Phase I and biomarker study of plerixafor and bevacizumab in recurrent high-grade glioma.


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PURPOSE: Although anti-angiogenic therapy for high-grade glioma (HGG) is promising, responses are not durable. Correlative clinical studies suggest that the SDF-1α/CXCR4 axis may mediate resistance to VEGFR inhibition. Preclinical data have demonstrated that plerixafor (a reversible CXCR4 inhibitor) could inhibit glioma progression after anti-VEGF pathway inhibition. We conducted a Phase I study to determine the safety of plerixafor and bevacizumab in recurrent HGG.

EXPERIMENTAL DESIGN: Part 1 enrolled 23 patients with a 3x3 dose escalation design to a MTD of plerixafor 320µg/kg subcutaneously on days 1-21 and bevacizumab 10 mg/kg intravenously on days 1 and 15 of each 28-day cycle. CSF and plasma samples were obtained for pharmacokinetic analyses. Plasma and cellular biomarkers were evaluated before and after treatment. Part 2 enrolled 3 patients and was a surgical study to determine plerixafor's penetration in tumor tissue.

RESULTS: In Part 1, no DLTs were seen at the MTD of plerixafor+bevacizumab. Treatment was well tolerated. After plerixafor 320µg/kg treatment, the average CSF drug concentration was 26.8±19.6ng/mL. Plerixafor concentration in resected tumor tissue from patients pre-treated with plerixafor was 10-12µg/g. Circulating biomarker data indicated that plerixafor + bevacizumab induces rapid and persistent increases in plasma SDF1α and PIGF. PFS correlated with pre-treatment plasma sMET and sVEGFR1, and OS with the change during treatment in CD34+ progenitor/stem cells and CD8-T cells.

CONCLUSIONS: Plerixafor + bevacizumab was well tolerated in HGG patients. Plerixafor distributed to both the CSF and brain tumor tissue, and treatment was associated with biomarker changes consistent with VEGF and CXCR4 inhibition.

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