The potential of nanotherapeutics to target brain tumors: current challenges and future opportunities

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“Enhancement of existing conventional chemotherapy treatment is necessary to help improve patients’ survival rate and time, and nanomedicine offers a promising approach for brain tumor therapy.”

According to WHO, cancer is the second leading cause of death worldwide [1]. While some cancers are treatable and considered less life threatening if detected at an early stage, others may have a poorer prognosis and higher fatality rate. For example, both primary and metastatic brain tumors are often difficult to treat due to inadequate drug response. Additionally, brain tumors are also challenging to detect before symptoms arise. As a result, diagnosis can often only be made at a later stage, making brain tumors even harder to treat [2]. For instance, glioblastoma multiforme is one of the most common forms of brain cancer (WHO grade IV), and its aggressive metastatic feature results in a poor prognosis and survival rates [3,4]. The median survival time is only 12–15 months after diagnosis, along with <10% of 5-years overall survival [5]. The general treatment regime includes surgery, radiation therapy and chemotherapy. Although recent advances in combination therapy promise superior treatment success, the survival rate is still unsatisfactory [2,6].

One of the biggest obstacles in brain cancer treatment is passing through the blood–brain barrier (BBB). The BBB naturally protects the brain from foreign substances as a physical barrier, and it is responsible for providing hemostasis in the brain by regulating the transport of molecules to the brain [7]. Endothelial cells forming the BBB have very tight junctions and fenestrations, hindering the passage of both hydrophilic drugs and >95% of hydrophobic drugs [8]. Some small drugs like temozolomide with hydrophobic characteristics may be allowed to transport through BBB via passive diffusion; however, larger molecules with polar, charged or hydrophilic features need to rely on active transport pathways using specialized transport proteins [9]. The burden of brain tumor treatment is mainly encountered due to the inability to transport chemotherapeutic drugs effectively to the brain. It is therefore necessary to develop more efficient drug-delivery systems to assist anticancer agents in reaching the brain at clinically sufficient quantities.

Over the last two decades, many different techniques have emerged to provide better drug transport to the brain, such as prodrugs [10], applying drug modifications, implanting drugs with brain surgery [11], temporarily disrupting the BBB using ultrasound or osmotic differences [12], as well as employing nanoparticles to help the drug delivery [9]. However, modifying the molecular structure of drugs may lead to a decrease in drug efficacy, implantation of drugs requires brain surgery and there is a risk of permanently damaging the BBB integrity using ultrasound [13]. On the other hand, carefully designed nano-enabled drug delivery can potentially deliver anticancer agents selectively to the target site at the required doses and offers an alternatively safer treatment and diagnostics means for brain cancers [9,14].
In recent years, nanotechnological advances have led to a nanomedicine revolution that has provided promising vehicles for the delivery of conventional drugs as well as macromolecules such as proteins, peptides and oligonucleotides [15]. Nanocarriers have proven to improve the stability and bioavailability of anticancer drugs [16]. Besides, these systems provide longer circulation time and fewer side effects [17], and have the potential for controlled drug release. Their small size (<200 nm) helps them penetrate through various biological barriers better [9]. Smaller particles may also have the ability to pass through the BBB via diffusion, depending on the surface properties. However, since the pore size of BBB is <1 nm [18], transporting nanoparticles through the BBB mainly relies on specialized transport techniques such as carrier-, receptor- and absorptive-mediated transport [9,19]. These transport methods may be achieved by modifying particles’ surface properties and attaching specific peptides or antibodies onto the drug-delivery systems that are recognized by receptors presenting in the BBB [19]. For this reason, one must consider the critical quality attributes of the nanoparticles/delivery systems. For example, considerations of the potential harmful impacts the drug-delivery system may have on the BBB barrier or the brain due to the physicochemical properties of the system, and the mechanism of action of the drug molecule itself. Preferably, biodegradable and nontoxic excipients are used in the formulation. An adequate amount of drug, offering selective delivery to the target site(s) with sufficient residence time in the desirable sites should also be considered.

It is important to note that nonspecific adsorptive-mediated transport of nanosystems generally rely on the electrostatic interactions of cationic nanoparticles and the BBB endothelium [19]. However, since the cell membranes are also negatively charged, the possible nonspecific uptake of nanocarriers by peripheral tissues would require particular attention to ensure the safety and efficacy of such systems. This would require using a higher amount of particles reaching the target site(s) in order to mediate the required pharmacological effect, which may also result in greater risks of potential toxicity [20]. Receptor-mediated transport with endocytosis/transcytosis is the most commonly used means for drug delivery using nanoparticles. Nanocarriers that have particular ligands on their surface can target specific receptors on the BBB. These ligands include folic acid, transferrin, α-mannose, melanotransferrin, lactoferrin and antibodies target transferrin receptor [21]. Compared with conventional treatments, nanocarrier-mediated brain tumor treatment has been demonstrated to be more effective and successful [22]. Following passage through the BBB barrier, the enhanced permeation and retention effect helps nanoparticles accumulate at the tumor region, which minimizes interaction with healthy cells and allows slow release of the drug over a prolonged period of time [4,19].

Many nano-enabled drug-delivery systems developed over the years use various materials, including polymers, lipids, as well as metals. The properties of these nanocarriers depend on the biomaterials employed, the particle size and shape, and its functionalization [23]. Polymer-based systems have been designed using polymers such as poly(amicidomine), poly(e-caprolactone), poly(ethyleneimine) and poly(lactic-co-glycolic acid) [24]. These polymer systems may be presented in the form of nanoparticles, capsules, polymer-drug conjugates, micelles and dendrimers. The use of metals like silver, gold, iron, zinc and quantum dots have also been exploited [24]; however, the in vivo potential of some of the inorganic materials may be limited by their toxicity. To prepare lipid-based systems; phospholipids, solid lipids and liquid oils can be employed. Various morphological and vesicular structures can be formed, such as liposomes, transfereosomes and niosomes, and solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) [17].

