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EXPERT REVIEW

Overcoming the Blood-Brain Barrier in Chemotherapy Treatment of Pediatric Brain Tumors

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ABSTRACT Pediatric brain tumors are most common cancers in childhood and among the leading causes of death in children. Chemotherapy has been used as adjuvant (i.e. after) or neoadjuvant (i.e. before) therapy to surgery and radiotherapy for the management of pediatric brain tumors for more than four decades and gained more attention in the recent two decades. Although chemotherapy has demonstrated its effectiveness in the management of some pediatric brain tumors, failure or inactiveness of chemotherapy is commonly met in the clinics and clinical trials. Some of these failures might be attributed to the blood-brain barrier (BBB), limiting the penetration of systemically administered chemotherapeutics into pediatric brain tumors. Therefore, various strategies have been developed and used to address this issue. Herein, we review different methods reported in the literature to circumvent the BBB for enhancing the present of chemotherapeutics in the brain to treat pediatric brain tumors.

KEY WORDS blood-brain barrier · by-passing the BBB · chemotherapy · disrupting the BBB · nanocarriers · pediatric brain tumors

INTRODUCTION

Brain tumors are the third most common type of childhood cancers and second leading cause of death in children excluding trauma (1). The brain tumors in pediatric patients are generally quite different from those in adult patients in terms of incidence, tumor type and treatment (2,3). Brain tumors occur more often in the lower portion of the pediatric brain *vs.* the upper portion of the adult brain (4). The most common pediatric brain tumors are astrocytoma, medulloblastoma, ependymoma and brain stem glioma (5,6). Gliomas account for 75% of pediatric brain tumor while less than 50% of adult brain tumors. On the other hand, metastatic lesions are rarely seen in pediatric tumor patients but occur most frequently in adult patients (3,6). In addition, about 50% of pediatric brain tumors are benign (3). However, as the pediatric especially infant brain grows with time, it becomes difficult to make decisions for treating pediatric brain tumors (3). In general, pediatric brain tumors are treated using the methods developed for adult tumors with approved efficacy with some modifications (5–7). Surgery, radiotherapy, and chemotherapy have been used as standard treatments for pediatric brain tumors in clinical trials and clinics (2,6,8). The prognosis for these pediatric patients varies depending on many factors such as type of tumor, child's age, and whether the tumor has just been diagnosed or has recurred. While the benefits of surgery and radiotherapy for treating pediatric brain tumors have been well-recognized for a long time, chemotherapy has recently found its role in the management of pediatric brain tumors.

Existing chemotherapeutic agents such as vincristine, carmustine, lomustine, carboplatin, cisplatin, procarbazine, and temozolamide etc. for adult brain tumors have been shown significant effects (5,9–11), and evaluated to a great extent in myriad of different schedules, doses, and combinations in treating pediatric brain tumors. These agents are usually used at reduced adult dose in the management of pediatric brain tumors (6), and pediatric malignancies are more responsive to chemotherapy than malignancies in adults. Apart from the traditional chemotherapeutic small molecules, there are other few new agents in the development that hold promise for pediatric brain tumor therapy known as molecularly targeted agents (9). These agents inhibit tumor growth by targeting immune response, signal transduction pathways, angiogenicity, and gene expression in cancer cells. The following is a list of potential molecularly targeted agents that are in development: Bevacizumab (VEGF inhibitor)

