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Nanobiotechnology-based delivery strategies: New frontiers in brain tumor targeted therapies

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ABSTRACT

Despite recent technological advancements and promising preclinical experiments, brain tumor patients are still met with limited treatment options. Some of the barriers to clinical improvements include the systemic toxicity of cytotoxic compounds, the impedance of the blood brain barrier (BBB), and the lack of therapeutic agents that can selectively target the intracranial tumor environment. To overcome such barriers, a number of chemotherapeutic agents and nucleic acid-based therapies are rapidly being synthesized and tested as new brain tumor-targeted delivery strategies. Novel carriers include liposomal and polymeric nanoparticles, wafers, microchips, microparticle-based nanoplatforms and cells-based vectors. Strong preclinical results suggest that these nanotechnologies are set to transform the therapeutic paradigm for brain tumor treatment. In addition to new tumoricidal agents, parallel work is also being conducted on the BBB front. Preclinical testing of chemical and physical modulation strategies is yielding improved intracranial concentrations. New diagnostic and therapeutic imaging techniques, such as high-intensity focused ultrasound and MRI-guided focused ultrasound, are being used to modulate the BBB in a more precise and non-invasive manner. This review details some of the tremendous advances that are being explored in current brain tumor targeted therapies, including local implant development, nanobiotechnology-based delivery strategies, and techniques of BBB manipulation.

1. Introduction

Glioblastoma (GB) is the most common and aggressive primary brain tumor, and remains one of the most lethal cancers in humans with a median survival after maximal therapy of less than 2 years after initial diagnosis [1–3]. The nature of the tumor, such as high invasiveness, a high proliferative index, immunologic escape, genetic heterogeneity, and genetic instability as well as the unique intracranial environment and the physio-anatomic barriers between the brain and the tumor [4] have limited the efficacy of standard chemotherapeutic agents.

One of the major obstacles in the development of agents for the treatment of central nervous system (CNS) diseases is formulating a therapeutically relevant concentration of a compound that can effectively cross the blood brain barrier (BBB). Antitumor molecules need to circumvent specific brain- and tumor-related physio-anatomical barriers, including: i) the neuro-vascular unit (NVU) which regulates the trafficking of substances between the blood stream and the CNS [4]; ii) the extra-cellular space (ECS) that affects the flow of nutrients, metabolites, cytokines, neurotransmitters, and other molecules between tumors and brain tissue [4]; and iii) the enhanced permeability and retention effect (EPR effect) which, though directly proportional to tumor growth, is significantly altered in the intracranial microenvironment [5].

Strategies to circumvent the impermeability of the BBB have followed both local and systemic routes. The first local delivery strategy to be used clinically was interstitial chemotherapy, which employed a polymeric wafer, Gliadel®, to bypass the BBB and deliver a sustained release of the chemotherapeutic agent carmustine directly at the site of tumor resection. The development and subsequent FDA approval of Gliadel® was a hallmark of both technology and translational medicine. Gliadel® increased the median survival for patients with brain tumors after tumor resection from 15 months with radiation and oral chemotherapy to 21.3 months [1]. The approval of these drugs filled a 25 year gap when no new brain tumor therapies were developed and not much hope was offered to brain tumor patients. Gliadel® also opened the door for other agents to be tested at the local intracranial level and was the beginning of further advancements combining technology and innovation for clinical benefit.

The biomedical revolution of recent years has opened new therapeutic avenues for the treatment of brain tumors using both local and systemic routes of administration depending on the physical and chemical features of the nano- and bio-vectors used. Promising strategies have included the use of different families of liposomal and polymeric nanoparticles, thermosensitive gels, dendrimers, as well as immunocytes and stem cells used as "Trojan horses" due to their innate tumor homing capacity. Among the most exciting is the introduction of

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nanomedicine-based approaches to tumor-targeted drug delivery. These nanoparticles can enter the brain tumor through the endothelial gaps on the microvessels of brain tumors by taking advantage of the glioma EPR effect and/or their ligand- and receptor-coated surfaces [6]. These nanostrategies have also been combined with classical methods to cross the BBB as well as novel techniques, such as ultrasound (US) and magnetic resonance imaging (MRI), thereby developing new scenarios in CNS drug-delivery strategies [7]. Another biomedical innovation is the use of immune cells and stem cells for gene delivery to the brain. In this review we detail current efforts focused on the role of new nano- and bio-technologies to optimize the delivery of therapeutic drugs and genes as well as repurposing theranostic techniques such as US, MRI and high intensity focused ultrasound (HIFU) to facilitate the penetration of these vectors through the BBB for brain tumor targeted therapy.

