Drug Delivery Methods in Childhood Brain Tumors

Subjects: Oncology

Contributor: Ruman Rahman , Miroslaw Janowski , Clare L. Killick-Cole , William G. B. Singleton , Emma Campbell , Piotr Walczak , Soumen Khatua , Lukas Faltings , Marc Symons , Julia R. Schneider , Kevin Kwan , John A. Boockvar , Steven S. Gill , J. Miguel Oliveira , Kevin Beccaria , Alexandre Carpentier , Michael Canney , Monica Pearl , Gareth J. Veal , Lisethe Meijer , David A. Walker

Only four drugs have been licensed globally for brain tumors. Most new cancer drugs in clinical trials do not cross the blood–brain barrier (BBB). Developing appropriate delivery techniques could improve patient outcomes by ensuring efficacious drug exposure to tumors (including those that are drug-resistant), reducing systemic toxicities and targeting leptomeningeal metastases. This drug delivery strategy seeks to enhance the efficacy of new drugs and enable re-evaluation of existing drugs that might have previously failed because of inadequate delivery.

drug delivery | blood–brain barrier | brain tumor model | childhood brain tumors

1. Introduction

Annual global incident cases of cancer in children and young people (CYP) aged 0–19 years are estimated at around 400,000 [1][2]. Childhood malignancies are classified into 12 major categories, grouped by the tissues of origin [3]. Tumors of the central nervous system (CNS) are the most common solid tumors in children between 0 and 14 years, accounting for 10–37% of all cancers across 0–19 years of age. The age groupings with the highest and lowest incidence frequencies are the 5–9- and 15–19-year-old age groups, respectively [4].

Targeted treatment for brain tumors can be proposed for three tumor situations. First, primarily resistant tumor types with very poor survival rates. For these tumors, experimental interventions are directed at the primary tumor, and the aim is to develop delivery techniques that ensure adequate drug exposure at the tumor site. Examples include diffuse midline glioma (DMG), ependymoma, atypical teratoid rhabdoid tumor (ATRT), high-grade glioma (HGG) and malignant rare variants. Second, malignant tumor types with established sensitivity to drug therapy. For these tumors, treatment of metastatic disease is currently reliant upon extended-field radiotherapy. A promising alternative is the use of intracerebrospinal fluid (CSF) delivery approaches to target leptomeningeal spread [8]. Third, brain tumors where novel approaches are being considered such as viral vector, immunologically or molecularly targeted treatments. The aim here is to target drug delivery to the precise anatomical tumor locations in the brain, to increase effectiveness and reduce systemic toxicities in the developing child.

For innovative approaches to be adopted, it needs to be proven that the extent of drug delivery to the tumor location is sufficient to achieve its therapeutic effect. Unfortunately, most cancer drugs do not penetrate the blood–

brain barrier (BBB) effectively, which may explain the recurrent failure that has been the history of brain tumor drug development. Indeed, the BBB presents a significant obstacle to a wide range of anticancer drugs, from cytotoxic agents and small molecules to immunotherapies and antibody–drug conjugates.

The BBB is structurally complex, composed of endothelial cells, pericytes and astrocytes, forming a neurovascular structural and functional barrier that is highly effective at maintaining homeostatic levels of intracerebrospinal fluid (CSF) concentrations and preventing the influx of circulating pollutants [5][6]. Several factors restrict drug compounds passing the BBB, including endothelial tight junctions and drug-transporter-mediated efflux. Tight junctions create physical links that impair or block molecules in circulation from entering brain parenchyma directly, based on molecular size, lipophilicity, ionization and polarity. Both direct cellular interactions and paracrine signaling from CNS astrocytes and pericytes lead to the formation of tight junctions [7]. Transcellular drug entry is governed by endocytosis, passive diffusion and the ratio of inward- to outward-facing membrane drug transporters [8]. The BBB surrounding capillaries in the brain parenchyma is then modified to form a blood–tumor barrier upon the initiation and progression of primary brain (or metastatic) tumors [9]. This barrier thus limits the delivery of systemically administered drugs, a physiologic dilemma that has limited the therapeutic efficacy of chemotherapies directed toward pediatric tumors. Failures in chemotherapy trials can be partially attributed to poor drug delivery, as fewer than 5% of chemical compounds have been shown to achieve therapeutic concentrations in the CNS [10][11].

