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Review **Open Access**

Nanocarrier drugs in the treatment of brain tumors

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ABSTRACT

Nanoparticle-mediated targeted delivery of drugs might significantly reduce the dosage and optimize their release properties, increase specificity and bioavailability, improve shelf life, and reduce toxicity. Some nanodrugs are able to overcome the blood-brain barrier that is an obstacle to treatment of brain tumors. Vessels in tumors have abnormal architecture and are highly permeable; moreover, tumors also have poor lymphatic drainage, allowing for accumulation of macromolecules greater than approximately 40 kDa within the tumor microenvironment. Nanoparticles exploit this feature, known as the enhanced permeability and retention effect, to target solid tumors. Active targeting, i.e. surface modification of nanoparticles, is a way to decrease uptake in normal tissue and increase accumulation in a tumor, and it usually involves targeting surface membrane proteins that are upregulated in cancer cells. The targeting molecules are typically antibodies or their fragments; aptamers; oligopeptides or small molecules. There are currently several FDA-approved nanomedicines, but none approved for brain tumor therapy. This review, based both on the study of literature and on the authors own experimental work describes a comprehensive overview of preclinical and clinical research of nanodrugs in therapy of brain tumors.

Quick Response Code:

INTRODUCTION

Brain tumors are divided into two groups: (i) primary, originating and residing within the brain and (ii) secondary (metastatic), originating from a primary cancer outside the central nervous system and spreading into the brain. Metastatic tumors are more frequent than primary tumors in adult patients while primary ones are the most frequent solid tumors of childhood. The histological spectrum of brain tumors in children and adolescents differs from that in adults.[1]

Primary brain tumors represent a heterogeneous group as classified according to WHO. According to the Central Brain Tumor Registry of the United States (CBTRUS) 2005-2009 report, the incidence in the US of CNS tumors was 20.6 cases per 100,000 persons/year, the incidence of malignant tumors was 7.3/100,000 persons/year and the incidence of low-grade tumors was 13.3/100,000 persons/year.[2]

The most frequent brain tumors in all age groups are tumors originating from glial cells - gliomas that represent a wide spectrum of tumors ranging from slow growing to highly aggressive tumors. WHO classifies gliomas within four grades: grade I (pilocytic astrocytoma), grade II (diffuse astrocytoma), grade III (anaplastic astrocytoma), and grade IV (glioblastoma multiforme). The grade III and IV are considered high-grade gliomas (malignant gliomas) and are associated with very poor prognosis. In particular, 5 year survival rate of glioblastoma multiforme, which accounts for half of primary brain tumors, is less than 10%.[3] Brain metastases are the most common intracranial tumors in adults, with more than 150,000 cases in the USA. In adults with cancer, 8-10% develop brain metastases, although the incidence of metastases varies considerably among different primary tumor types. Lung, breast, colorectal, renal cell cancer or melanoma can metastasize to the brain and 70% of brain metastases are due to lung and breast cancer.[4,5] High-grade brain tumors, such as glioblastoma, and brain metastases are often lethal because of their invasiveness and resistance to surgical procedures as well as chemo- and radiotherapy.[6] The urgent need for novel therapies has led to great emphasis on the development of new anticancer drugs including nanoparticles as cytostatic drug delivery vehicles.

Nanoparticles are structures between one and several hundred nanometers in diameter. There are three major physical properties of nanoparticles: (i) they are highly mobile in the free state; (ii) they have large surface areas; and (iii) they may exhibit quantum effects due to the movement of electrons. They have unique material characteristics, and manufactured nanoparticles may find practical applications in a variety of areas, including medicine. The nanoparticle-mediated targeted delivery of drugs might significantly reduce the dosage required, increase drug specificity and bioavailability, overcome chemoresistance and reduce side effects.

