Nanomedicines for the local and targeted treatment of glioblastoma

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Abstract

Glioblastoma (GBM) treatment includes, when possible, surgical resection of the tumor followed by chemoradiotherapy but the survival remains low. The local and targeted systemic delivery of anticancer drug-loaded nanomedicines to treat GBM after surgical resection of the tumor could be a promising strategy.

Introduction

Among central nervous system tumors, glioblastoma (GBM) is the most common, aggressive and neurological destructive primary brain tumor in adults. Standard care therapy for GBM consists in surgical resection of the accessible tumor (without causing neurological damage) followed by radiotherapy and oral chemotherapy with an alkylating agent temozolomide (TMZ). However, recurrences quickly develop around the resection cavity borders leading to patient death. Despite the efforts of the scientific community to increase the long-term benefits of GBM therapy, at the moment GBM remains incurable. Several obstacles limit the effectiveness of GBM treatments: (i) the anatomical location of the tumor in the brain often impedes a complete surgical resection (ii) the central nervous system barriers such as the blood brain barrier (BBB) represent a challenge to the delivery of cytotoxic drugs at therapeutic concentrations at the tumor site (iii) GBM is highly heterogeneous at all levels (iv) the hallmark characteristics of GBM are uncontrolled cellular proliferation, propensity for necrosis and angiogenesis, resistance to apoptosis, high genomic instability and chemoresistance. GBM cells are able to extend their tendrils into the normal surrounding parenchyma infiltrating diffusely beyond the primary lesion in the early stages of tumor development [1].

In vitro and in vivo models of experimental glioma are useful tools to gain a better understanding of GBM and to investigate novel treatment strategies. However, the majority of preclinical models focus on treating solid intracranial tumours, despite surgical resection being the mainstay in the standard care of patients with GBM today. The lack of resection and recurrence models therefore led us to develop a novel orthotopic tumour resection and recurrence model that has potential for the investigation of local and systemic delivery strategies in the treatment of GBM. We showed that tumour resection is well tolerated, does not induce deleterious neurological deficits, and significantly prolongs survival of mice bearing U87MG GBM tumours. In addition, the resulting cavity could accommodate adequate amounts of hydrogels for local delivery of chemotherapeutic agents to eliminate residual tumour cells that can induce tumour recurrence [2].

Local delivery of nanomedicine

Among the strategies that have been adopted in the last two decades to find new and efficacious therapies for the treatment of GBM, the local delivery of chemotherapeutic drugs in the tumor resection cavity emerged [3]. We developed two formulation of anticancer nanomedicines that can be included perisurgically in the resection cavity of orthotopic GBM.

We hypothesized that a polyethylene glycol dimethacrylate (PEG-DMA) injectable hydrogel would provide a sustained and local delivery of TMZ. The hydrogel photopolymerized rapidly (<2min) and presented a viscous modulus (≈10kPa). The in vivo tolerability study showed that the unloaded hydrogel did not induce apoptosis in mice brains nor increased microglial activation. In vivo, the anti-tumor efficacy of TMZ-hydrogel was first evaluated on xenograft U-87MG tumor-bearing nude mice. The tumor weight of mice treated with the photopolymerized TMZ hydrogel drastically decreased compared with all other groups [4]. The photopolymerizable TMZ-loaded hydrogel was also tested in the resection model of U-87MG GBM. When combined with paclitaxel (PTX)-loaded nanoparticles, it significantly prolonged the mice survival compared to mice undergoing the resection (unpublished data).

Gemcitabine is a chemotherapeutic agent that has a different mechanism of action compared to alkylating agents and shows excellent radio-sensitizing properties. We developed an injectable gel-like nanodelivery system consisting in lipid nanocapsules loaded with anticancer prodrug lauroyl-gemcitabine (GemC12-LNC) in order to obtain a sustained and local delivery of this drug in the brain and to bypass the blood brain barrier, thus reaching high local concentrations of the drug. The GemC12-LNC formed a gel and showed a sustained and prolonged in vitro release of the drug over one month. GemC12 and the GemC12-LNC increased in vitro cytotoxic activity on U-87MG glioma cells compared to the parent hydrophilic drug. The GemC12-LNC hydrogel reduced significantly the size of a subcutaneous human GBM tumor model compared to the drug. Short-term tolerability studies showed that this system is suitable for local treatment in the brain. This proof-of-concept study demonstrated the feasibility, safety and efficiency of the injectable GemC12-LNC hydrogel for the local...
treatment of GBM [5]. We then administered GemC12-LNC hydrogel for the local delivery of GemC12 in an orthotopic xenograft model of GBM. The GemC12-LNC hydrogel was well tolerated when injected in mouse brain. After intratumoral administration, GemC12-LNC significantly increased mice survival compared to the controls. Moreover, its ability to delay tumor recurrences was demonstrated after perisurgical administration in the GBM resection cavity. In conclusion, we demonstrate that GemC12-LNC hydrogel could be considered as a promising tool for the post-resection management of GBM, prior to the standard of care chemo-radiation [6].

Targeted delivery of nanomedicines

Targeted nanotheranostics are promising multifunctional system with nano-size, possibility of surface functionalization, diagnostic and therapeutic capabilities. Loss of BBB integrity is a characteristic of GBM that could justify the systemic treatment. Super Paramagnetic Iron Oxides (SPIO) have dual advantage of detection by magnetic resonance imaging (MRI) (reduction of relaxation times) and magnetic property for a targeting strategy using external magnet [7]. We hypothesized that PTX/SPIO loaded PLGA-based nanoparticles could be a potential nanotheranostic system to image and treat gliomas. PTX/SPIO loaded PLGA-based nanotheranostic particles were prepared [7]. In vitro cellular studies U-87MG cell line confirmed that the cytotoxic effect was solely due to PTX. By investigating BBB disruption in U87MG glioma tumor model using MRI after intravenous injection of T1 contrast agent, we validated that the BBB was disrupted. In vivo biodistribution studies showed that NP did not cross the intact BBB in healthy mice whereas in GBM bearing mice, brain samples were traced with significant quantities of SPIO. Magnetic targeting increased the amount of SPIO detected. Preliminary in vivo efficacy results of PTX/SPIO-PLGA NP intracranial injection in orthotopic U-87MG GBM tumour showed significantly improved mice survival rate when compared to controls. Intravenous injection associated with magnetic targeting also increased mice survival. (unpublished data).

References