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(12,13), Veliparib [poly(ADP-ribose) polymerase inhibitor] (14,15), Gefitinib (EGFR tyrosine kinase inhibitor) (16,17), Imatinib mesylate (PDGFaR tyrosine kinase inhibitor) (18), Erlotinib (ERBB2 receptor tyrosine kinase inhibitor) (19), Rapamycin and Everolimus (mTOR inhibitor) (19,20), Tipifarnib and lonafarnib (Farnesyl transferase inhibitors) (20,21), Cilenglitide (anti-angiogenic integrin receptor antagonist) (20), Sunitinib (PDGFRb/VEGFR/c-kit inhibitor) (11), Vandetanib (VEGFR-2 inhibitor) (22), dasatinib (23) and crenolanib (PDGFR inhibitor) (14). There is still an uncertainty in the role of these agents and several clinical trials are ongoing to better define the role of these emerging therapies in pediatric brain tumors (9). Besides being used alone, chemotherapy is more often used as adjuvant (after) or neoadjuvant (before) therapy to surgery or radiotherapy in the management of pediatric brain tumors (6,24,25). In some cases, especially for patients younger than 3 years old, chemotherapy is used to prevent or postpone the onset of radiotherapy in order to minimize the toxicity of radiotherapy on these patients (25–27). Chemotherapy can also be used as a radiation "sensitizer" during the radiotherapy treatment in order to enhance the treatment effectiveness in some brain tumors. Clinically, chemotherapy has demonstrated its activeness in the treatment and control of some pediatric brain tumors while failed in other cases (5,25,27–33). The reasons for these failures are complicated and varied, but some of these failures might be attributed to the blood-brain barrier (BBB), which limits chemotherapy response in certain pediatric brain tumors by preventing the chemotherapeutics from entering the tumor lesions in the brain (24,34). In this review, we will discuss the BBB in children, and various strategies that have been developed to circumvent the BBB for brain delivery of chemotherapeutics to treat pediatric brain tumors.

THE BLOOD-BRAIN BARRIER

Although there is a widespread belief that the BBB in newborns is immature or even absent, evidences reported in the literature strongly support that the BBB is formed before the infant is born maturely suggesting that there is not much difference between the BBB of adults and children including infants in terms of its barrier functions (35–38). Anatomically, the BBB is composed of endothelial cells which are lining the cerebral microvessels and in the meantime buttressed by astrocyte and pericyte cells (Fig. 1a) (39). The BBB functions as a physical barrier due to tight junctions between the adjacent endothelial cells, a selective 'transport barrier' due to specific transport systems on the luminal and abluminal membranes of the endothelial cells, and a 'metabolic barrier' due to the presence of intracellular and extracellular enzymes (40–43). The tight junctions are composed of three integral membrane proteins including claudin, occluding and junction adhesion molecules, and a number of cytoplasmic accessory proteins including ZO-1, ZO-2, ZO-3, cingulin, etc. (39,40). Fully developed tight junctions serve as a gatekeeper to restrict the paracellular transport across the BBB. The transport systems are influx and efflux transporters. The influx transporters include solute carrier superfamily facilitating brain uptake of glucose, amino acids, ions, and other nutrients; while the efflux transporters are ATP-binding cassette (ABC) efflux transporters such as P-glycoproteins and multidrug resistance associated proteins (44), which efflux lipophilic toxins including many therapeutics away from the brain to reduce the penetration of these molecules into the brain. The intracellular and extracellular enzymes are monoamine oxidase and cytochrome P450 (CYP1B1), and ectoenzymes, respectively, responsible for inactivating many neuroactive and toxic compounds in the BBB (39,43,45). While the three physical, transport and metabolic barriers allow nutrients in the blood stream and waste generated in the brain to cross the intact BBB, they prevent or limit non-selected substances to penetrate the intact BBB and get into the brain. It has been well-known that 98% of small molecule drugs including many chemotherapeutics such as carboplatin, vincristine, cyclophosphamide, cisplatin, methotrexate and etoposide cannot cross the intact BBB to get into the brain. Almost 100% of large molecule drugs also cannot penetrate the intact BBB by themselves (41).

It has been known that the BBB in some lesions of brain diseases/disorders such as Alzheimer and brain tumors does break down, losing its integrity and barrier function to some extent (46,47). The broken-down BBB can allow molecules to enter into the brain from the blood. These observations led researchers to conclude that the BBB was not a factor impeding the success of brain tumor chemotherapy (48) and was not important in brain tumor chemotherapy (49) before 1995. Continuous research in this field (50–58) revealed that the BBB in brain bearing tumors is more complicated than what was thought previously. Schlageter *et. al*. (51) reported that depending on the type of brain tumor, the capillaries in brain bearing tumors might be continuous and nonfenestrated, continuous and fenestrated, and/or discontinuous with or without fenestrations (Fig. 1b). The continuous nonfenetrated BBB is like the intact BBB, the continuous fenestrated BBB has increased permeability to small but not to large molecules, and the discontinuous BBB with/without fenestration has increased permeability to both small and large molecules. It has also been demonstrated that individual tumor cell or small tumor clusters can penetrate into the normal brain tissues in patients having infiltrative brain tumors (47). Moreover, the BBB disruption in a particular brain tumor lesion might exhibit heterogeneity and the BBB adjacent to brain tumors might be even intact (34,57,59). Even for the BBB disrupted by brain tumors, its permeability is just slight higher than that for the normal BBB while still lower than that for capillaries in

