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Neural stem cell-based anti-cancer gene therapy: a first-in-human study in recurrent high grade glioma patients.

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Abstract

PURPOSE: Human neural stem cells (NSCs) are inherently tumor-tropic, making them attractive drug delivery vehicles. Toward this goal, we retrovirally transduced an immortalized, clonal NSC line to stably express cytosine deaminase (HB1.F3.CD.C21; CD-NSCs), which converts the prodrug 5-fluorocytosine (5-FC) to 5-fluorouracil (5-FU).

EXPERIMENTAL DESIGN: Recurrent high grade glioma patients underwent intracranial administration of CD-NSCs during tumor resection or biopsy. Four days later, patients began taking oral 5-FC every 6 hours for 7 days. Study treatment was given only once. A standard 3+3 dose escalation schema was used to increase doses of CD-NSCs from 10 million to 50 million and 5-FC from 75 to 150 mg/kg/day. Intracerebral microdialysis was performed to measure brain levels of 5-FC and 5-FU. Serial blood samples were obtained to assess systemic drug concentrations as well as to perform immunologic correlative studies.

RESULTS: Fifteen patients underwent study treatment. We saw no dose-limiting toxicity (DLT) due to the CD-NSCs. There was 1 DLT (grade 3 transaminitis) possibly related to 5-FC. We did not see development of anti-CD-NSC antibodies and did not detect CD-NSCs or replication competent retrovirus in the systemic circulation. Intracerebral microdialysis revealed that CD-NSCs produced 5-FU locally in the brain in a 5-FC dose-dependent manner. Autopsy data indicate that CD-NSCs migrated to distant tumor sites and were non-tumorigenic.

CONCLUSIONS: Collectively, our results from this first-in-human study demonstrate initial safety and proof-of-concept regarding the ability of NSCs to target brain tumors and locally produce chemotherapy.

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