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Nanotherapeutic approaches for brain cancer management

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Abstract

Around the world, cancer remains one of the most important causes of morbidity and mortality. Worldwide, approximately 238,000 new cases of brain and other central nervous system tumors are diagnosed every year. Nanotherapeutic approaches hold tremendous potential for diagnosis and treatment of brain cancer, including the ability to target complex molecular cargoes to the tumor sites and the capacity of crossing the blood–brain barrier and accessing to the brain after systemic administration. A new generation of "smart" nanoparticles has been designed as novel targeted delivery devices for new therapies including gene therapy, anti-angiogenic and thermotherapy. This review highlights the latest research, opportunities and challenges for developing novel nanotherapeutics for treating brain cancers.

Key words: Biomaterials; Drug delivery; Targeted delivery; Magnetic therapy; Anticancer drugs

Introduction

Cancer remains one of the most important causes of morbidity and mortality around the world. Among them, brain tumors account for 85% to 90% of all primary central nervous system (CNS) tumors.[1] Worldwide, approximately a quarter of million new cases of brain and other CNS tumors were diagnosed in the year 2008, of which around 81% suffered from glioma, the most common type of primary brain tumor and the most aggressive one.[2–4] According to *The World Health Organization (WHO) Classification of Tumors of the Central Nervous System*, gliomas are neuroepithelial tumors of grade IV that diffusely penetrate throughout the brain and extend far beyond the original tumor mass that is observable with neuroimaging.[5,6] Unfortunately, this characteristic means that not every last tumor cell can be surgically removed.

Since the late 1970s when the surgical resertion of brain tumors led to a median survival of 3 months, many efforts have been carried out with the only purpose of increasing the effectiveness of treatments as complete elimination of the tumor is not usually accomplished. In fact, how much is removed depends on the type of glioma and its location within the brain.[7] Nowadays, additional radiotherapy and chemotherapy successfully prolong median survival of the patient up to more than a year.[8] The most harrowing thing is that several achievements toward the treatment of the disease have failed to profoundly impact in patient survival. These therapeutic agents suffer from poor pharmacokinetics and inappropriate biodistribution which causes insufficient penetration to tumors. They are rapidly cleared from the circulation and tend to accumulate in and cause toxicity toward many healthy organs.

Nanomedicine can be defined as the use of nanotechnology with several medical purposes. This new and promising

Abbreviations: 5-ALA, 5-amino-levulinic acid; RGD, arginine–glycine–aspartic acid; BBB, blood–brain barrier; BCNU, carmustine; CASANT, carmustine sustained-release implant; CNS, central nervous system; CED, convection-enhanced delivery; c(RGDyK), cyclic arginine–glycine–aspartic acid–D-tyrosine–lysine; DGL, DendriGraft poly-L-lysine; EPR effect, enhanced permeability and retention effect; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Fc-diOH, ferrocenyl diphenol; FDA, Food and Drug Administration; GFAP, glial fibrillar acidic protein; GLUT1, glucose transporter 1; LNC, lipid nanocapsule; LRP1, lipoprotein receptor-related protein 1; MR, magnetic resonance; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; MEMS, micro-electro-mechanical system; MAb, monoclonal antibody; PAMAM, poly(amido amine); CPP:SA, polyanhydre poly(1, 3-bis-[*p*-carboxyphenoxy propane]-co-]sebacic anhydride]); PCL, poly(ε-caprolactone); PEG, polyethylene glycol; PLA, polylactic acid; PLGA, poly(lactic-co-glycolic acid); PEI, polyethyleneimide; PEEP, poly(ethyl ethylene phosphate); RES, reticular–endothelial system; SLN, solid lipid nanoparticle; TMZ, temozolomide; Tf, transferrin; TfR, transferrin receptor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