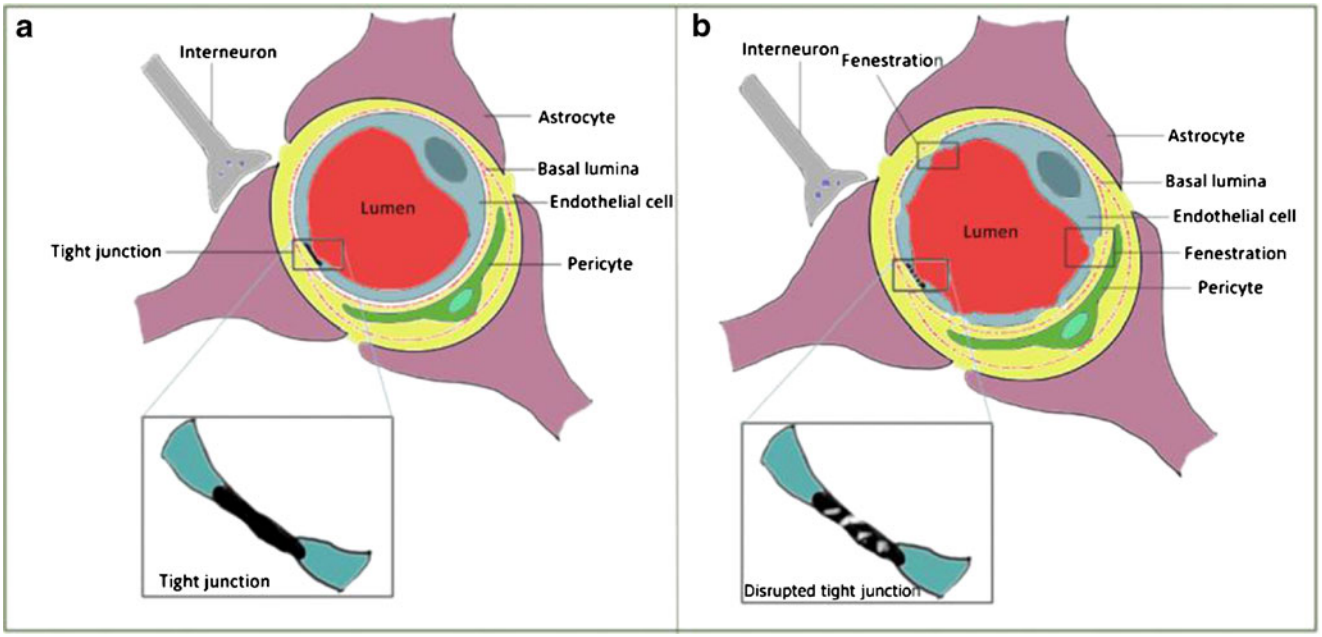

Fig. 1 (**a**) Intact BBB; (**b**) BBB disrupted by brain tumors (34,39,51,60).

organs such as lung and liver (60). More paradoxical is that efforts to normalize the tumor vasculature during chemotherapy might repair the disrupted BBB back to normal BBB, limiting further chemotherapy response from brain tumors. These notions re-enforce the research devoted to searching for strategies to circumvent the BBB (53,61–63).

STRATEGIES FOR CIRCUMVENTING THE BBB IN PEDIATRIC BRAIN TUMORS

The strategies to circumvent the limitation of the BBB could be categorized into: 1) by-passing the BBB by directly administrating chemotherapeutics into the brain, 2) disrupting the BBB by temporarily opening the tight junctions in the BBB, and 3) active transport across the BBB by exploiting transport mechanisms associated with the BBB (64–68).