2. Local implant development

Despite the number of new chemotherapeutic agents produced every year, as well as the prospects of personalized medicine and nucleic acid-based therapies offered by recent advances in genomics, all drug delivery approaches face similar challenges in the intracranial environment. These challenges include crossing the blood–brain barrier (BBB) to reach the tumor efficiently and selectively, and successfully achieving the balance between maximizing antitumor efficacy and minimizing risks of toxicity. To ensure that therapies are kept within the beneficial side of this equation, considerable effort has been expended to improve strategies of tumor-targeting drug delivery. These methods permit the highest drug concentration at the tumor site with the lowest risks of systemic toxicity. A variety of technologies has been modeled in a similar manner to wafer implants, ranging from tablets, liquids and injectable gels, to sophisticated systems utilizing bioengineered products to deliver different categories of drugs for brain tumor treatment (Table 1). Many of these products use polymer-based drug delivery systems with each technology offering unique advantages to drug delivery and, insofar as they enhance BBB penetration and help to specifically target brain tumor cells [8,9], most should merit inclusion in the armamentarium for the treatment of malignant brain tumors. However, local drug delivery has attracted concerns due to the risks to healthy brain tissue, the need of a surgical procedure for implantation, and the limitations associated with either a single administration of therapy or controlled drug release over time [10–13].

2.1. Polymeric wafers

Of the many biomaterial drug-polymer devices developed to date, the Food and Drug Administration (FDA) and the National Institute for Health and Clinical Excellence (NICE) have only approved the use of polymeric wafers (Gliadel®) for local chemotherapy in the treatment of primary and recurrent malignant glioma [14,15]. These wafers, which are neurosurgically implanted at the time of tumor resection, gradually release the chemotherapeutic agent carmustine, which then diffuses into the surrounding brain and targets the residual cancer cells that have infiltrated the brain tissue. The polymer used in patients is composed of polyanhydride poly[1,3-bis (carboxyphenoxy) propane-*co*-sebacic-acid] (PCPP:SA) and incorporates the chemotherapeutic drug, carmustine, or BCNU [16,17].

Preclinical studies of BCNU incorporated into the polymeric wafer, BCNU:pCPP:SA, included cytotoxicity studies using rodent and human glioma and gliosarcoma cells and extensive release kinetic analyses in vitro [18]. In vivo safety, biodistribution and efficacy studies were then conducted in rodents and non-human primates to confirm the utility of the intracranially implanted wafer [19,20]. A Phase I trial was conducted demonstrating the safety of the wafer and establishing the dose at which Gliadel® would be delivered [16]. In 1996, the FDA approved Gliadel® for use in patients with recurrent glioblastoma as an adjunct to surgery. In 2003, Gliadel® was approved for use in patients with newly diagnosed high grade malignant glioma as an adjunct to surgery and radiation and, in 2004, Medicare created a new diagnosis-related group, or DRG, to allow for Gliadel® to be prescribed for patients. Combining Gliadel®, radiation and oral Temozolomide has since led to an increase in the median survival for patients with malignant glioma, ranging from 18 to 21 months [1]. Multiple clinical reports have verified these findings and a recent meta-analysis supported the conclusion that Gliadel® has played a significant role in improving the survival for patients with newly diagnosed glioblastomas [21]. Gliadel® became a pioneer for intra-cavity drug delivery and still represents an important yardstick for intracranial delivery approaches for brain tumor therapy.

Other preclinical local delivery approaches have included various polymeric formulations, including ethylene-vinyl acetate copolymer (EVAc), fatty acid dimer-sebacic acid copolymer (FAD:SA), poly(lactide-*co*-glycolide) polymers, and polyphosphoester polymer p(DAPG-EOP) in the form of microspheres at 10% (w/w) for the sustained release of paclitaxel (Paclimer®) [22]. These polymers differ in multiple ways, including the variety of drugs that can successfully be incorporated and reliably delivered, subsequent release kinetics and overall stability. Preclinical studies show that several drugs, otherwise limited by systemic toxicity or poor brain penetration, report higher survival in experimental glioma models when delivered intracranially by polymeric wafers than the same drug delivered by systemic administration. Among them are temozolomide [23], taxol [22,24], minocycline [25], doxorubicin [26], rapamycin [27], camptothecin [28], carboplatin [29], as well as many others [28,30–34].

2.2. Thermosensitive and thermodependent gels

Thermosensitive hydrogels have recently gained increased interest. These gels can be used to deliver hydrophilic and hydrophobic compounds in their free state, as well as nanoparticle-encapsulated compounds [35]. Injectable thermosensitive hydrogels with lower sol-gel transition temperatures, in which the solution gradually changes into the formation of a gel at physiological temperatures, hold great potential as they can be injected directly into the tumor cavity. Dhillon et al. and Rahman et al. developed a novel temperature-sensitive and

Table 1
Categories of compounds delivered via local implants.

Categories	Compounds	Type of implants
Alkylating agent	BCNU, cyclophosphamide, temozolomide, carboplatin	Polymeric wafers
Glycolytic inhibitor	3-Bromopyruvate, dichloroacetate	Polymeric wafers
Topoisomerase Inhibitor	Camptothecin, *Etoposide*	Polymeric wafers and matrices
Antibiotic	Doxorubicin, minocycline, lactacystin	Polymeric wafers
Plant alkaloid	Docetaxel	Polymeric wafers
Antineoplastic	Epirubicin	Polymeric wafers
Anti-angiogenetic agent	Endostatin: synthetic endostatin fragment (EF) and Fc-endostatin	Polymeric wafers
Plant alkaloid	Paclitaxel	Polymer matrix
mTOR inhibitor	Rapamycin	Polymeric wafers
Immune modulator	Interleukin-2 (IL-2)	Polymeric matrices and wafers