The history of therapeutic nanoparticles began in the 1950s with a polymer-drug conjugate designed by Jatzkewitz, followed by Bangham who discovered the liposomes in mid-1960s. In 1972, Scheffel and colleagues first reported albumin based nanoparticles, which formed the basis of albumin-bound paclitaxel (Abraxane).[7]

Targeted delivery in cancer therapy is an important challenge for oncologists. Nanovectors for drug delivery typically contain a core material or matrix, a therapeutic payload, and surface modifications in some cases. Possible advantages of nanoparticle delivery systems over conventional anticancer chemotherapy include: (i) protection of drugs from degradation in the body; (ii) enhanced absorption into tumor cells; and (iii) decreased interaction of drugs with normal cells.[8] Ideal properties of nanoparticles for drug delivery are shown in Table 1. Nano-based drug delivery carriers, or nanocarriers, can consist of a wide variety of materials, both organic (polymeric, lipid, protein, or viral) and inorganic. The largest nanocarriers are liposomes (80-200 nm diameter), polymeric nanoparticles (40-100 nm) or micelles (20-60 nm); the smallest ones are dendrimers (< 10 nm diameter).[9] There have been several reports describing the delivery of multiple anticancer agents using nanocarriers, some having been evaluated in clinical trials. Some nanodrugs have been FDA approved.[10] The approved nanodrugs for anticancer therapy are given in Table 2.

The blood-brain barrier (BBB) protects brain neural tissues and works as a diffusion barrier that impedes the influx of toxins and other compounds, including

Table 1: Ideal properties of nanoparticles for drug delivery. Modified from[78,79]

Ideal properties of nanoparticles for drug delivery
Non-toxic
Biocompatible
Biodegradable
Physically stable in blood
Prolonged time in circulation
Non-immunogenic/non-activating neutrophils/non-inflammatory
Non-trombogenic/non-agregating platelets
Avoidance of reticuloendothelial system
Amenable to small molecules, peptides, proteins and nucleic acids
Inexpensive/easy manufacturing

Table 2: FDA-approved anticancer nanodrugs. Modified from[80]

Name	Description	Indication	Approval (year)
DaunoXome	Liposomal daunorubicin	HIV-releated Kaposi sa	FDA 96
DepoCyt	Liposomal cytarabin	Lymphomatous meningitis	FDA 96
Oncaspar	PEG asparaginase	Acute lymphoblastic leukemia	FDA 94
Abraxane	Albumin-bound paclitaxel nanospheres	Various cancers Pancreatic ca	FDA 05 EMEA 08, FDA 13
Myocet	Liposomal doxorubicin	Breast ca	Europe + Canada
Marqibo	Liposomal vincristin	Acute lymphoblastic leukemia	FDA 12
Genexol	Paclitaxel loaded polymeric micelle	Breast ca, small cell lung ca	Europe + Korea
Onivyde	Liposomal irinotecan	Pancreatic ca	FDA 15

sa: sarcoma; ca: carcinoma

drugs, from blood to the brain.[11] Its main components are brain endothelial cells, basal membranes, pericytes embedded in the basal membrane, and astrocytic end-feet. The BBB is characterized by the presence of tight intercellular junctions, minimal pinocytotic activity, and a lack of fenestrations, qualities that distinguish BBB endothelial cells from peripheral cells. Endogenous and exogenous compounds including drugs may cross the BBB by passive diffusion, carrier-mediated transport, endocytosis, or active transport. The efflux and influx transporters of BBB comprise transporters like ATP-binding cassette transporters and solute carrier transporters.[12] The different types of transport across the BBB are shown in Figure 1.

The inability of drugs to cross the BBB is one of the major impairments to developing treatments for neurological diseases.[13-16] This highly restrictive, physiologic barrier prevents 98% of small-molecule drugs and virtually 100% of large-molecule drugs from reaching the central nervous system from blood circulation. Numerous methods to bypass the BBB have been investigated, such as transient disruption of the BBB, inhibition of efflux pumps, or transport using endogenous transcytosis systems, including receptor-mediated transcytosis. Nanodrugs are another approach to overcoming this obstacle to brain tumor treatment.

This review presents a comprehensive overview of preclinical *in vitro* and *in vivo* research and clinical studies of nanodrugs in therapy of brain tumors.

NANOCARIERS FOR ANTICANCER DRUGS

Drug nanodelivery has gained a great deal of attention from researchers.[17-19] However, some difficulties related to drug delivery may occur, such as troublesome solubility and biological availability, short time in circulation, and inconvenient biodistribution to the target organ. The key features of anticancer nanoparticles are principally large size, surface properties (e.g. hydrophobicity), and in some cases also targeting ligands. The development of a broad range of nanoparticles with varying size, composition, and functionality has provided a significant resource for nanomedicine.

