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LETTER TO THE EDITOR

Nanoparticle drug delivery system for the treatment of brain tumors: Breaching the blood−brain barrier

KEY WORDS

Nanoparticle;
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Blood−brain barrier;
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Glioma

To the Editor:

Malignant brain tumors represent a substantial morbidity and mortality burden globally, with 308,102 new cases and 251,329 cancer-related deaths in 2020[1]. Brain tumors encompass primary tumors originating in the brain and brain metastases (BM) that have been spread from cancer lesions of other organs. Besides, BM are the most prevalent intracranial malignant tumor affecting approximately 20%−40% of cancer patients[2]. The presence of BM and leptomeningeal metastases in diverse cancers is associated with a poor prognosis due to lack of effective treatment strategies, primarily because of the blood−brain barrier (BBB). BBB is composed of tightly connected neurovascular units, mainly consisting of a single layer of endothelial cells, glycoproteins, and basal lamina surrounding neuronal synapse[3] (Fig. 1A). This intricate structure presents a significant challenge for drugs to penetrate the BBB for the treatment of brain diseases. To overcome this challenge, several novel technologies have been proposed and exhibited promising translational potential, especially the utilization of nanoparticle drug delivery system (NDDS). However, the precise efficacy of these novel nanomedicines remains uncertain and requires further clarification through clinical trials. In this work, we conduct an analysis and comprehensive summary of the current status of clinical trials utilizing NDDS for brain tumors. This analysis is based on published papers and publicly available clinical trial databases, providing insights into the latest advancements in pre-clinical and clinical progress in this field.

1. Challenges and opportunities in the brain tumor treatment

Brain tumors have been a formidable problem for decades. The key challenge remains how to efficiently deliver drugs to the brain and achieve the best therapeutic response with minimum toxic effects. Regarding related challenges, drug-related (such as drug resistance, drug diffuse, systemic toxicity) and biological factors of the brain (such as BBB, blood−tumor barrier (BTB), tumor heterogeneity, tumor microenvironment (TME), cancer stem cells, efflux pump of drugs) are the main influencing factors hindering the effective treatment.

Apart from surgery, radiotherapy and combination therapy regimens, brain delivery technology is a hot spot in current drug development (Fig. 1B) to overcome the above challenges: 1) Drug modification: peptide−drug conjugate is a new class of drugs that links BBB permeable peptides (*e.g.*, arginine-glycine-aspartic acid, somatostatin) with cytotoxic agents[4]. 2) NDDS: nanocarriers are employed to cross the BBB/BTB, which could penetrate the BBB through several pathways (Fig. 1B), with receptor-, transporter- and adsorptive mediated transcytosis most commonly used. Currently, brain-targeting ligand and cell membrane coating technology of nanoparticles are being widely researched for the treatment of brain tumors. 3) BBB modulation: osmotic opening, biochemical reagents (*e.g.*, TNFα), and mechanical disruption of the BBB/BTB (*e.g.*, through focused ultrasound, stereotactic radiation) are under investigation. 4) Bypass BBB/BTB: intrathecal, intraventricular, intratumoral and intracavitary delivery, as well as convection enhanced delivery (CED) are available for invasive

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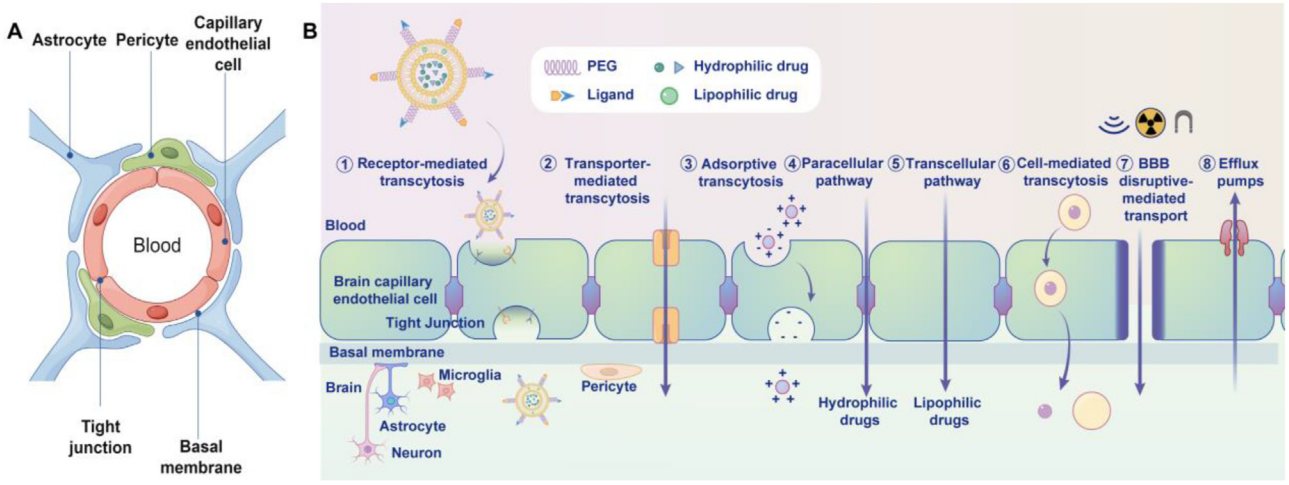

