Aglatimagene besadenovec

An adenoviral vector engineered to express the herpes simplex virus thymidine kinase (HSV-tk) gene, which, when administered in conjunction with a synthetic acyclic guanosine analogue, possesses potential antineoplastic activity. Aglatimagene besadenovec is transduced into tumor cells, sensitizing tumor cells that overexpress HSV-tk to synthetic acyclic guanosine analogues. Subsequently, a low dose of a synthetic acyclic guanosine analogue such as valacyclovir (VCV) or ganciclovir (GCV) is given, which may preferentially kill tumor cells containing the adenoviral vector and overexpressing HSV-tk. Release of tumor-associated antigens (TAAs) by dying tumor cells may then stimulate an antitumor cytotoxic T lymphocyte (CTL) response.

Gene mediated cytotoxic immunotherapy (GMCI) is a tumor-specific immune stimulatory strategy implemented through local delivery of aglatimagene besadenovec (AdV-tk) followed by anti-herpetic prodrug. GMCI induces T-cell dependent tumor immunity and synergizes with radiotherapy. Clinical trials in adult malignant gliomas demonstrated safety and potential efficacy. This is the first trial of GMCI in pediatric brain tumors.

This phase I dose escalation study was conducted to evaluate GMCI in patients 3 years of age or older with malignant glioma or recurrent ependymoma. AdV-tk at doses of 1 × 1011 and 3 × 1011 vector particles (vp) was injected into the tumor bed at the time of surgery followed by 14 days of valacyclovir. Radiation started within 8 days of surgery, and if indicated, chemotherapy began after completion of valacyclovir.

Eight patients (6 glioblastoma, 1 anaplastic astrocytoma, 1 recurrent ependymoma) were enrolled and completed therapy: 3 on dose level 1 and 5 on dose level 2. Median age was 12.5 years (range 7-17) and Lansky/Karnofsky performance scores were 60-100. Five patients had multifocal/extensive tumors that could not be resected completely and 3 had gross total resection. There were no dose-limiting toxicities. The most common possibly GMCI-related adverse events included Common Terminology Criteria for Adverse Events grade 1-2 fever, fatigue, and nausea/vomiting. Three patients, in dose level 2, lived more than 24 months, with 2 alive without progression 37.3 and 47.7 months after AdV-tk injection.

GMCI can be safely combined with radiation therapy with or without temozolomide in pediatric patients with brain tumors and the present results strongly support further investigation.

CLINICAL TRIAL REGISTRY: ClinicalTrials.gov NCT00634231 [1].

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Kieran MW, Goumnerova L, Manley P, Chi SN, Marcus KJ, Manzanera AG, Polanco MLS, Guzik BW, Aguilar-Cordova E, Diaz-Montero CM, DiPatri AJ, Tomita T, Lulla R, Greenspan L, Aguilar LK, Goldman S. Phase I study of gene-mediated cytotoxic immunotherapy with AdV-tk as adjuvant to surgery and radiation for pediatric malignant glioma and recurrent ependymoma. Neuro Oncol. 2019 Mar 18;21(4):537-546. doi: 10.1093/neuonc/noy202. PubMed PMID: 30883662.