Although nanoparticles avoid renal clearance, they tend to accumulate in the mononuclear phagocyte system (MPS).[20] Surface conjugation with polyethylene glycol (PEG) and other polymers improves particle

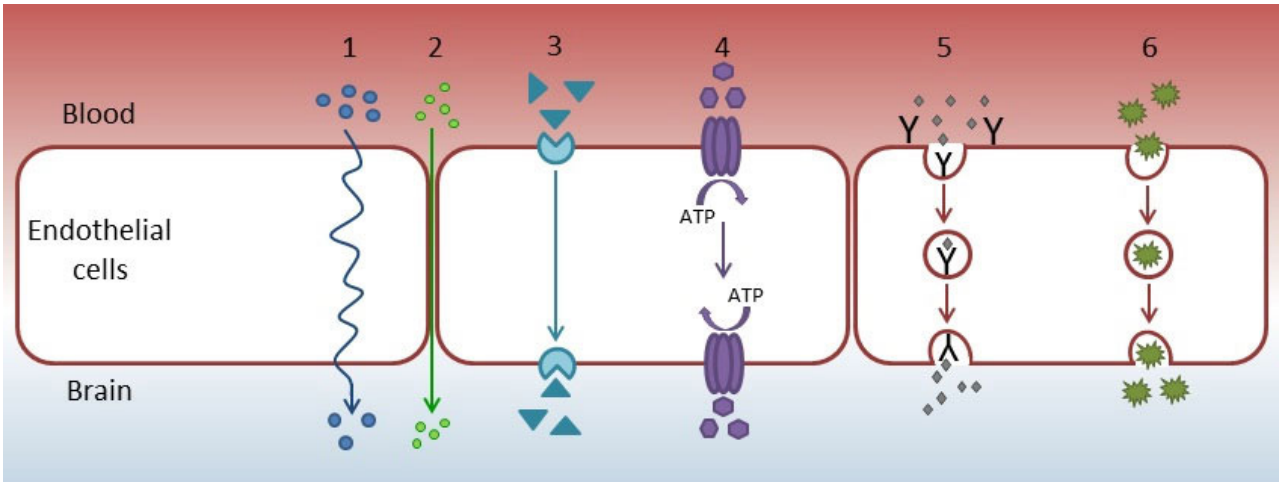

Figure 1: Mechanisms of transport across the blood-brain barrier. (1) Transcellular diffusion (small hydrophobic molecules); (2) paracellular diffusion (small water soluble molecules); (3) carrier-mediated transport (e.g. glucose, amino acids, vinca alkaloids); (4) active efflux transport; (5) receptor-mediated transport (e.g. insulin, leptin, transferrin); (6) adsorptive-mediated endocytosis (e.g. albumin, plasma proteins). ATP: adenosine triphosphate

circulation by reducing uptake into the MPS. The requirements for nanoparticle properties also depend on tumor characteristics, including cancer type, stage of disease, and location. Delivering multiple agents *in vivo* is complicated because of their independent pharmacokinetics, biodistribution, and clearance. A delivery system also has to transport a drug with high efficiency to target cells, with minimal toxicity and immune response. Drug toxicity can be reduced by encapsulating the free drug (e.g. liposomes) or by local activation of a pro-drug.[21]

Nanoparticles designed for cancer therapy consist of various components, generally a nanocarrier and an active agent.[22] Drug-carrier nanoparticles are considered as submicroscopic colloidal systems that may act as drug vehicles, either as nanospheres (the matrix system in which the drug is dispersed) or nanocapsules (reservoirs in which the drug is confined in hydrophobic or hydrophilic core surrounded by a single polymeric membrane).[23]

Nanoparticles as carriers for anticancer drugs make them promising candidates to overcome chemoresistance of cancer cells, because nanoparticles loaded by cytostatic drugs promote their cellular uptake and considerably decrease their efflux, prolong drug systemic circulation lifetime, and enable targeted drug delivery.[26] These particles can be modified with various types of materials including biomolecules. Altering the organizations of atoms can modify the properties of nanoparticles, such as elasticity, plasticity, strength, and conductivity.