Bypassing the BBB

Chemotherapeutics could be directly administrated into the central nerve system (i.e. brain and spine), thus bypassing the BBB and blood-cerebrospinal fluid (CSF) which are formidable obstacles faced by systemic administrated (e.g. oral and intravenous) drugs. Intrathecal administration and convection-enhanced delivery are mainstays of such administration methods. For intrathecal administration, drugs are injected into the fluid-filled space in spine via a needle or under the scalp via an outlet catheter connected to the ventricles (Fig. 2a) (69–71). Compared to systemic administration in which the whole body acts as a sink for the administrated drugs, intrathecal administration needs much lower drug dose to achieve higher drug concentrations in the brain due to the small volume of CSF (about 150 ml). Moreover, the chemotherapeutics are administrated behind the BBB and thus the BBB is not a concern or obstacle for such chemotherapeutics administration. Intrathecal drug administration has been used in the management of pediatric brain tumors for several decades (70,72). Success of application of intrathecal chemotherapy has been observed in the treatment of acute lymphoblastic leukemia, neoplastic meningitis, cerebral lymphoma, atypical teratoid rhabdoid tumor, and neuroectodermal tumors such as medulloblastoma and pineoblastoma, germ cell tumors and ependymomas in children (53,72–75). One disadvantage for intrathecal administration is that intrathecal drug administration can result in non-targeted drug distribution, inhomogeneous dispersion, and ineffective volume of drug distribution due to drug molecular weights and infuscate diffusivities. It has also been recognized that intrathecal administration is not practical and efficient for the treatment of intraparenchymal tumors.

Convection-enhanced delivery (CED) is another regional drug administration method introduced by Oldfield and his associates to overcome the limitations for intrathecal administration (76). In CED, intracranial catheters are connected to target sites (e.g. brain tumor or nearby) to deliver chemotherapeutics under a continuous pressure gradient over periods of hours to days and thus enhance the distribution of chemotherapeutics by convection rather than diffusion (Fig. 2b) (77). This method allows delivery of high concentration of chemotherapeutics directly into brain tumors and the adjacent parenchyma, thus eluding the BBB and limiting systemic toxicity. Small chemotherapeutics, macromolecules, and even nanocarriers (to be discussed in the section "Active Transport

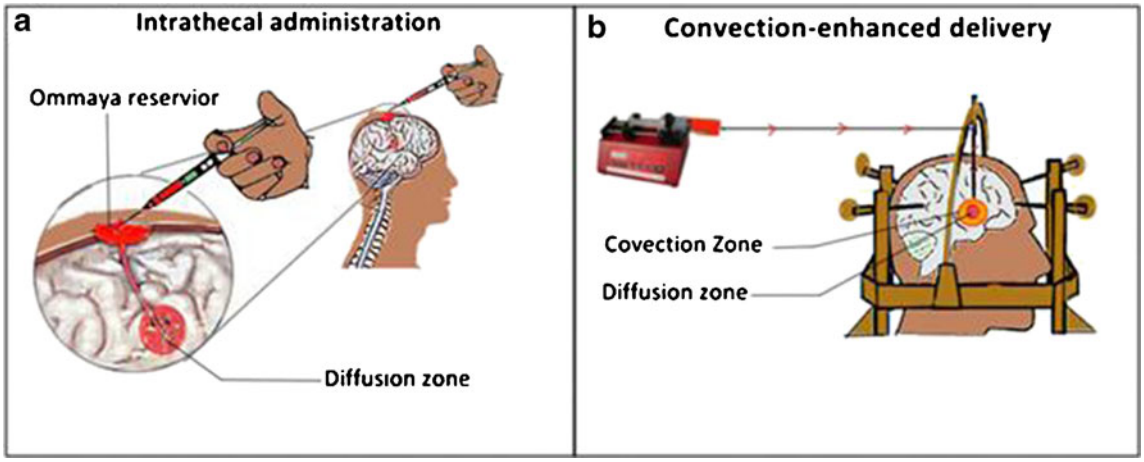

Fig. 2 (**a**) Intrathecal administration; (**b**) Convection-enhanced delivery (71,76,80).

Across the BBB") have been successful delivered into brain tumors using CED (76–80). CED has been used in the clinic and clinical trials to manage brain tumors such as recurrent/progressive glioblastoma, and high grade glioma (77–79,81–83). Positive response and tumor regression have been observed in the clinical studies using CED to administrate chemotherapeutics (83,84). In particular, regression in recurrent glioblastoma infiltrating the brainstem was observed in a 13-year-old boy who received convection-enhanced delivery of nimustine hydrochloride (84). Even though CED as well as intrathecal injection is effective in delivering drugs into the brain, these two administration methods are invasive in general.