Figure 1 Transport mechanisms for nanoparticles crossing the blood−brain barrier. (A) Schematic diagram of BBB structure. (B) Schematic diagram of different mechanisms for nanoparticles crossing the BBB. ①Receptor-mediated transcytosis (*e.g.*, transferrin, insulin, angiopep-2, folate). ②Transporter-mediated transcytosis (*e.g.*, glucose, amino acids, nucleosides). ③Adsorptive transcytosis (*e.g.*, albumin, other plasma proteins). ④Paracellular pathway (hydrophilic nanoparticles). ⑤Transcellular pathway (lipophilic nanoparticles). ⑥Cell-mediated transcytosis (*e.g.*, monocytes, macrophages, other immune cells). ⑦BBB disruptive-mediated transport (*e.g.*, TNFα, focused ultrasound, stereotactic radiation, electromagnetic field, laser). ⑧Efflux pumps (*e.g.*, P-glycoprotein, multidrug resistance proteins).

methods and the intranasal delivery route is investigated for the non-invasive approach.

2. Pre-clinical studies of NDDS in the treatment of brain tumors

Several nanocarriers have been explored in pre-clinical studies, especially in the *in vivo* study using orthotopic xenograft models. In a radiopharmaceutical study, lipid nanocapsules loaded with Rhenium-188 increased the survival time of mice with glioblastoma, a malignant brain tumor[5]. Additionally, nanocarriers loading cytotoxic drugs were the most researched and several techniques were applied to the modification of nano-delivery vectors. For instance, temozolomide-conjugated gold nanoparticles[6], bio-polymeric transferrin-targeted temozolomide nanoparticles[7], and paclitaxel/melittin co-loaded lipodisks[8] all showed survival benefits in glioma mice/rats. In addition to primary brain tumors, hyaluronic-doxorubicin dual-targeting nanoparticles[9] and liposomal irinotecan[10] both significantly prolonged the survival of mice with BM from breast cancer. Recently, nanocarrier studies focusing on targeted therapy, immunotherapy, and gene therapy are increasing (Supporting Information Table S1). Except for nanoparticle-encapsulated microRNA-124 (LUNAR-301) with no improvement in survival, four studies in Table S1 presented great antitumor efficacy, and 11 studies exhibited smaller tumor size and burden and extended the survival duration than control groups in animals.

3. Surface coating of NDDS for the treatment of brain tumors

An efficient NDDS is difficult to develop and requires an ideal combination of the particle, BBB-targeting ligand, and the therapeutic agent[3]. Surface coating is a popular method to optimize NDDS.

3.1. Research status of PEGylated NDDS in the treatment of brain tumors

A long half-life is crucial for the nanoparticles to enter the brain. Typically, PEGylation can extend the half-life by reducing clearance from the mononuclear phagocyte system[3]. Furthermore, with the rapid resistance to single agent, combination regimens of drugs or NDDS deliver different drugs are required. Chongqing Upgra Biotechnology Co., Ltd. (Upgra) of China has developed a PEG-(small molecule multidrug) conjugates (PEG-MD) nano-targeting drug delivery system (Supporting Information Fig. S1). This nanomedicine uses specific peptides to simultaneously conjugate the PEG carrier with various small molecule drugs, active targeting moieties or enhancers. Besides, the payload proportion can be adjusted. Possibly, like the micelle of pegylated small molecule, PEG-MD will be able to penetrate the BBB to treat brain tumors. Notably, similar products from Starpharma in Australia have reached phase II clinical trials.

3.2. Research status of NDDS targeting BBB receptors in the treatment of brain tumors

BBB-targeting ligands (such as antibodies, proteins, peptides, nucleic acids, or small molecules) could facilitate the delivery of more drugs to the brain[3]. Receptor-mediated endocytosis (RMT) is one of the most efficient BBB transporting pathways with high selectivity. Various ligands, including transferrin, insulin or anti-insulin receptor monoclonal antibody, angiopep-2, and folate, etc., were explored to target the receptors related to BBB regulation and crossing to promote RMT. For instance, the statins-loaded angiopep-2-anchored nanoparticles containing doxorubicin were reported to improve survival of mice with BM[4].

3.3. Research status of cationic NDDS in the treatment of brain tumors

The charge of NDDS is another major factor in determining BBB permeability. It is widely used to modify nanoparticles with cationic surfactants. For example, an amphetamine decorated cationic lipid nanoparticles containing paclitaxel and PDL1-siRNA, as well as a dual-modified cationic liposome carrying paclitaxel and survivin siRNA, both exhibited survival benefits in glioma mice.

3.4. The application of other NDDS in the treatment of brain tumors

With the remarkable advancements in nanotechnology, a variety of nanoparticles with novel surface modification methods have been created, such as the pH-sensitive nanoparticle. Particularly, cell membrane coating for active strategy has gained wide focus. For example, the paclitaxel nanosuspension coated with glioma-C6-cancer-cell-membrane was investigated in glioma.