Nanoparticle systems have unique properties that allow for both passive and active targeting of tumors.[27] Tumor neovasculature has abnormal architecture and vessels are highly permeable. The tumor mass has also poor lymphatic drainage, allowing for accumulation of macromolecules greater than approximately 40 kDa within its microenvironment. Nanoparticles utilize this feature, known as the enhanced permeability and retention (EPR) effect, to target solid tumors. The ideal size range to benefit from the EPR effect is between 10 and 200 nm. Outside this range, smaller particles will be cleared by the kidney, preventing accumulation within the tumor site, while larger particles will not adequately penetrate the tumor vasculature and interstitial space. However, some clinical trials have not shown the efficacy of the EPR effect.[28] One possible cause of EPR effect failure could be increased interstitial pressure in the tumor microenvironment. It has also been assumed that the EPR effect cannot be employed after an operation. Attempts have been made to increase the efficiency of the EPR effect by induction of hypertension, by repairing the abnormal vasculature, or by targeting of perivascular cells.[28]

Targeting molecules

Active targeting, i.e. surface modification of nanoparticles, is a method to decrease uptake in normal tissue and increase accumulation in a tumor. Strategies for active targeting of tumors usually involve targeting surface membrane proteins that are upregulated in cancer cells.[25] Targeting molecules are typically antibodies or their fragments, aptamers, small molecules, or oligopeptides. Nanoparticles coupled with surface ligands or antibodies can localize to tissue, expressing the associated receptors or antigens and improving delivery efficacy.[10] Some ligand receptor interactions will facilitate receptor-mediated endocytosis, further enhancing payload delivery. Surface ligand or antibody coupling can achieve densities high enough to interact efficiently with target sites, qualities well suited to cancer therapies.

Monoclonal antibodies, particularly IgG, are frequently used for targeting. Antigen binding sites represent only a small part of the overall size of antibodies. F(ab)2 fragments retain both antigen binding sites of the antibody, coupled by disulfide linkages. Many tumors up-regulate growth factor receptors, such as HER2/neu in certain breast cancers, which can be targeted with anti-HER2/neu surface antibodies.[29] Liposomes modified with monoclonal antibodies against glial fibrillary acidic proteins or human insulin receptors have been studied to determine if they cross the BBB.[30] Transferrin receptor (TfR) is another primary target investigated for receptor-mediated transcytosis across the BBB because of its high expression on BBB endothelium.[31]

Aptamers are folded single strand oligonucleotides, 25-100 nucleotides in length, that bind to molecular targets.[32] For example, EpCAM-fluoropyrimidine RNA aptamer-modified doxorubicin-loaded PLGA-b-PEG nanoparticles, which bond specifically to the extracellular domain of epithelial-cell adhesion molecules, have been investigated in non-small lung cancer model. Aptamer-conjugated nanoparticles *in vitro* have displayed increased cytotoxicity and decreased volume of xenografts compared with non-targeted nanoparticles.

Small molecules used for targeting include peptides, growth factors, carbohydrates and receptor ligands. Specific examples of small molecules include folic acid, transferrin and the RGD peptides. Example of small-molecule targeting protein is an HER2/neu ligands (AHNP) for targeting of poly (lactide-coglycolide) nanoparticles with docetaxel, which has

been investigated *in vitro* with HER2+ breast cancer cells.[33]

Folic acid (FA) is essential for DNA synthesis, DNA repair, and methylation of DNA and is therefore necessary for cell survival and proliferation. The human folate receptor (FR), a glycosylphosphatidylinositol-anchored membrane protein of 38 kDa, has high affinity for FA, and is currently considered an essential component in the cellular accumulation of FA required in chemotherapy. FR expression is very low or undetectable in most normal cells and tissues, but it is upregulated in ovarian, breast, brain, lung, colorectal cancers as well as brain tumors.[34,35] Through the process of endocytosis, ligand-bound receptor is internalized and released from the receptor through intravesicular reduction in pH.[36] Ligand-free receptor is then recycled to the cell surface. Interestingly, covalent conjugation of small molecules, proteins and even liposomes to the gamma-carboxyl moiety of FA does not alter FA ability to bind to the FR and undergo endocytosis by receptor bearing cells. FR-mediated liposomal delivery has been shown to enhance the antitumor efficacy of doxorubicin both *in vitro* and *in vivo*, and to overcome P-glycoprotein-mediated multi-drug resistance.[37]

