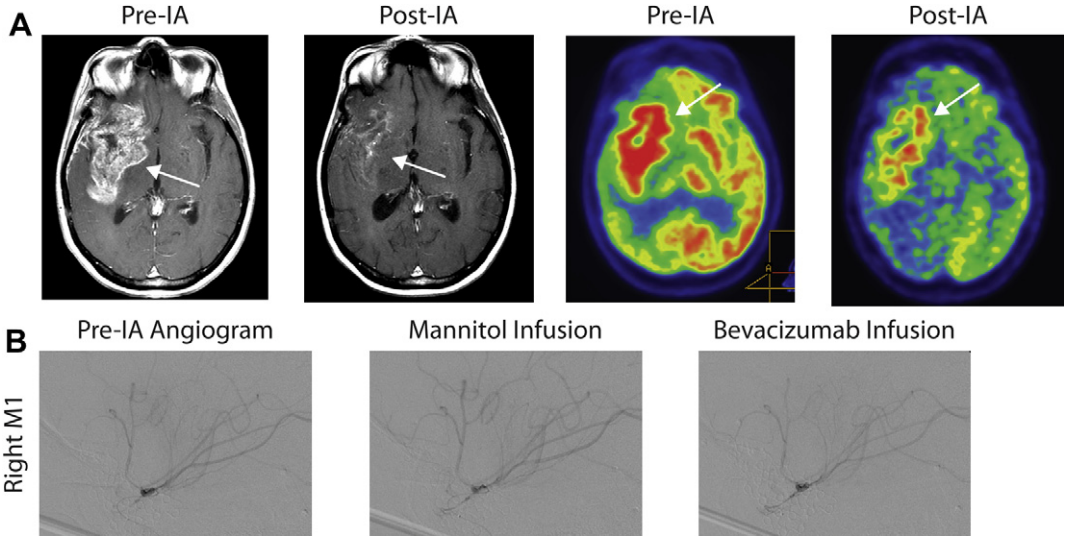

Fig. 1. (*A*) T1 axial magnetic resonance image (MRI) with contrast and fused metabolic positron emission tomography imaging before and 1 month after IA bevacizumab with BBBD treatment. A decrease in the heterogenous enhancement of the right temporofrontal mass on MRI (*arrows*) and a diminished F-18 fluorodeoxyglucose uptake in the same area are present (*arrows*). (*B*) Lateral fluoroscopic imaging of the pre-IA angiogram, after mannitol infusion, and after bevacizumab infusion. The right M1 segment of the right middle cerebral artery was selectively catheterized for infusion of mannitol and bevacizumab to treat the right temporofrontal lesion.

Case Two: BBBD/IA Temozolamide

History and examination

A 40-year-old man who presented in the emergency room with a 2-week history of nausea, vomiting, lethargy, and lower-extremity weakness became bradycardic with loss of consciousness. MRI revealed a heterogenous enhancing mass in the parasagittal left frontal lobe. The patient underwent craniotomy and gross total resection of the left parasagittal frontal lesion and was started on 2 months of chemoradiation with temozolomide. In January 2011, the patient reported clinical progression with some blurry vision in the left eye. MRI revealed recurrent left frontal mass with increased involvement of the corpus callosum (**Fig. 2**A). At this point, the patient was enrolled in our Phase I IA temozolamide trial.

IA temozolamide treatment: technical description

In February 2011, the patient was consented for selective IA infusion of temozolamide after BBBD with mannitol. The right common femoral artery was palpated, and a 19-gauge needle was inserted and then exchanged for a 6F catheter sheath connected to a continuous heparin saline flush. A 6F Envoy catheter was then advanced into the left common carotid artery over a 0.035-in guidewire under fluoroscopic guidance. Diagnostic angiograms were performed for the left common and internal carotid arteries to ensure normal anterograde flow. Afterward, heparin was administered intravenously after measurement of a baseline ACT. Then, using roadmap guidance, an Excelsior SL 10 microcatheter angled to 45 degrees was advanced into the A1-A2 junction over a Synchro 2

