BACKGROUND: Diffuse intrinsic pontine glioma is one of the deadliest central nervous system tumours of childhood, with a median overall survival of less than 12 months. Convection-enhanced delivery has been proposed as a means to efficiently deliver therapeutic agents directly into the brainstem while minimising systemic exposure and associated toxic effects. We did this study to evaluate the safety of convection-enhanced delivery of a radioimmunotherapy agent targeting the glioma-associated B7-H3 antigen in children with diffuse intrinsic pontine glioma.

METHODS: We did a phase 1, single-arm, single-centre, dose-escalation study at the Memorial Sloan Kettering Cancer Center (New York, NY, USA). Eligible patients were aged 3-21 years and had diffuse intrinsic pontine glioma as diagnosed by consensus of a multidisciplinary paediatric neuro-oncology team; a Lansky (patients <16 years of age) or Karnofsky (patients ≥16 years) performance score of at least 50 at study entry; a minimum weight of 8 kg; and had completed external beam radiation therapy (54.0-59.4 Gy at 1.8 Gy per fraction over 30-33 fractions) at least 4 weeks but no more than 14 weeks before enrolment. Seven dose-escalation cohorts were planned based on standard 3 + 3 rules: patients received a single infusion of 9.25, 18.5, 27.75, 37, 92.5, 120.25, or 148 MBq, respectively, at a concentration of about 37 MBq/mL by convection-enhanced delivery of the radiolabelled antibody [124I]-8H9. The primary endpoint was identification of the maximum tolerated dose. The analysis of the primary endpoint was done in the per-protocol population (patients who received the full planned dose of treatment), and all patients who received any dose of study treatment were included in the safety analysis. This study is registered with ClinicalTrials.gov, number NCT01502917, and is ongoing with an expanded cohort.

FINDINGS: From April 5, 2012, to Oct 8, 2016, 28 children were enrolled and treated in the trial, of whom 25 were evaluable for the primary endpoint. The maximum tolerated dose was not reached as no dose-limiting toxicities were observed. One (4%) of 28 patients had treatment-related transient grade 3 hemiparesis and one (4%) had grade 3 skin infection.
treatment-related grade 4 adverse events or deaths occurred. Estimated volumes of distribution (Vd) were linearly dependent on volumes of infusion (Vi) and ranged from 1·5 to 20·1 cm$^3$, with a mean Vd/Vi ratio of 3·4 (SD 1·2). The mean lesion absorbed dose was 0·39 Gy/MBq $^{124}$I (SD 0·20). Systemic exposure was negligible, with an average lesion-to-whole body ratio of radiation absorbed dose higher than 1200.

**INTERPRETATION:** Convection-enhanced delivery in the brainstem of children with diffuse intrinsic pontine glioma who have previously received radiation therapy seems to be a rational and safe therapeutic strategy. PET-based dosimetry of the radiolabelled antibody $[^{124}]$-8H9 validated the principle of using convection-enhanced delivery in the brain to achieve high intra-lesional dosing with negligible systemic exposure. This therapeutic strategy warrants further development for children with diffuse intrinsic pontine glioma.


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