Transferrin (Tf) is a single-chain iron-transporting glycoprotein that supplies iron into cells via receptor-mediated endocytosis. The TfR is expressed at low levels in most normal tissues but is overexpressed in many tumor types. The crucial aspect of Tf for molecular targeting applications, the binding of Tf to TfR on the external surface of tumor cells, is 10 times to 100 times more effective in tumor cells than in normal cells.[38] Drug delivery systems can take advantage of this feature, most often by labeling the surface of the drug carrier with Tf, which is recognized by, and actively transported into, tumor cells. Therefore, Tf-modified liposomes, nanoparticles and dendrimers have been widely investigated in recent years. Despite the perceived potential of anti-TfR antibody-drug conjugates, a BBB-permeable drug using this approach has not yet been introduced for clinical use.[16]

Ferritin protein also self-assembles naturally into a hollow nanocage called apoferritin, useful for encapsulation of any molecule of interest.[39] Apoferritin can be modified with recognition ligands to achieve tumor-specific targeting. These extra surface modifications can avoid renal clearance and ensure EPR effect; however, they also eliminate the intrinsic tumor-specific binding of natural ferritin and disturb its *in vivo* performance and biocompatibility due to altered surface physicochemical properties of ferritin.

The authors have studied antibody targeted apoferritin mediated transport of doxorubicin, in which the surface of apoferritin can be modified with antibodies to enhance its targeting ability. These studies compared the cytotoxic effect of doxorubicin-loaded apoferritin, with and without surface targeting antibody anti-GCPII (PSMA), with that of free doxorubicin *in vitro* on prostatic cancer cell line (LNCaP) expressing PSMA as well as human umbilical vein endothelial cells (HUVEC) as a model of nonmalignant cells. The effect of doxorubicin-loaded apoferritin nanocarriers on cancer and healthy cells was similar to that of free doxorubicin. However, the real-time impedance-based platform demonstrated lower toxicity to HUVEC with doxorubicin loaded apoferritin than with free doxorubicin [Figure 2]. Entry of doxorubicin-loaded apoferritin nanocarriers with and without targeting antibody was higher into LNCaP than into HUVEC (Cerna *et al*., unpublished results).

Oligopeptides are also molecules used for targeting. The RGD (Arg-Gly-Asp) oligopeptide is a component of the extracellular matrix protein fibronectin and promotes cell adhesion and regulates migration, growth, and proliferation.[25,40] RGD is known to serve as a recognition motif in multiple ligands for several different integrins. RGD-containing peptide can be internalized into cells by integrin-mediated endocytosis. Recently, integrin-mediated carriers have been investigated as gene vehicles to enhance gene transfection and as vehicles to deliver anticancer agents. The upregulation of integrins is known to be promoted by angiogenic factors in several cancer types.

NANOPARTICLES IN THERAPY OF BRAIN TUMORS

Nanoparticles represent one of the possibilities of overcoming the BBB and delivering anticancer drugs to the brain. Therapy for brain tumors, particularly glioblastoma, using nanoparticles has been the subject of several preclinical experiments and clinical studies, but no nanodrug is as yet approved for brain tumor therapy.

Preclinical studies in brain tumors

Lipid nanoparticles loaded with doxorubicin have been investigated as a potential drug carrier to the brain, although doxorubicin cannot cross the BBB. The pharmacokinetics and tissue distribution of doxorubicin were studied in healthy rats, using i.v. administration of either free doxorubicin or doxorubicin incorporated into solid lipid nanoparticles (NANO DOX) in equivalent doses.[42] Several blood samples and tissue samples of liver, spleen, heart, lung, kidney, and brain were collected. The mean peak plasma concentrations of