Furthermore, existing approved drugs might have been discounted for development as a brain tumor treatment due to their inability to reach the brain. By harnessing the new delivery techniques that are in development, these should now be reconsidered and evaluated as potential brain tumor treatments [12]. The World Health Organization (WHO) has recently made a powerful economic case for commissioning child cancer therapies globally to exploit a 3:1 economic payback in societal terms [13]. Repurposing approved drugs with drug delivery techniques offers an attractive economic strategy for innovation. The CNS drug delivery systems in development would also be compatible with new molecularly targeted drugs emerging from the cancer drug pipeline.

2. Overview of CNS Drug Delivery Methods

Extensive research has generated clinical trials of existing cytotoxic chemotherapy agents and new, biologically targeted drugs, and is ongoing. Despite this significant effort, there are only four drugs approved for use in brain tumors by the Food and Drug Administration (US) and European Medicines Agency: lomustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CCNU) [14], temozolomide [15], carmustine wafers [16] and everolimus [17]. CCNU and temozolomide are alkylating agents with physicochemical properties permitting enhanced access across the BBB. Carmustine wafers are placed in tumor cavities at resection. Everolimus is an mTOR inhibitor that targets the mutated mTOR pathway in tuberous sclerosis where tissue overgrowth in brain tissue can lead to a type of brain tumor called sub-ependymal giant cell astrocytoma (SEGA) [18]. It is licensed for treatment of SEGA in children and young adults where the tumor cannot be safely resected. Three of these four approved drugs, therefore, were selected for their properties to either cross or bypass the BBB. All other drugs in use for the treatment of brain tumors in children are either experimental or used off-label, including regimens containing vinca alkaloids, alkylating agents, topoisomerase inhibitors, folic acid antagonists, anthracyclines and anti-angiogenic agents [19].

3. Augmenting Drug Passage through the BBB

3.1. Pharmacological Modulation of the BBB

The innate pharmacokinetic properties of a particular chemotherapy agent, which facilitate its passage through the BBB and thereby its delivery into brain tissue, are vital for its therapeutic efficacy. Drugs that were more likely to permeate the BBB included compounds that had a molecular weight of ≤500 Da, were lipophilic (logP (partition coefficient) > 1), were relatively nonpolar (≤5 hydrogen bond donors, ≤10 hydrogen bond acceptors) and had <90% protein binding (thereby facilitating unbound drugs to cross the BBB) [20].The presence of luminal membrane transporters on brain capillaries commonly results in efflux of a limited number of lipophilic drugs possessing the appropriate physicochemical properties to achieve meaningful BBB penetration [21].

3.2. Ultrasound-Induced BBB Disruption

Ultrasound (US)-induced opening of the BBB was first described by Bakay et al. in 1956 [22]. Hynynen et al. later demonstrated that the intravenous injection of microbubbles prior to pulsed low-intensity US allowed for a reduction in the acoustic pressure necessary to safely open the BBB [23]. By inducing expansion and contraction of injected microbubbles (cavitation), four different cellular mechanisms may occur, leading to an increased transport of drugs across the BBB: transcytosis; transendothelial fenestrations; opening of tight junctions; and free passage of molecules through the permeable endothelium [24].

3.3. Intra-Arterial Chemotherapy

The intra-arterial (IA) route for drug delivery to brain tumors has been explored since the early 1950s [25][26]. IA chemotherapy for brain tumors is administered through a catheter inserted into the carotid or vertebral artery. The drugs then travel through the capillary networks of the bloodstream and, eventually, into brain tissue. Studies to date have shown that the intra-arterial route is significantly more effective for drug delivery to the brain than the intravenous route (also via the bloodstream). To target treatment more specifically to a brain tumor, chemotherapy can be infused into the main tumor-supplying arteries rather than into the carotid or vertebral arteries. This is called super-selective intra-arterial chemotherapy (IAC).

