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Phase IB Study of Gene-Mediated Cytotoxic Immunotherapy Adjuvant to Up-Front Surgery and Intensive Timing Radiation for Malignant Glioma.

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Abstract

PURPOSE Despite aggressive therapies, median survival for malignant gliomas is less than 15 months. Patients with unmethylated O(6)-methylguanine-DNA methyltransferase (MGMT) fare worse, presumably because of temozolomide resistance. AdV-tk, an adenoviral vector containing the herpes simplex virus thymidine kinase gene, plus prodrug synergizes with surgery and chemoradiotherapy, kills tumor cells, has not shown MGMT dependency, and elicits an antitumor vaccine effect. **PATIENTS AND METHODS** Patients with newly diagnosed malignant glioma received AdV-tk at 3×10^{10} , 1×10^{11} , or 3×10^{11} vector particles (vp) via tumor bed injection at time of surgery followed by 14 days of valacyclovir. Radiation was initiated within 9 days after AdV-tk injection to overlap with AdV-tk activity. Temozolomide was administered after completing valacyclovir treatment. Results Accrual began December 2005 and was completed in 13 months. Thirteen patients were enrolled and 12 completed therapy, three at dose levels 1 and 2 and six at dose level 3. There were no dose-limiting or significant added toxicities. One patient withdrew before completing prodrug because of an unrelated surgical complication. Survival at 2 years was 33% and at 3 years was 25%. Patient-reported quality of life assessed with the Functional Assessment of Cancer Therapy-Brain (FACT-Br) was stable or improved after treatment. A significant CD3(+) T-cell infiltrate was found in four of four tumors analyzed after treatment. Three patients with MGMT unmethylated glioblastoma multiforme survived 6.5, 8.7, and 46.4 months. **CONCLUSION** AdV-tk plus valacyclovir can be safely delivered with surgery and accelerated radiation in newly diagnosed malignant gliomas. Temozolomide did not prevent immune responses. Although not powered for efficacy, the survival and MGMT independence trends are encouraging. A phase II trial is ongoing.

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