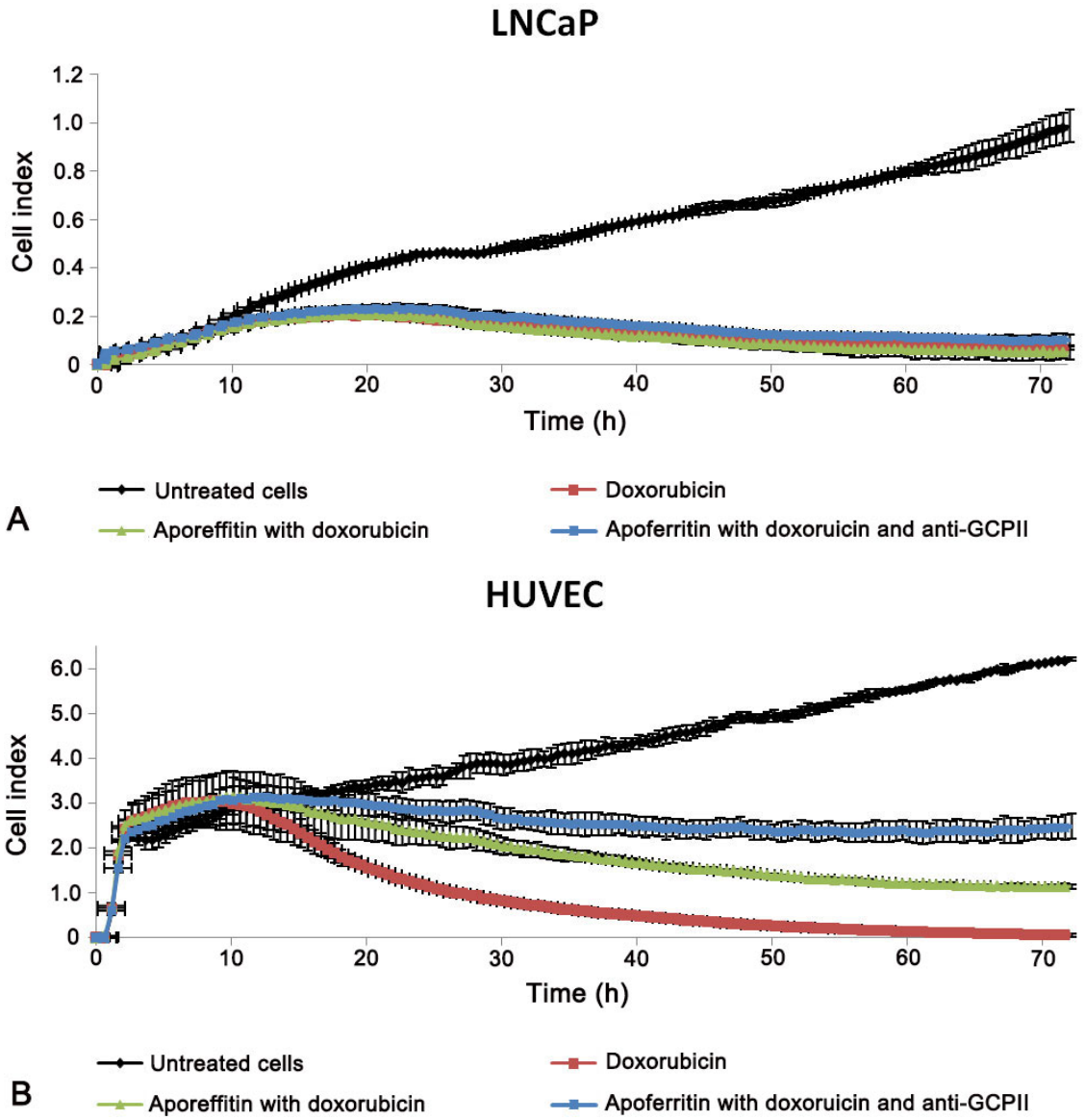

Figure 2: Cytotoxic effect of doxorubicin loaded apoferritin with and without targeting antibody anti-GCPII (PSMA) on its surface and free doxorubicin on (A) prostatic cancer cell line (LNCaP) expressing PSMA and (B) human umbilical vein endothelial cells (HUVEC)