Super-selective IAC is safe and technically feasible due to advancements in microcatheter design and imaging systems that facilitate navigation through the delicate intracranial vasculature. Selective IA cerebral infusion (SIACI) of chemotherapy is a technique designed to selectively increase the local concentration of a drug in the peri-tumoral vascular supply, thereby bypassing first-pass metabolism. Current studies are directed toward utilizing SIAC in conjunction with methods to disrupt the BBB, as there is little evidence to show that SIACI can be effective alone. IAC for retinoblastoma has been the most widely accepted and successful neuro-oncologic application of IAC and is now a standard treatment option for retinoblastoma.

4. Bypassing the BBB

4.1. Polymer Therapeutics for Local Delivery

The potential benefits of local treatment are significant as they address major shortcomings associated with systemic delivery [27]. These shortcomings include low drug concentration at tumor site and systemic dose-limiting toxicities, as well as low efficacy due to rapid inactivation while circulating in the bloodstream. The concept of local delivery of anticancer therapeutics immediately post-surgical resection is based on embedding the drug in a biodegradable biomaterial or polymer for controlled release. A multitude of implantable materials have been developed for that purpose, which can be prepared as wafers, discs, films, rods, particles, meshes/scaffolds or injectable hydrogels [28]. Conventional fabrication techniques include electrospinning, solvent casting, spray drying, freeze drying, extrusion and compression molding.

Biodegradable copolymers impregnated with the alkylating agent carmustine (BCNU) (Arbor Pharmaceuticals, Atlanta, GA, USA) are the only approved drug delivery implant for local treatment of high-grade glioma. A phase III multicenter, double-blind trial in recurrent adult isocitrate dehydrogenase wild-type glioblastoma patients demonstrated improved overall survival from 23 to 31 weeks [29]. While this is clear benefit, the effect was modest and likely due to developing resistance towards BCNU and insufficient diffusion into brain parenchyma beyond the infiltrative margin.

Optimized formulations of polymers have been developed for improved diffusion throughout the cerebral/brain tumor interstitium. Examples of such approaches are nanocomplexes composed of DNA condensed into a blend of biodegradable polymer, poly(β-amino ester) (PBAE), with PBAE conjugated with 5 kDa polyethylene glycol (PEG) molecules (PBAE-PEG) [30].

Incorporation of BBB-permeating moieties into the structure of polymer therapeutics is highly desirable. Receptor-mediated transcytosis is one of the most frequently applied strategies, exploiting mechanisms for active transcellular transport of hormones or growth factors [31]. Polymers are furnished with ligands of receptors that are highly expressed on the BBB, such as the transferrin receptor or low-density lipoprotein receptors.

Transferrin-conjugated silica nanoparticles have been successfully used to enhance the delivery of doxorubicin and paclitaxel with high activity against glioma in mouse U87 xenograft model [32].

4.2. Convection-Enhanced Delivery

In 1994, the concept of convection-enhanced delivery (CED) was introduced as a solution to the BBB obstacle, enabling direct delivery of therapeutic drugs to the CNS [33]. The drug is infused at precisely controlled infusion rates with the aim of creating a pressure gradient at the tip of an implanted intraparenchymal catheter. This positive pressure drives fluid out from the catheter tip through the extracellular space, with the aim of replacing the extracellular fluid with infusate. CED has several potential advantages over conventional systemic drug delivery methods and other novel methods of bypassing the BBB. CED facilitates highly accurate anatomical targeting and delivery of higher drug concentrations throughout clinically relevant volumes of brain tissue or tumor. Direct administration means that a negligible concentration of drug enters the systemic circulation, meaning that

theoretically high local drug concentrations can be achieved without causing any associated systemic toxicity. CED enables the controlled, homogeneous distribution of drugs through large brain volumes, offering an opportunity to manipulate the extracellular environment of intrinsic malignant brain tumors [34][35].