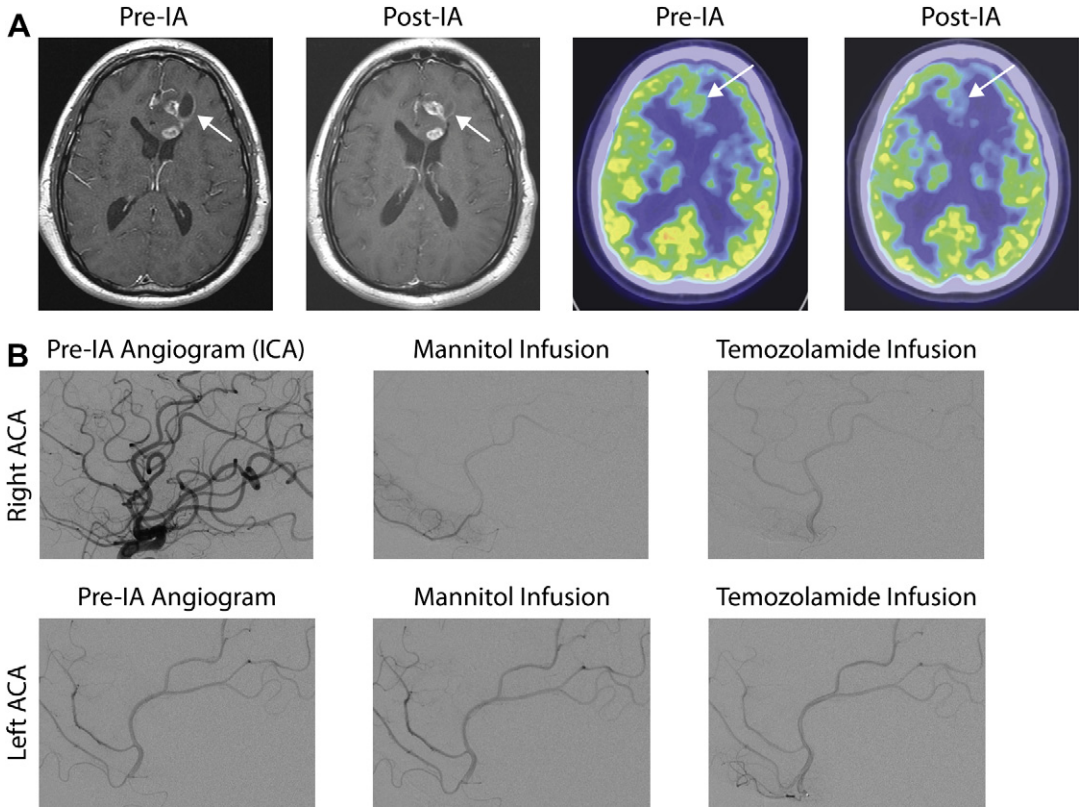

Fig. 2. (*A*) T1 axial MRI with contrast and fused metabolic PET imaging before and 1 month after IA temozolomide with BBBD treatment. There is decreased size in the cystic component of the left frontal mass on MRI (*arrows*) and decreased F-18 FDG uptake in the left frontal parasagittal lesion (*arrows*). (*B*) Lateral fluoroscopic imaging of the pre-IA angiogram, mannitol infusion, and temozolamide infusion. The right A1 segment and left A1-A2 junction of the right and left anterior cerebral artery, respectively, were selectively catheterized for infusion of mannitol and temozolamide to treat the left pericallosal frontal lesion, which may be crossing the midline over the corpus collosum.

soft microwire. After removal of this microwire, 10 mL of 25% mannitol was infused for 2 minutes (see Fig. 2B). Then, 83 mL of temozolamide (199 mg) was infused for 60 minutes. Postinfusion angiography was performed to ensure no arterial injury had occurred. The catheter was then advanced into the right common carotid artery under fluoroscopic guidance. An angiogram was performed for the right common and internal carotid arteries to ensure normal anterograde flow followed by intravenous heparin. Just as for the left anterior cerebral artery, 10 mL of 25% mannitol and subsequent 22 mL of temozolamide (53 mg) was infused into the right A1 segment.

Immediate postoperative course

Postoperative hospital course was unremarkable and 1-month follow-up MRI is illustrated in Fig. 2A, which demonstrated decrease in size of the cystic component of the left frontal mass and decreased FDG uptake in the left frontal parasagittal lesion.