free doxorubicin were lower than after NANO DOX treatment. In all rat tissues except the brain, the amount of doxorubicin was always lower after the injection of NANO DOX than after the injection of free doxorubicin. In the brain, however, NANO DOX increased the doxorubicin concentration significantly. The same study design, repeated in healthy rabbits, showed similar pharmacokinetic behavior and tissue distribution parameters.[43] Docetaxel-incorporated albumin-lipid nanoparticles (DNPs) *in vitro* induce apoptosis of several cancer cell lines, and *in vivo*, accumulate at the experimental glioma site.[44] This phenomenon is believed to be due to EPR effect. Liposomes containing temozolomide (TMZ) combined with anti-transferrin receptor single-chain antibody fragments were found to be more effective than free TMZ in both TMZ-resistant and TMZ-sensitive glioblastoma cells in mouse models.[45] Moreover, these liposomes showed significantly reduced toxicity. These results show that these liposomes may be an efficient vehicle for delivering BBB-impermeable drugs to the brain.

Biodegradable polymer-based nanoparticles and gold nanoparticles have both shown promise for delivering drugs across the BBB to treat glioma.[46] Gromnicova *et al.*[47] found that glucose-coated gold nanoparticles cross brain endothelium three times faster than non-brain endothelium. Huwyler *et al.*[48] investigated daunorubicin-loaded liposomes with anti-transferrin receptor antibody, using an animal model, and found increased brain daunorubicin concentration compared with free drug.

Nanoparticles show promise for specific and efficient intracerebral delivery of drugs for the treatment of glioma.[49] A two-dose regimen of topotecan non-PEGylated liposomes, locally administered with paramagnetic gadodiamide nanoparticles, increased survival rates in a U87MG glioblastoma intracranial xenograft model compared with controls; the effect was topotecan dose-dependent.[50]

Gadolinium nanoparticles enhance MRI monitoring and are well tolerated. These nanoparticles can penetrate the BBB and be uptaken by the brain tumor parenchyma.[51] Metal nanoparticles are also frequently integrated with other techniques such as microwave-induced hyperthermia to further increase their cellular transduction.[52] The α-helical right handed coiled coils associated with platinum (PtIV) compound showed higher toxicity to human malignant glioma cells compared with free Pt(IV) *in vitro* and *in vivo*, without affecting healthy astrocytes *in vitro*.[53]

Carrier-mediated transport (CMT) can transport small molecules from the blood to the brain. Receptor-mediated transport (RMT) systems are expressed on the BBB and provide transport of large endogenous biomolecules[54] [Figure 1]. During RMT, macromolecules move across the endothelial cells into the brain, due to the expression of several peptide-specific receptors, e.g. neonatal Fc receptor,[55] low-density lipoprotein receptor-related protein receptor, transferrin receptor,[56] lactoferrin receptor,[57] and insulin receptor.[58] Some of the above-mentioned receptors have been used for drug delivery as a molecular "Trojan horse". Shilo *et al*.[59] demonstrated that insulin-targeted gold nanoparticles cross the BBB after systemic administration.

Gao *et al*.[60] investigated transferrin-folate doxorubicin-loaded liposomes. The amount of doxorubicin transported across the BBB in the transferrin-folate doxorubicin-loaded liposome group of glioma bearing rates was sevenfold higher than in the non-targeted doxorubicin-loaded liposome-treated group. Boado *et al*.[61] found that fused lysosomal enzyme with anti-human insulin receptor monoclonal antibody could deliver fusion protein across the BBB at therapeutic levels, while free lysosomal enzyme did not cross the BBB. Yang *et al*.[62] tested dual peptide-modified (using low-density lipoprotein receptor-related protein receptor and neuropilin-1 receptor) liposomes loaded with vascular endothelial growth factor siRNA and docetaxel; the target was human glioblastoma xenografts in mice. These dual-modified liposomes showed the highest uptake compared with single modified or non-modified liposomes.

In another study, cetyl alcohol/polysorbate nanoparticles loaded with paclitaxel were more cytotoxic to glioblastoma cells and had higher brain uptake in an experimental animal model than paclitaxel alone.[63] The investigators speculated that nanoparticles may limit binding of paclitaxel to p-glycoprotein, causing higher brain and tumor cell uptake.

