Targeted intra-arterial anti-VEGF therapy for medically refractory radiation-induced necrosis in the brain

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Introduction

Radiation necrosis (RN) is a serious complication that can occur in up to 10% of brain radiotherapy cases. Available medical treatment for RN includes steroids, vitamin E, pentoxiphylline, and hyperbaric oxygen. A significant number of patients however, are medically refractory and experience neurological decline, disabling headaches, and decreased quality of life.

Vascular endothelial growth factor (VEGF) is a known mediator of cerebral edema in radiation necrosis. Recent reports have shown successful treatment of RN with intravenous bevacizumab, a monoclonal antibody for VEGF. Bevacizumab however, is associated with significant systemic complications including pulmonary embolus, GI perforation, wound dehiscence, and severe hypertension. Using lower drug doses may lower systemic exposure and decrease complication rates. By using intra-arterial route of drug administration following blood-brain-barrier disruption (BBBD), we aim to lower the bevacizumab dose while increasing target delivery.

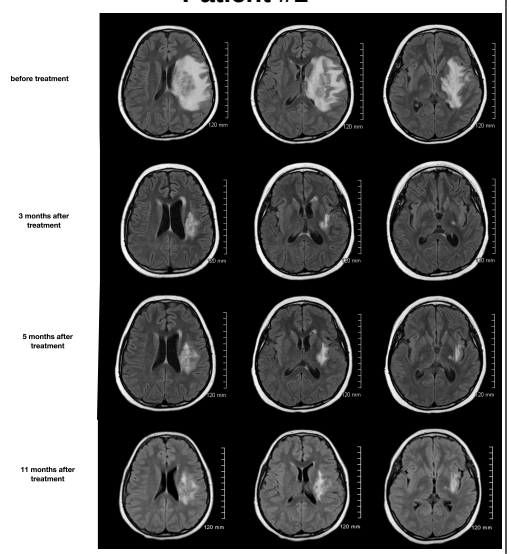
Methods

Two pediatric patients presented with medically intractable RN following stereotactic radiosurgery for cerebral AVM. Both patients were steroid dependent for a prolonged period and were severely cushingoid. Both had suffered a significant decline in quality of life with severe headache and need to withdraw from school. Patient #1 had progressively worsening hemiparesis. They received a single intra-arterial infusion of 2.5 mg/kg bevacizumab after BBBD.

Results

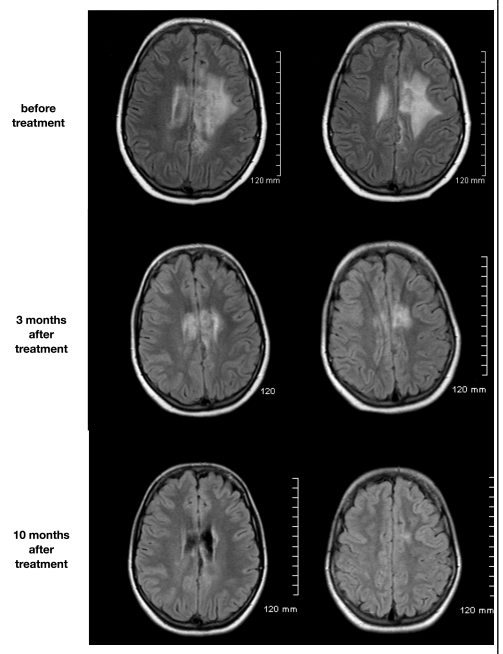
Both patients experienced immediate and permanent resolution of their previously intractable headaches. They experienced reversal of cushingoid features as they were successfully weaned off steroids. Patient#1 experienced progressive and continuous improvement in motor strength that was still ongoing 1 year later. There was an associated greater than 80-90% reduction in cerebral edema.

Patient #1



There is significant and sustained reduction in cerebral edema after IA-bevacizumab treament.

Patient #2



There is 74% and 90% reduction in cerebral edema 3 months and 10 months respectively, after IA-bevacizumab treament.

Discussion

Bevacizumab is a recombinant humanized version of a murine anti-human vascular endothelial growth factor (VEGF) monoclonal antibody. Bevacizumab binds circulating VEGF receptors with high specificity, blocking the down-stream signaling cascade. IV-bevacizumab was shown in a blinded, placebo-controlled, randomized trial (n=14) to be effective in treatment of refractory radiation necrosis after radiation therapy in brain tumors. Patients received 7.5 mg/kg IV-bevacizumab every 3 weeks for 4 cycles. There was however, a high rate of adverse events (55%), and major adverse events (27%).

We utilized a combination of IA-route of delivery and BBB disruption to reduce bevacizumab dose while maintaining efficacy. This is supported by the durable clinical and radiographic response in these two patients after a single 2.5 mg/kg dose of bevacizumab. This approach may reduce the incidence of serious systemic toxicities compared to the IV-bevacizumab regimen (7.5 mg/kg every 3 weeks for 4 cycles).

Conclusion

We have shown that intra-arterial bevacizumab after blood-brain-barrier disruption appears to be safe, effective, and durable treatment for medically refractory radiation necrosis in the brain. Advantages over intravenous route may include higher concentration of drug delivery to the target brain tissue, decreasing systemic toxicity because of the much smaller dose of bevacizumab used, as well as significantly lower cost.

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