Case Three: BBBD/IA Cetuximab

History and examination

This 61-year-old male patient presented with ataxia and memory difficulties and subsequently underwent resection of a posterior right parietooccpital GBM in December 2008. Postoperatively, the patient underwent radiation therapy and temozolamide chemotherapy for only 6 weeks because of noncompliance. He was then continued on maintenance temozolamide for 6 months. In August 2009, the patient was started on bevacizumab in addition to temozolamide. While on this treatment regimen, the patient progressed on MRI, showing a 3.5-cm enhancement in the parietal lobe and new heterogeneous enhancement in the right posterior lobe. Irinotecan was added to his treatment. From March 2010 to July 2010, the patient also underwent gamma knife radiation. Bevacizumab was discontinued in August 2010. At that point, the patient reported visual deficit and decreased ambulation. He denied seizures or weakness. However, MRI revealed increased signal enhancement and mass effect within the right parietal, temporal, and occipital lobes (Fig. 3A). In September 2010, the patient underwent a right parietal craniotomy and subtotal resection of brain tumor by the senior author (J.B.). Postoperative MRI revealed persistent T2 hyperintensity in the left lateral thalamus and residual tumor. Pathology showed robust (70%) expression of epidermal growth factor receptor on immunohistochemistry.

IA cetuximab treatment: technical description

In October 2010, after obtaining informed consent, the patient was prepped for IA infusion of cetuximab and placed in the angiography suite under general anesthesia. The right common artery was found by palpation, and a 19-gauge needle was inserted. The needle was replaced by a sheath (5F catheter), which was connected to a continuous source of heparin saline flush. A guide catheter (6F catheter) was fluoroscopically advanced to the right common carotid artery over a 0.035-in guidewire. An angiogram was then performed in the posteroanterior and lateral projections to ensure anterograde flow into the right common, external, and internal carotid arteries. An ACT was measured, and heparin was given intravenously. The guide catheter proceeded into the right internal carotid catheter. An Excelsior SL 10 microcatheter angled to 45 degrees was advanced over a Silverspeed 14 microwire and placed into the M1 segment of right middle cerebral artery using the roadmap technique (see Fig. 3B). Repeat angiogram was performed to ensure anterograde flow.

After removal of the microwire, 10 mL of 25% mannitol was injected through the microcatheter for 2 minutes. After a postinfusion angiogram, 210 mg of cetuximab (100 mg/m^2) solution mixed in 105 mL of normal saline was infused for 30 minutes (see Fig. 3B). To ensure no arterial injury, postinfusion angiography was performed for the right M1 segment. Afterward, a 6F guide catheter was replaced by a smaller 5F catheter, which was advanced into the right vertebral artery over a guidewire. A right vertebral artery angiogram was performed to ensure anterograde flow. The microcatheter was then inserted into the right posterior cerebral artery (P1 segment), and 10 mL of 25% mannitol and 210 mg (100 mg/m^2) cetuximab was infused as previously described for the M1 segment (see Fig. 3B). Again, a repeat angiogram of the P1 segment was performed to ensure no arterial injury.

Immediate postoperative course

Postoperative hospital course was unremarkable and immediate follow-up MRI is as illustrated in Fig. 3A, which demonstrated decreased in size of the right parietal periventricular lesion.

DISCUSSION

Bevacizumab, Cetuximab, and Temozolomide in GBM

We describe in this case series the technical aspects of selective arterial infusion of cetuximab, bevacizumab, and temozolamide after BBBD.

