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Intrathecal delivery of nanoparticle PARP inhibitor to the cerebrospinal fluid for the treatment of metastatic medulloblastoma

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Abstract

The morbidity associated with pediatric medulloblastoma, in particular in patients who develop leptomeningeal metastases, remains high in the absence of effective therapies. Administration of substances directly into the cerebrospinal fluid (CSF) is one approach to circumvent the blood-brain barrier and focus delivery of drugs to the site of tumor. However, high rates of CSF turnover prevent adequate drug accumulation and lead to rapid systemic clearance and toxicity. Here, we show that PLA-HPG nanoparticles, made with a single-emulsion, solvent evaporation process, can encapsulate talazoparib, a PARP inhibitor (BMN-673). These degradable polymer nanoparticles improve the therapeutic index when delivered intrathecally and lead to sustained drug retention in the tumor as measured with PET imaging and fluorescence microscopy. We demonstrate that administration of these particles into the CSF, alone or in combination with systemically administered temozolomide, is a highly effective therapy for tumor regression and prevention of leptomeningeal spread in xenograft mouse models of medulloblastoma. These results provide a rationale for harnessing nanoparticles for the delivery of drugs limited by brain penetration and therapeutic index and demonstrate important advantages in tolerability and efficacy for encapsulated drugs delivered locoregionally.