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Preclinical Experimental Therapeutics

Convection-enhanced delivery of Ls-TPT enables an effective, continuous, low-dose chemotherapy against malignant glioma xenograft model[1]

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Treatment of malignant gliomas represents one of the most formidable challenges in oncology. The combination of surgery, radiation, and chemotherapy yields median survivals of less than one year. Here we demonstrate the use of a minimally invasive surgical technique, convection-enhanced delivery (CED), for local administration of a novel nanoparticle liposome containing topotecan. CED of this liposomal topotecan (Ls-TPT) resulted in extended brain tissue retention ($t_{1/2}$ = 1.5 days), whereas free topotecan was rapidly cleared ($t_{1/2}$ = 0.1 days) after CED. The favorable pharmacokinetic profile of extended topotecan release for about seven days, along with biodistribution featuring perivascular accumulation of the nanoparticles, provided, in addition to the known topoisomerase I inhibition, an effective antiangiogenic therapy. In the rat intracranial U87MG tumor model, vascular targeting of Ls-TPT with CED was associated with reductions in laminin expression and vascular density compared to free topotecan or control treatments. A single CED treatment on day 7 showed that free topotecan conferred no survival benefit versus control. However, Ls-TPT produced a significant (P = 0.0002) survival benefit, with six of seven complete cures. Larger U87MG tumors, where CED of Ls-TPT on day 12 resulted in one of six cures, indicated the necessity to cover the entire tumor with the infused therapeutic agent. CED of Ls-TPT was also efficacious in the intracranial U251MG tumor model (P = 0.0005 versus control). We conclude that the combination of a novel nanoparticle Ls-TPT and CED administration was very effective in treating experimental brain tumors.

Key Words: antiangiogenesis • brain tumor • convection-enhanced delivery • liposome • topotecan