Evaluation of Intra-arterial Bevacizumab Delivery on Tumor Growth, Oncogenic Signaling, and Stem Cell Microenvironment in a Human GBM Xenograft

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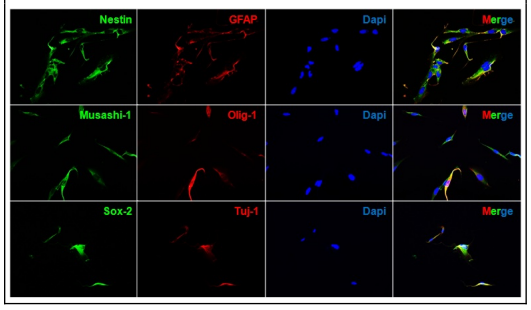
Introduction

We used a human GBM xenograft mouse model to compare the effects of intra-arterial (IA) and intra-peritoneal (IP) bevacizumab (BV) delivery in the stem cell perivascular niche, on tumor growth, and stem cell signaling.

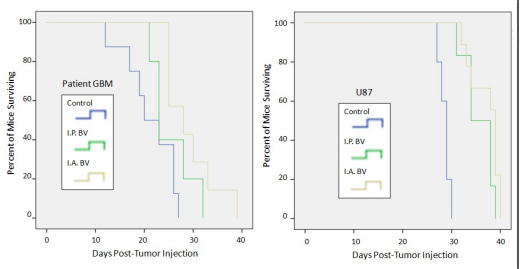
Methods

U87 and a patient derived GBM stem cell line transduced with the firefly luciferase gene were injected into the left hemisphere of athymic mice, which were subsequently treated with a single dose of IA or IP BV or given no treatment at all. The IA BV dose was administered via a catheter in the left internal carotid artery and preceded by transient mannitol-mediated osmotic blood brain barrier disruption. Tumor growth was monitored by measuring the tumor's bioluminescence signal. The tumors were removed post-mortem and analyzed with immunohistochemistry and Western blot.

Patient Derived tumor stem cells

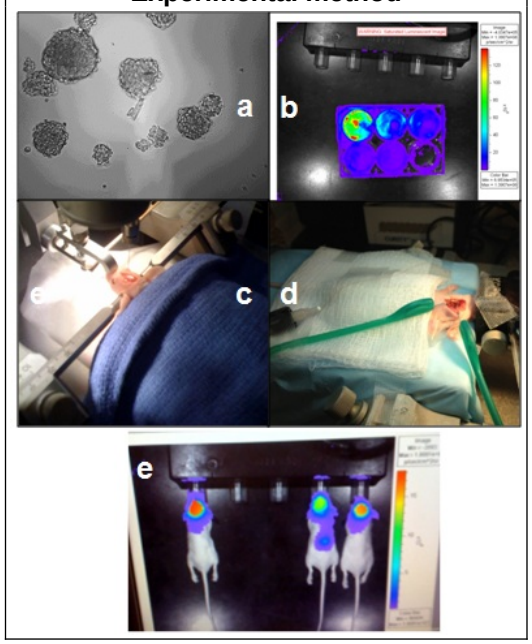


Mouse Survival

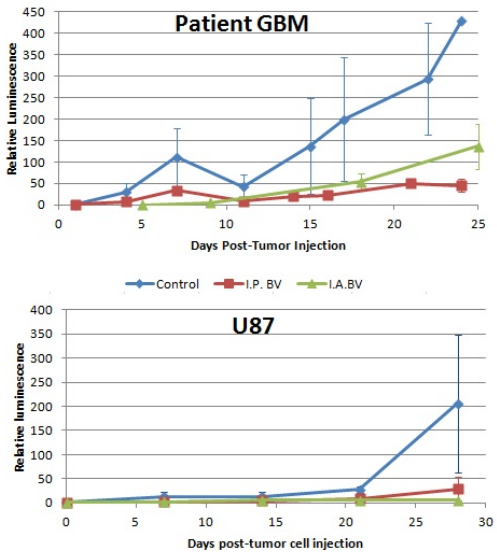


Kaplan-Meier survival curve for control, IP BV, and IA BV treated mice injected with U87 GBM cells and patient-derived GBM stem cells.

Experimental method



Tumor Signal

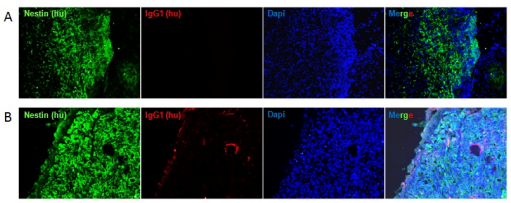


U87 GBM and patient-derived GBM luciferase tumor signal over time relative to baseline in control, IP BV treated, and IA BV treated mice.

Results

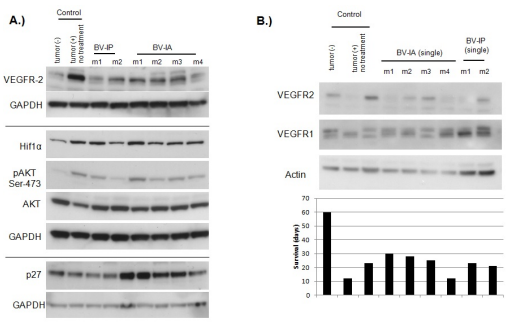
U87 control mice (n=5) lived 28.6+/- 0.5 days, IP BV mice (n=6) lived 35.7+/- 1.3 days, and IA BV mice (n=9) lived 37.1 +/- 1.06 days. Theere was a significant survival difference between the control and IP mice (p=0.01) and control and IA mice (p<0.001) but not between IP and IA (p=0.172.) Patient GBM control mice (n=8) lived 21.25 +/- 1.8 days, IP BV mice (n=5) lived 25.4 +/- 2.0 days, and IA BV mice (n=7) lived 29.3 +/- 2.0 days. There was not a significant difference between control and IP mice (p=0.137) nor IP and IA (p=0.15) but there was between control and IA (p=0.013).

Locating bevacizumab within the tumor



Immunohistochemistry on 12um section of U87 tumor without treatment (A) and with IA BV (B) looking for Nestin, a tumor stem cell marker, IgG, a marker for bevacizumab, and dapi.

Bevacizumab's effect on tumor signaling



Western blot analysis of various signaling pathways in tumor lysates from U87 (A) and patient GBM tumors (B) that were untreated and treated with IP or IA BV. Normal mice brains without tumor are included for comprison.