Phase I Trial of Superselective Intra-arterial Cerebral Infusion of Bevacizumab and Arboplatin

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Introduction

High-grade malignant brain tumors are the most common and most aggressive adult brain tumors with median overall survival durations of only 9-12 months for glioblastoma multiforme (GBM), and 3-4 years for anaplastic astrocytoma (AA).

All patients experience a recurrence after first-line therapy, so improvements in both first-line and salvage therapy are critical to enhancing quality-of-life and prolonging survival. Carboplatin is an intravenous alkylating agent that is thought to work by interacting with DNA to inhibit DNA repair.

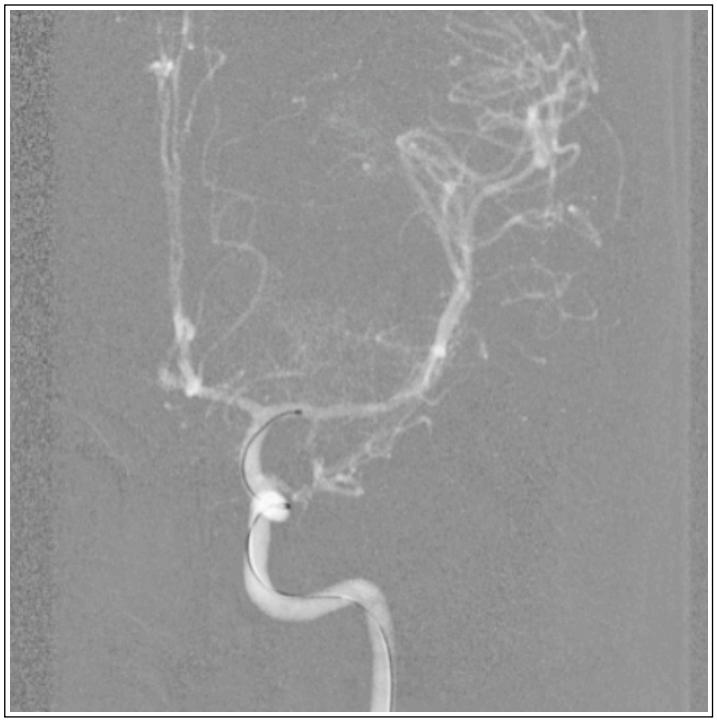
Bevacizumab is an antiangiogenic monoclonal antibody targeting vascular endothelial growth factor. The aim of combining these two drugs is to harness the potential synergy of their antiangiogenic and cytotoxic properties.

This phase I clinical research trial was designed to test the hypothesis that the combined administration of bevacizumab and carboplatin can be safely used by direct intracranial super-selective intra-arterial cerebral infusion (SIACI) to increase delivery to the brain and ultimately enhance survival of patients with primary GBM.

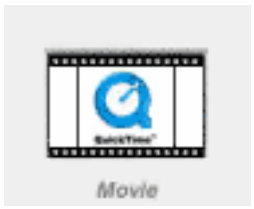
We have previously shown that SIACI of bevacizumab alone is safe in a phase I trial. By achieving the aims of this study we will determine the toxicity profile of SIACI of bevacizumab and carboplatin.

Methods

Subjects with high-grade glioma were treated with mannitol followed by a single SIACI of bevacizumab and carboplatin (Day 0). Bevacizumab was given at a fixed dose of 15 mg/kg. Carboplatin was given at a fixed dose of 150 mg/m2.



ICA-MCA junction with catheter



Superselective intra-arterial delivery of mannitol and bevacizumab

Results

Five patients have been enrolled to date. All patients had heavily-treated, refractory GBM and have recieved bevacizumab previously. Mean KPS at enrollment was 70. No treatment-related adverse events pertaining to seizures, wound healing, bleeding, or blood counts were observed in four patients. One patient suffered a subacute brainstem infarction after recieving an infusion at the top of the basilar artery, proximal to the origins of the superior cerebellar arteries for a left thalamic and midbrain GBM.

Future Directions

This trial is part of a larger phase I/II protocol. Starting on Day 28 (after the initial SIACI treatment), patients with multifocal or leptomeningeal disease recieved bi-weekly IV bevacizumab and monthly IV carboplatin. Progression of disease is treated with another round of SIACI of bevacizumab and carboplatin followed by IV therapy. Progression after three cycles of intra-arterial infusion results in removal from the trial. Patients with focal disease follow the same paradigm, but do not recieve IV therapy between intra-arterial infusions.

Conclusions

A combined infusion of bevacizumab and carboplatin can be safely tolerated through intra-arterial delivery at least up to a dose of 15 mg/kg of bevacizumab with 150 mg/m2 of carboplatin.

References

Boockvar, J. A., A. J. Tsiouris, et al. "Safety and Maximum Tolerated Dose of Superselective Intraarterial Cerebral Infusion of Bevacizumab after Osmotic Blood-Brain Barrier Disruption for Recurrent Malignant Glioma. Clinical Article." J Neurosurg 114, no. 3 (2011): 624-32.