Disrupting the BBB

The BBB can be disrupted by osmotic means, vasoactive substances, and focused ultrasound (50,52,55,59,62,63,85–88). The disruption induced transiently opens the BBB and thus allows therapeutics, which are normally prevented from entering the brain, to pass this barrier and get into the brain tissues. In the osmotic BBB disruption approach, a hypertonic solution is infused into arterial blood to cause brain microvascular endothelial cells in the BBB transiently and reversibly shrink so that the tight junctions in the BBB is transiently opened to allow the entrance of hydrophilic therapeutics into the brain (59). Mannitol is the most widely used hyperosmotic agent for this osmotic BBB disruption. In clinic, osmotic BBB disruption has been used to deliver chemotherapeutics into the brain for decades (89–92). Chemotherapeutics such as methotrexate and carboplatin have be delivered into brain via this osmotic BBB disruption method to manage pediatric patients having nonglial primary brain tumors, primary central nervous system lymphoma, or embryonal and certain germ cell tumors (86,91,93). However, this osmotic BBB disruption is global, non-selective disruption covering both normal brains region and brain tumors. This nonselective opening of the BBB may allow the entrance of other substances which might lead to adverse effects as seizures and chronic neurological changes (94). A delayed recovery of the BBB also increases the risk of neurotoxicity (94). These stimulated researchers and clinicians to seek methods to selectively open the BBB at the brain tumor lesions.

Vasoactive substances were found to be capable of stimulating receptors preferentially expressed in the brain tumor vascular vessels over normal brain vessels and thus initiate second messenger systems that induce reversible opening of the tight junctions in the brain tumor vascular vessels (94). This unique property was exploited by researchers and clinicians to selectively open the BBB at the brain tumor sites. Bradykinmin and its analogue lobradimil (i.e. Cereport®, RMP-7) are two major vasoactive substances used to selectively open the BBB at pediatric brain tumor sites without disturbing the tumor free sites (50,94–97). Hydrophilic chemotheracpeutics such as carboplatin have been delivered into brain tumors such as ependymoma, PNET, malignant glioma, high-grade gliomas and brainstem gliomas in combination of infused bradykimin or RMP-7 (30,52,95,98). Positive responses including tumor shrinkage, and stable disease were observed in these phase I clinical trials (52,98). However, further study in phase II clinical trial showed that the combination of lobradimil and carboplatin was inactive in childhood high-grade and brainstem gliomas (30). The reason for this unsuccessful combinatorial therapy is not clear at this time point.

Active Transport Across the BBB

It has recently been recognized that therapeutics could be successfully delivered into the brain after intravenous injection by crossing the BBB without the need of disrupting the BBB. The methods that have been developed are to utilize the transport mechanisms found in the BBB to rationally design

drugs and/or drug delivery systems to enhance drug permeability across the BBB. The transport mechanisms exploited include the transcellular lipophilic pathway responsible for the uptake of some lipid-soluble agents, carrier-mediated transcytosis for the transport of glucose, amino acids, purine bases, nucleosides, choline and other substances, receptor-mediated transcytosis for certain proteins such as insulin and transferrin, and adsorptive-mediated transcytosis for native plasma proteins such as albumin (39). Especially, in the recent 15 years nanocarriers such as polymeric micelles (99), dendrimers (100), polymer-drug conjugates (101,102), polymeric nanoparticles (58), liposomes (103–105), and inorganic nanoparticles including gold (106), mesoporous silica (107–109) and superparamagnetic iron oxide (SPIO) (110,111) with their structures illustrated in Fig. 3 have been actively investigated for enhancing drug delivery across the BBB to treat brain tumors (64–68,100,102,105,112–118). In some cases, cell penetrating peptides such as TAT (transactivator of transcription) or receptor targeting molecules such as transferrin, OX26 (anti-transferrin receptor IgG2a antibody) have also been conjugated to the nanocarriers to enhance drug penetration through the BBB after intravenous injection as transferrin receptor is expressed on the BBB and also overexpressed on brain tumor cells (119–121).