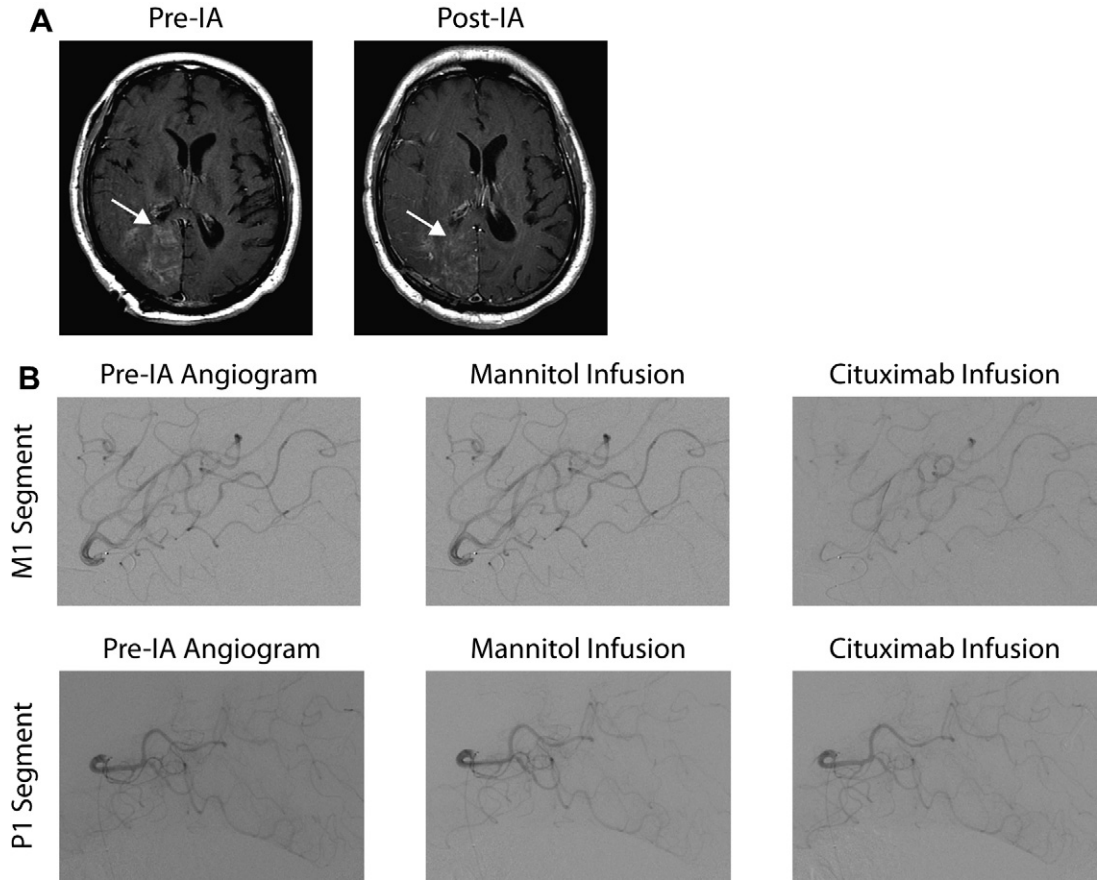

Fig. 3. (*A*) T1 axial MRI with contrast before and 1 month after IA cetuximab with BBBD treatment. There is a decrease in the size and enhancement of the right periventricular parietal lesion (*arrow*) from pre-IA to post-IA treatment. (*B*) Fluoroscopic imaging of the pre-IA angiogram, mannitol infusion, and cetuximab infusion. The right P1 and M1 segments of the right posterior cerebral artery and middle cerebral artery, respectively, were selectively catheterized for infusion of mannitol and cetuximab to treat the right periventricular parietal lesion.

Cetuximab, an epidermal growth factor receptor antibody, has been used intravenously in conjunction with irinotecan for the treatment of metastatic colorectal cancer and is currently in off-label use for recurrent GBM.[14] Likewise, bevacizumab, a vascular endothelial growth factor (VEGF) antibody, has been used intravenously with irinotecan for recurrent GBM.[15] However, survival after the intravenous application of these drugs is still unsatisfying and needs to be optimized. Although temozolamide has been successfully used as first-line chemotherapy in newly diagnosed GBMs,[3] no such success was achieved after the tumor recurred.[16] Up to now, the ideal treatment regimen for recurrent GBM is still missing and novel treatment modalities are needed to improve survival after GBM recurrence. At our institution, we recently completed a phase I trial[7,17] investigating the use of superselective IA infusion of bevacizumab after BBBD for the treatment of recurrent malignant glioma. We found that this modality is safe and well tolerated. The maximum tolerated dose for IA cetuximab and temozolomide are still under investigation. The three patients in this case series received 13 mg/kg bevacizumab, 4.6 mg/kg cetuximab, and 2 mg/kg temozolomide, respectively. All of the patients in this case series were included in either phase I or II trials, so outcomes and longer-term side effects will be evaluated in a separate study.