Over the years, polymeric nanoparticles have been extensively studied due to their high stability, ease of fabrication and manipulation allowing conjugation with multiple drugs, targeting ligands and imaging probes. It is relatively simpler to control the particle size, shape, surface functionalization of polymeric nanoparticles compared with lipid-based systems, although polymer–drug conjugates may have a wider polydispersity than other systems. In some cases, the potential toxicity of polymer-based systems could be a concern, particularly if nonbiodegradable polymers are used. Both chemical toxicity and nanotoxicity have been observed due to particles’ purity, organic solvent residues left during the manufacturing process, acidic by-products seen after degradation, and other particle-related characteristics such as morphology, charge and size [9,17,25]. Furthermore, scaling-up the manufacturing of the polymer-based systems is often seen as another challenge. Similarly, inorganic nanoparticles may cause neurotoxicity by inducing oxidative stress, cognitive dysfunction and inflammatory response, which to an extent, limits their use for therapeutic purposes [23,26].

In comparison, lipid-based nanocarriers are relatively biocompatible. Due to their lipidic nature and small size, some can pass through the BBB without employing any surface functionalization [23]. Lipid carriers are also generally biodegradable, nontoxic and nonimmunogenic. They can carry both hydrophobic [27] and hydrophilic drugs [7], depending on their design. Although there are also impurities and the usage of organic solvents may be
required during manufacture, lipid nanoparticles can be manufactured consistently on a large scale. Additionally, lipid systems can also mediate active and passive targeting for selective drug delivery [28]. Therefore, more attention has been given in the last decade in using lipid-based carriers as the nanomedicine of choice.

Liposomes are probably one of the most extensively researched lipid-based nanodrug delivery systems, with many products already authorized for therapeutic use in humans. Despite the benefits of liposomes, the applications might be limited due to stability issues and their relatively high cost associated with production. It should be borne in mind that since liposomes are made up of phospholipids, as in the case of other lipid-based systems, they are also susceptible to hydrolysis and oxidation. Additionally, early drug leakage could be another problem for liposomes [29]. The development of SLNs and NLCs improved the stability issue of liposomes with a better drug release trend. However, SLNs might also suffer from undesired gelation and low drug loading capacity. Besides, lipid recrystallization may also occur and result in unexpected drug release [29]. Therefore, careful consideration is essential to ensure successful drug delivery by optimizing and having an effective nanoparticle drug-delivery system. The compatibility between the drug, lipids and all other excipients used must be evaluated, and their impact on the physicochemical properties of the drug delivery vehicle, which ultimately affects the biological behavior, must also be investigated. For this reason, it is acknowledged that given the enhanced analytical techniques and manufacturing processes available to date, formulation scientists still have a massive challenge in designing a system that is tolerable, nontoxic, biocompatible, biodegradable, stable and have a high drug loading capacity; yet to pass across the BBB, to be selective to tumor region and release the drug in a controlled manner at an appropriate time.

Nevertheless, liposomes, SLNs and NLCs continue to be the most commonly employed lipid-based carriers in nanoformulation design to help deliver therapeutic agents to the brain. There are also many successful preclinical studies of these particles, and translation to routine clinical use is awaited to help provide better treatment options for brain cancers. For example, one study showed that using NLCs for delivering temozolomide drug to the affected brain region proved to be more efficient and successful against glioblastoma inhibition than polymer-based systems both in vitro and in vivo [50]. Angiopep-2 conjugated SLNs targeting receptor-related protein-1 receptor improved brain delivery of docetaxel and demonstrated higher drug accumulation in the brain and improved survival of tested animals than the drug’s marketed formulation [31]. In another study, multifunctional targeted liposomes with RGD and p-hydroxybenzoic acid ligands help deliver doxorubicin across the BBB and selectively reach the tumor region [32]. An enhanced antglioma effect and improved survival time in mouse models were also displayed. However, to date, neither SLNs nor NLC particles could reach to clinical trials stage. Perhaps the most critical uncertainty here is the possible toxicity associated with these substances, including these nanosystems, passing through the BBB. For this reason, more studies are required to establish the safety of these nanocarriers for long-term applications, including further preclinical and clinical evaluations.

In summary, brain cancers can be highly aggressive, invasive and metastatic. Brain cancer treatment is highly challenging due to the origin of the tumor, the BBB and the ability to resist anticancer agents. Enhancement of existing conventional chemotherapy treatment is necessary to help improve patients’ survival rate and time, and nanomedicine offers a promising approach for brain tumor therapy. The opportunity of targeted delivery of chemotherapeutic agents to the brain with increased drug accumulation and residence in the required tumor region would help reduce side effects. The selective delivery allows higher doses of drugs to be delivered and thus better results in tumor inhibition. Due to their safety margin and opportunity for scaling-up, lipid-based carriers are considered the next generation of drug-delivery systems for both therapeutic and preventative medicines [23]. Multitargeted lipid-based systems are shown to offer better tumor regression and improved survival times in vivo [32]. However, more research is required to evaluate the long-term applications of nano-enabled drug-delivery systems in the treatment of brain tumors. Additionally, the promising preclinical results observed need to be further translated to clinical studies. As a future perspective, it is highly anticipated that using innovative nanocarrier systems to assist the delivery of anticancer agents to the brain will improve brain tumor patients’ survival rates.

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