Polymer Nanoparticles Delivered by Convection-Enhanced Delivery For Treatment of Brain Tumors

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Summary

Current therapy for malignant brain tumors is insufficient, with nearly universal recurrence. Because the blood-brain barrier prevents the entry of most systemically administered agents into the brain, local administration of agents has been tested as a means for treatment of glioblastoma multiforme (GBM). Two methods for local delivery have been tested clinically. GLIADEL®, a degradable polymer implant that slowly releases carmustine, was approved by the US Food and Drug Administration in 1996. Convection-enhanced delivery, where drug solutions are infused so fluid penetrates away from the infusion site, has been tested for delivery of an immunotoxin in adults with GBM. CED of a radiolabelled antibody is also being tested in children with pontine gliomas.

Polymer wafer implants and CED have been shown to be safe, but tumors still recur, because each approach has limitations. Implants provide for sustained, high drug levels, but drug penetration is limited to a relatively small volume near the implant. CED can distribute drugs over larger tissue volumes, but drug levels are not sustained beyond the infusion period. In addition, the drugs that have been tested by both of these methods fail to kill the cells most responsible for recurrence, brain cancer stem cells (BCSCs).

We have addressed these challenges by focusing on two technologies: 1) brain-penetrating polymeric nanoparticles that can be loaded with drugs and optimized for intracranial CED; and 2) re-purposed, FDA-approved compounds, which were identified through library screening to target BCSCs. Nanoparticle distribution during CED is critical for success. Using fluorescence imaging and positron emission tomography, we found that brain-penetrating nanoparticles can be delivered intracranially by CED, achieving substantial volumes of distribution in both rat and pig. By incorporating iron oxide into the nanoparticles, we tracked the distribution of brain-penetrating nanoparticles over time after a single CED infusion. Our nanoparticles penetrate through the brain, and remain in position for many weeks.

By screening a library of agents against BCSCs, we have identified several FDA-approved agents that potently inhibit cell proliferation and self-renewal in BCSCs. When loaded into brain-penetrating nanoparticles and administered by CED, one of these agents dramatically increased survival in rats bearing BCSC-derived xenografts.

This new approach to controlled delivery in the brain should have a significant impact on treatment of GBM. Further, the use of polymer nanoparticles opens the door to use of drug combinations and biologics as more effective and specific antitumor agents. For example, our recent work shows that polymer nanoparticles are capable of effective delivery of anti-tumor siRNA, antisense to oncogenic microRNA, and drug/gene combinations.

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References