Coated poly (butylcyanoacrylate) (PBCA) nanoparticles have been studied as a delivery system for drugs in the brain.[64,65] Polysorbate 80 was found to be the most efficient modifier of nanoparticles. Transport across the BBB of polysorbate 80-coated nanoparticles has been presumed to involve receptor-mediated endocytosis by endothelias. Polysorbate 80 absorbs plasmatic apolipoprotein E (Apo-E) and nanoparticles coated with Apo-E are internalized by the LDL uptake system.[66] In one study in rats, PBCA nanoparticles with doxorubicin increased brain doxorubicin concentrations to levels more than 60 times that of free drug, while heart levels were very low.[67] In another rat brain model, polysorbate 80 coated poly-lactic-co-glycolic acid nanoparticles loaded with methotrexate-transferrin conjugates were investigated and showed better penetration, lower organ toxicity and higher anti-tumor activity as compared with non-targeting nanoparticles.[68]

Doxorubicin bound to polysorbate-coated nanoparticles was associated with significantly longer survival of glioblastoma-bearing rats compared with groups treated with free doxorubicin or noncoated nanoparticles with doxorubicin.[69] Poly-lactic-co-glycolic acid (PLGA) camptothecin-loaded nanoparticles were investigated in orthotopic murine glioma. Nanoparticles were well tolerated and effective against glioma.[70] Cetuximab-magnetic iron-oxide nanoparticles (IONP) that bind to both wild-type EGFR+ and mutated EGFR+ patient-derived glioblastoma cells are internalized by tumor cells and promote internalization of the EGFR, resulting in enhanced apoptosis. Treatment with cetuximab-IONPs proved efficacious in orthotopic glioblastoma xenografts in mouse and rats, and showed a favorable safety profile, as no toxicity to healthy immunocompetent mice was observed.[71]

The *in vitro* and *in vivo* studies described above seem promising for the treatment of brain tumors, particularly glioblastoma, the tumor with the worst prognosis. The inclusion of the most efficacious and safe nanoparticles designed for cancer therapy in clinical studies is warranted. Nevertheless, despite the successful results of preclinical experiments, the progress in applying these strategies in brain tumors is still modest when compared with treatments in other types of tumors.

Clinical studies in brain tumors

A phase I clinical study of paclitaxel-Angiopep-2 peptide-drug conjugate that binds to the low-density lipoprotein receptor-related protein-1 receptor (GRN1005) has been carried out in patients with recurrent glioma grade 2-4. The clinical data show that GRN1005 facilitated the penetration of paclitaxel into tumor tissue.[72] However, interim analysis of the phase II trial did not show therapeutic response.[73]

Transferrin conjugated with diphteric toxin (Tf-CRM107) demonstrated *in vitro* and *in vivo* toxicity to glioma cells and was effective when administrated locally to xenografts. Using local administration, low toxicity and tumor response were demonstrated in patients with recurrent high grade brain tumors in phase I and II clinical trials. The response rate was 35% and overall survival of responders was 74 weeks.[74] Unfortunately, an early phase III clinical trial using this therapy had to be terminated due to disappointing preliminary results.[75]

In a clinical study of liposomal doxorubicin in patients with high-grade gliomas, Fabel *et al*.[75] found improved overall survival than in past trials using conventional therapies. Hau *et al*.[77] demonstrated that pegylated liposomal doxorubicin in patients with recurrent high-grade glioma was efficacious and well tolerated.

These results presented above suggest that some nanodrugs may be efficient in therapy of high grade brain tumors, a topic of great potential interest for clinicians.

FUTURE DIRECTIONS AND CONCLUSIONS

Although the available clinical trial data are limited, evidence suggests that nanoparticles have potential in diagnosis, operative management and adjuvant therapy for brain tumors. Because the field of nanotechnology is young, the long-term health effects of nanoparticles are currently unknown. More study of nanoparticle biodistribution, pharmacokinetics, toxicity and role in therapeutic protocols is warranted if nanoparticles are to attain regular clinical use.

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Conflict of interest

There are no conflicts of interest.

Patient consent

No patient involved.

Ethics approval

This article does not contain any studies with human participants or animals.

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