4.3. Intra-CSF or Interstitial Administration

Leptomeningeal malignancy complicates up to 55% of childhood cancers, including brain tumors, and represents a rate-limiting step to cure [36][37]. In brain tumors, dissemination from the primary tumor, before or after surgery, via CSF pathways is assumed. However, evidence exists to support the vascular route of dissemination. For primary brain tumors, the standard therapy is craniospinal radiotherapy, but the attendant risk of acute and delayed brain injury and endocrine deficiencies compounds post-radiation impairment of spinal growth. Alternative ways of treating leptomeninges by intensifying drug therapy delivered to CSF are being investigated [36][38]. Current methods of bolus administration are complex and burdensome clinically. There is a need to establish devices and techniques to deliver intra-CSF therapy more easily, especially if prolonged infusions or sustained release preparations are to be developed. Sharing the development of such delivery systems and testing repurposed drugs with the needs of adult practice would create synergy for their commercial development.

5. Repurposing Drugs in Pediatric Neuro-Oncology

Microtubule inhibitors have been used for the treatment of both pediatric and adult brain tumors, despite a lack of evidence of their efficacy as a monotherapy in either animal models or clinically [39][40]. The primary reason for this poor efficacy appears to be a lack of BBB permeability [41][42]. Moreover, microtubule drugs, such as vincristine, tend to have severe, dose-limiting toxicities due to cumulative neurotoxicity [43].

Mebendazole was serendipitously found to be active against high-grade astrocytoma by the Riggins group at Johns Hopkins University, when their mouse colony was infected by pinworms and treated with fenbendazole, an analog of mebendazole, causing a strong inhibition in tumor take rate [44]. Subsequently, mebendazole was shown to be highly active in several orthotopic models of medulloblastoma [45].

The probable mechanism of action of mebendazole is through inhibition of microtubule polymerization [39][44]. Generally, mebendazole is well tolerated with few side effects [46]. Two clinical trials examining the safety of mebendazole for the treatment of pediatric brain tumors are ongoing: a phase I/II study examining mebendazole in combination with vincristine, carboplatin and temozolomide in pediatric high-grade glioma patients (NCT01837862); and a phase I study examining the safety of mebendazole monotherapy in a wider range of pediatric brain tumor patients, including medulloblastoma (NCT02644291).

The voltage-gated potassium channel, EAG2, is enriched on the trailing edge of migrating medulloblastoma cells and facilitates cell motility [47]. Subsequently, researchers tested a number of approved drugs in the in vitro growth of medulloblastoma cell lines, which led to the discovery of the novel EAG2-blocking action of the anti-psychotic

drug thioridazine [47]. This action was accompanied by a reduction in medulloblastoma tumor growth and metastasis [47].

Epigenetic modifying drugs such as the histone deacetylase (HDAC) inhibitors panobinostat and sodium valproate have shown high efficacy against DMG and ETMR. In medulloblastoma, sodium valproate reduced the clonogenicity of cells in vitro, and exerted additive effects in combination with 5-aza-2′-deoxycytidine [48].

Clinical translation has led to the utilization of sodium valproate as an adjuvant chemotherapeutic in several clinical studies, notably in six trials studying its effects in brain tumor patients, three of which were for the treatment of childhood brain tumors (NCT00879437, NCT00107458, NCT03243461). Importantly, sodium valproate has been reported to be BBB-permeable [49], yet only 15% of serum levels reach the brain. A retrospective study demonstrated that pediatric HGG patients who were taking valproate as an anti-epileptic exhibited no additive toxicity when the drug was combined with radio-chemotherapy, and determined that valproate is well tolerated in pediatric HGG patients [50]. Sodium valproate is currently being delivered via CED in early trials, where it is being directly administered to the brain tumor via microcatheters [51].

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