Up to date most nanocarriers are still at experimental and preclinical investigation stages for delivering chemotherapy to the brain (58,122). Most of these investigations focus on the toxicity and delivery of therapeutics into the brain. Less is carried out to investigate the fate of the nanocarriers after entering the brain. There are a few liposome and polymer-drug conjugate based nanocarrrers that have gone into clinical trials and Table I summarizes the development status of these nanocarriers including Marqibo, CT2103, NLCPT-11, 2B3-101, and ANG1005/GRN1005. Marqibo is a vincristine sulfate-encapsulated liposome made by Talon Therapeutics and has just been approved by FDA to treat rare leukemia and is in clinic trial for the management of pediatric brain tumors (104). CT2103 is a conjugate of paclitaxel and poly-L-glutamate and was developed to resolve the issues of poor water solubility and hypertensensivity reaction related with Taxol® (102). CT-2103 have been studied in clinical trials to manage different cancers including esophageal and gastric cancer, advanced ovarian cancer, metastatic breast cancer, and brain tumor (101). The mechanisms for CT2103 and Marqibo to enter the brain after intravenous injection have not been reported yet. NLCPT-11 is an irinotecan-encapsulated liposome which is delivered into the brain via convection-enhanced method by-passing the BBB. 2B3-101 is doxorubicin-encapsulated PEGylated liposome developed by to-BBB Company. Targeting moiety endogenous antioxidant glutathione is incorporated at the tips of polyethylene glycol (PEG) to enhance brain delivery of doxorubicin (117). ANG1005 (GRN1005) is a paclitaxel-Angiopep-2 conjugate that can enhance the delivery of paclitaxel across the BBB via

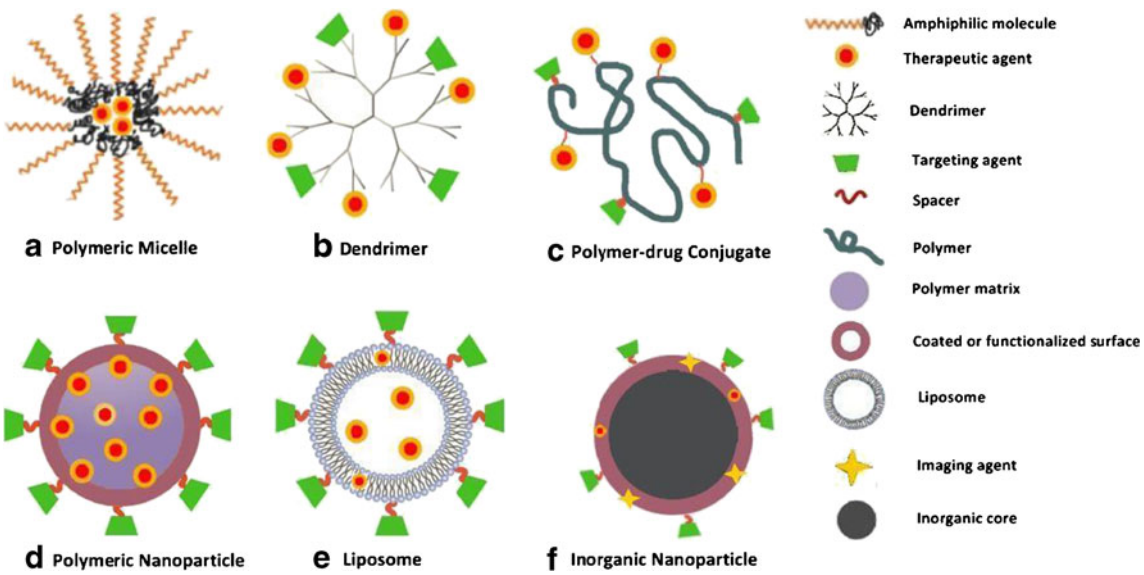

Fig. 3 Nanocarriers for brain drug delivery to treat brain tumors (123). (**a**) Polymeric micelles: core-shell nanosized structures formed by a spontaneous self-assembly of polymers as a result of ionic or hydrophobic interactions between polymer chain segments (99); (**b**) dendrimers: macromolecules with highly branched 3D structure offering a high degree of surface functionality and versatility (100); (**c**) polymer-drug conjugates: nano-sized and multi-component constructs with therapeutics and targeting ligands covalently attached to the polymer chains (101,102); (**d**) polymeric nanoparticles: submicron sized particles prepared from pre-synthesized polymers or through *in-situ* polymerization from monomers/macromers directly (58); (**e**) liposomes: spherical and self-closed lipoidal vesicles (unilamellar or multilamellar) of colloidal dimensions formed as result of self-assembly of phospholipids in an aqueous media into closed bilayered structures (103–105); and (**f**) inorganic nanoparticles: nanosized inorganic core including gold (106), mesoporous silica (107–109) and SPIO (110,111), coated with polymers and conjugated with targeting and imaging agents on the surface (124,125).