4. Clinical trials of NDDS in the treatment of brain tumors

Trials utilizing NDDS to explore BBB penetration were performed continuously from 2000 to 2022. In total, 39 trials (searched on *informa,* https://pharma.id.informa.com, up to 12 August 2022) were conducted and most of them were in the early stages (phases I−II) (Supporting Information Fig. S2A). Almost more than 1 trial was initiated every year and six trials were performed in 2017 (Fig. S2B). Across all these trials, 66.7% of the investigated therapies were cytotoxic drugs (Fig. S2C). Regarding the mechanism of action, 59.0% of the drugs targeted the DNA topoisomerase. Of note, the drug in one trial targeted the ErbB-2 pathway (Fig. S2D).

Liposomal doxorubicin and liposomal irinotecan were the most explored. Liposomal doxorubicin showed no additional therapeutic benefits in several trials but demonstrated encouraging activity in breast cancer with BM when used with temozolamide in one trial. The efficacy of liposomal irinotecan needs to be determined in clinical trials with larger sample size. Notably, ADI-PEG 20 (pegylated arginine deiminase) plus temozolomide and radiotherapy showed encouraging preliminary overall survival in a phase I trial. Across these studies, only one trial reached phase III stage, which investigated the efficacy of etirinotecan pegol for patients with breast cancer and BM and demonstrated no significant improvements when compared with chemotherapy (Supporting Information Table S2). The majority of the trials were in their early phases, making the outcomes of the forthcoming confirmatory studies highly anticipated.

5. Challenges of the clinical translation of NDDS for the treatment of brain tumors

Multiple nanomedicines with NDDS exhibited anti-tumor efficacy in preclinical studies. However, several obstacles hinder their potential clinical application. The main challenges of clinical translation and proposed strategies are as follows:

5.1. Physicochemical properties

An effective NDDS for tumor treatment should meet the standard as 1) stability, 2) efficient drug loading, and 3) low immunogenicity. These issues may be solved after optimizing the design or fabrication process of nanomedicines. For example, lipid nanoparticles can be prepared with excipients such as PEGylated lipids or cholesterol to enhance stability. To improve drug loading capacity, novel synthesis methods (*e.g.* phase separation-induced nanoprecipitation for producing polymer nanoparticles) are developed. Recently, some cell-derived nanocarriers (*e.g.*, exosomes, erythrocyte membranes) have demonstrated lower immunogenicity than synthetic nanoparticles.

5.2. Physiological properties

1) Distinct inconsistencies between animal models and the human cancer situation are observed in pre-clinical studies. Application of the patient-derived models may help establish credible models. 2) Toxicities and nano−bio interactions remain unclear due to the complexity of nanoparticle structures. 3) Tumor heterogeneity is another important issue in anti-cancer drug development. 4) The complexity of the TME poses significant challenges to the development of novel therapies. The interactions between NDDS and various tumor infiltrating immune cells should be further clarified.

5.3. Technical challenges

Technical challenges are focused on limited reproducibility and scaled-up manufacturing. Complexity of chemistry, manufacturing and controls (CMC) and high costs impose a huge burden on the industry. Reproducible and scaled-up preparation could be optimized by using particle replication in non-wetting template (PRINT) technology or microfluidic technology.

6. Future perspectives

In this correspondence, we provide a summary of drugs utilizing NDDS to penetrate the BBB for the treatment of brain malignancies. Various nanotechnologies to deliver therapeutics to the brain elucidated efficacy in pre-clinical studies. Additionally, the PEG-MD is of potential to cross the BBB. Particularly, we highlight the progress of drugs entering phase I/II clinical trials and found the combination regimen of ADI-PEG 20 (pegylated arginine deiminase), temozolomide and radiotherapy illustrated encouraging preliminary overall survival in a phase I trial, representing a promising therapeutic option.

Passive targeting (*e.g.*, liposome, PEG-MD, niosome, nanoemulsion) and active targeting (*e.g.*, transferrin receptor, EGFR, HER2, glucose transporter) strategies have been researched to enhance drug delivery to the brain. To address the clinical challenges associated with brain malignancies, accelerating NDDS optimization and clinical translation is urgent. Furthermore, different combination strategies based on temozolomide which has been approved as frontline therapy for glioblastoma, deserve further exploration in clinical trials to improve efficacy and reduce drug resistance.

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Author contributions

Ning Li, and Shuhang Wang conceived the study and oversaw the project; Qiyu Tang, Guo Zhao, and Hong Fang collected and assembled the data; Qiyu Tang, Guo Zhao, and Hong Fang analyzed and interpreted data; Qiyu Tang, Guo Zhao, Hong Fang, Yale Jiang, Peiwen Ma, Jiawei Zhou, Dongyan Liu, Shujun Xing,

Gaoquan Li, Nian Liu, Huiyu Chen, Shuhang Wang, and Ning Li wrote and revised the manuscript; All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supporting data to this article can be found online at https://doi.org/10.1016/j.apsb.2024.03.023.

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