Neural Stem Cell-Mediated Delivery of Irinotecan-Activating Carboxylesterases to Glioma: Implications for Clinical Use.

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Public Summary:
CPT-11 (irinotecan) has been investigated as a treatment for malignant brain tumors. However, limitations of CPT-11 therapy include low levels of the drug entering brain tumor sites and systemic toxicities associated with higher doses. Neural stem cells (NSCs) offer a novel way to overcome these obstacles because of their inherent tumor tropism and ability to cross the blood-brain barrier, which enables them to selectively target brain tumor sites. Carboxylesterases (CEs) are enzymes that can convert the prodrug CPT-11 (irinotecan) to its active metabolite SN-38, a potent topoisomerase I inhibitor. We have adenovirally transduced an established clonal human NSC line (HB1.F3.CD) to express a rabbit carboxylesterase (rCE) or a modified human CE (hCE1m6), which are more effective at converting CPT-11 to SN-38 than endogenous human CE. We hypothesized that NSC-mediated CE/CPT-11 therapy would allow tumor-localized production of SN-38 and significantly increase the therapeutic efficacy of irinotecan. Here, we report that transduced NSCs transiently expressed high levels of active CE enzymes, retained their tumor-tropic properties, and mediated an increase in the cytotoxicity of CPT-11 toward glioma cells. CE-expressing NSCs (NSC.CEs), whether administered intracranially or intravenously, delivered CE to orthotopic human glioma xenografts in mice. NSC-delivered CE catalyzed conversion of CPT-11 to SN-38 locally at tumor sites. These studies demonstrate the feasibility of NSC-mediated delivery of CE to glioma and lay the foundation for translational studies of this therapeutic paradigm to improve clinical outcome and quality of life in patients with malignant brain tumors.

Scientific Abstract:
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