Table I Development Status of Nanocariers for Brain Tumors (58)

Product	Marqibo	CT2103	NLCPT-11	2B3-101	ANG1005/GRN1005*
Nanocarrier	Liposomes	Polymer-drug conjugate	Liposomes	Liposomes	Polymer-drug conjugate
Main component	Lipids	Polyaminoacids	Lipids	Lipids	Polyaminoacids
Targeting moiety	n/a	n/a	n/a (by-passing the BBB)	Glutathione	Angiopep-2 peptide (LRP-1)
Drug	Vincristine sulfate	Paclitaxel	Irinotecan	Doxorubicin	Paclitaxel
Clinical phase	Phase I	Phase II	Phase I	Phase I/II	Phase II
	http://clinicaltrials.gov, NCT01222780	http://clinicaltrials.gov, NCT00763750, NCT01402063	http://clinicaltrials.gov, NCT00734682	http://clinicaltrials.gov, NCT01386580	http://clinicaltrials.gov, NCT01480583, NCT01497665
Patients	Children and adolescents	18 Years and older	18 Years and older	18 Years and older	18 Years and older
Tumor targeted	Primary brain tumors	Newly diagnosed brain tumors/glioblastoma	Recurrent high-grade gliomas	Brain metastases or recurrent malignant glioma	Malignant gliomas and brain metastases
Company	Talon Therapeutics	Cell therapeutics	University of California	To-BBB	AngioChem/Geron Corporation

*http://angiochem.com/grn1005

receptor LRP (i.e. low density lipoprotein receptor-related proteins) mediated transcytosis as angiopep-2 binds the LRP receptors (113). The nanocarriers CT2103, NLCPT-11, 2B3-101, and ANG1005/GRN1005 are currently studied in clinical trials for only adults who are 18 years or older. If these clinical trials will be successful, the further development of the related nanocarrier-chemotherapy for treating pediatric brain tumors is expected in the near future.

SUMMARY AND FUTURE DIRECTION

In summary, intrathecal and convection-enhanced delivery methods that bypass the BBB to deliver chemotherapeutics into the brain have demonstrated effectiveness in treating pediatric brain tumors. However, these two methods are invasive. The BBB disruption method using osmotic pressure or vasoactive substances can transiently open the BBB and also show some effectiveness in treating pediatric brain tumors. However, the osmotic disruption method can cause side effects due to its global and non-selective disruption in the BBB. The vasoactive substances can selectively disrupt the BBB, but are ineffective in treating high-grade and brainstem gliomas. Focused ultrasound has been reported as an alternative approach to transiently and reversibly disrupt the BBB in animal studies, thus allowing the delivery of chemotherapeutics into the brain. One unique advantage of this technology over the other two BBB disruption methods mentioned above is that it is capable of selectively disrupting the BBB at the targeted sites. However, this focused ultrasound approach has not been used clinically to disrupt the BBB for chemotherapy yet and is still under extensive investigation at experimental and pre-clinical stages. Clinical trials in adults and children are expected along the maturity of the technology in the future. Nanocarriers are new technology that can actively transport chemotherapeutics across the BBB with some studies under clinical trials for treating adult brain tumors. The application of nanocarriers for treating pediatric tumors is just beginning with few studies.

Future direction will be further development of currently existing technologies that can overcome the BBB to first successfully treat adult brain tumors and then apply the similar technologies to treat pediatric brain tumors. Nanocarriers functionalized with targeting, sensoring and reporting moieties for targeted and sustained delivery of one or more drugs across the BBB will hold promising future. Factors such as drug properties, interaction between drugs and nanocarriers, dose and duration of drugs, and biocompatibility and fate of nanocarriers and their degradable components, need to be taken into account while designing a nanocarrier for delivering drugs across the BBB to treat adult as well as pediatric brain tumors. Furthermore, the toxicology associated with long term exposure of these nanocarriers in the human and environment needs to be fully evaluated. The future of this field is intimately tied to and relies on a better understanding and identification of biologically relevant targets, the cellular mechanisms, and the molecular biology of pediatric brain tumors. Better knowledge of all these will ultimately lead to personalized medicine for treating pediatric brain tumors.

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