Superselective IA Cerebral Infusion and BBBD

Previous studies have shown that superselective IA chemotherapy increases the concentration of Tc-hexamethylpropyleneamine compared with the equivalent intravenous route.[18] In addition to increased parenchyma drug concentrations, localized IA therapy may prevent more systemic effects, as shown by our study.[7] To further increase local drug delivery disruption of the BBB is an established method. Passive transfer

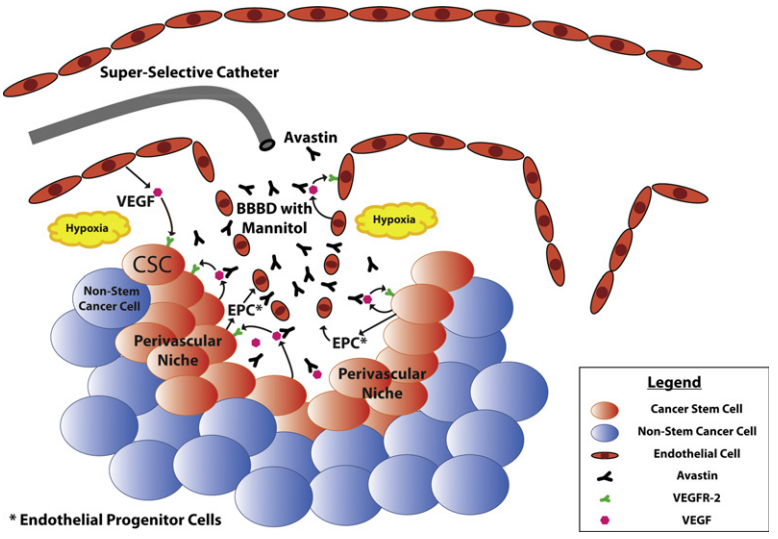

Fig. 4. Example of selective intra-arterial niche disruption and delivery using mannitol and bevacizumab. In addition to intravascular VEGF, VEGF within the perivascular niche needs to be targeted to disrupt mitogenic signaling and the generation of endothelial and tumor progenitor cells. This model can also be applied to cetuximab, temozolamide, or any drug designed to target signaling involving GBM stem-like cells. Cancer stem cell, endothelial progenitor cell.

across any membrane is proportional to both the concentration gradient and the diffusion coefficient of the membrane itself. To increase the diffusion coefficient, the BBB itself can be disrupted. Osmotic disruption of the BBB has been shown to increase uptake of monoclonal antibodies.[19] Although in malignant gliomas it is widely believed that the BBB is disrupted and not intact, Sarin and colleagues[20] showed that the maximal pore size of 12 nm in solid malignant brain tumors allows for only a partial opening of the BBB. Because the BBB is discontinuously open, we believe that agents with a bigger size, such as bevacizumab (size of 15 nm), reach the extravascular space more reliably after BBBD. Therefore, by using IA infusion and disrupting the BBB, we increase the concentration gradient and the transfer coefficient, thereby maximizing transfer of chemotherapy across the BBB.

Selective IA Niche Disruption and Delivery

By disrupting the BBB by IA fusion, we allow for maximal concentration of the infused drugs into the perivascular space known as the "perivascular niche." Calabrese and colleagues[21] have shown that cancer stem cells interact with endothelial cells in this niche and more specifically brain tumor blood vessels maintain the brain cancer stem-like cells and promote the growth of xenografts derived from stem-like cancer cells. Bevacizumab reduces the number of self-renewing tumor cells and especially inhibits the growth of xenografts derived from Daoy-positive cells. In addition, cancer stem-like cells themselves can also become endothelial cells under VEGF signaling, and bevacizumab prevents the maturation of these tumor endothelial progenitors.[22] As shown in the illustrative sketch (**Fig. 4**), VEGF needs to be targeted within the perivascular niche to disrupt mitogenic signaling and the generation of endothelial and maintenance of tumor progenitor cells. We believe that selective IA niche disruption and delivery is needed to allow monoclonal antibodies, such as bevacziumab, to enter the perivascular niche at a clinically sufficient concentration.

SUMMARY

In this technical case series, we have shown some examples of superselective IA cerebral infusion of chemotherapeutic drugs after BBBD with mannitol. Superselective IA cerebral infusion and selective IA niche disruption and delivery of bevacizumab, cetuximab, and temozolomide are safe methods for the treatment of patients with GBM. Treatment efficacy needs to be further determined in larger ongoing phase II and III trials. It is hoped that this technical case series provides a framework to impact positively the treatment of patients with recurrent GBM.

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