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discipline is based on the utilization of nanomaterials for various applications, including brain cancer treatment. In recent years the potential of nanomedicine to overcome the problems of traditionally administered anti-tumor drugs has been regarded as one of the most promising tools and has been extensively explored. For instance, nanocarriers can be of great help for overcoming cancer resistance. In fact, tumor cells can increase drug efflux pumps on their membrane, which decreases the intracellular concentration of the drug.[9] Nanomedicine can increase the intracellular levels of a drug by encapsulating it in different nanocarriers that will bypass the efflux pumps. In addition, new biomaterial-assisted drug administration systems can increase the concentration of anticancer agents in tumor site and improve their circulation times. Undoubtedly, the prospective of nanotechnology for improving specificity to tumors and reducing side effects of anticancer drugs, improving cancer treatment efficacy and enhancing patients' life expectancy has just begun. Since the development of the first nano-platforms, several new systems have emerged with distinct characteristics. On the one hand, nanocarriers are able to overcome the problem of passing the blood–brain barrier (BBB) as they can be administered directly to the brain.[10] Additionally, biomaterials can be tailored in the way of wafers or gels in order to obtain a sustained release of the loaded drug and then implanted intracerebrally.[11,12] On the other hand, the systemic administration of brain-targeted functionalized nanocarriers has become a challenge for the research community nowadays. These nanoscale particles, which also aim to overcome the BBB, are designed to be specifically taken up by tumor cells and to release their payload over an extended period of time in order to achieve an effective clinical response. This review aims to highlight the most innovative strategies, focusing on platforms and novel trends that will serve as a guide for the development of the next generation of chemotherapeutic formulations for brain cancer therapy.

The challenge of the blood–brain barrier

The BBB is a semi-permeable and selective barrier that protects the CNS from undesirable toxic or infectious agents and at the same time, supplies the brain with the required biologically essential molecules such as glucose or hormones. The BBB and the neurovascular unit are involved in various neuroinflammatory processes, and the pathophysiology at most brain barriers is affected by neuroinflammation (Figure 1).[13–15] But the BBB is not only a physical barrier. Further restricting the transfer of drugs to the CNS there is the "enzymatic barrier" formed by degrading enzymes present in large number inside the endothelial cells and specific transporters.[16] P-glycoprotein, for instance, is a prototypic active efflux transporter involved in multidrug resistance of cancer cells.[17] Some small-molecular-weight molecules with appropriate lipophilic and charge characteristics are able to diffuse from blood into the CNS. However, the BBB is often the rate-limiting factor in determining permeation of therapeutic drugs into the brain.[18] Bearing in mind all these characteristics, the nanomedicine field is restlessly trying to get smarter nanoscale platforms for biomedical applications in order

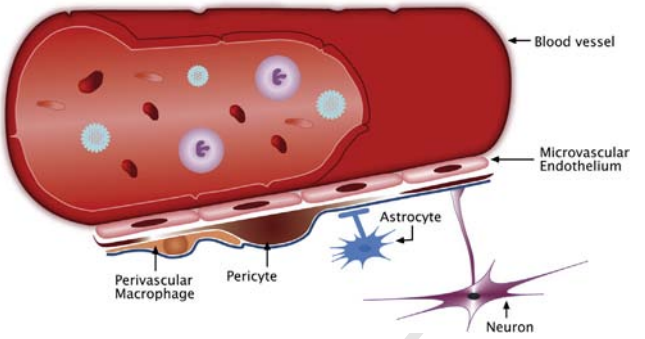

Figure 1. The neurovascular unit. The neurovascular unit includes circulating blood components, specialized endothelial cells, pericytes embedded in the endothelial cell basement membrane and neurons.

to improve both the delivery efficacy of therapeutics and the utilization of drugs otherwise too toxics for clinical use.[19,20]

As it will be reviewed later on the text, nanotechnology can improve the direct local treatment of brain tumors by increasing the half-life of the encapsulated drug or acting as a sustained-release delivery system (see Nanotherapeutic Approaches for Local Treatment of Brain Cancer). Also, systemically administered drug carriers can be modified for targeting specifically not only cancer cells but also tumor surrounding vasculature as well as the BBB in order to enhance the amount of drug that efficiently reaches the tumor cells (see Functionalization of Nanocarriers for Active Brain Targeting). In the last few years many approaches have been tested. For instance, methotrexate-loaded dendrimers have been modified with D-glucosamine for brain cancer treatment showing a higher concentration of the therapeutic drug.[21] More recently, fourth-generation poly(amido amine) (PAMAM) dendrimers encapsulating doxorubicine have been modified in their surface with transferrin for passing through the BBB and targeting the tumor cells.[22] Also, this kind of drug delivery systems can be functionalized with the purpose of inhibiting multidrug resistant (MDR) proteins such as P-glycoprotein. Through this method it is possible to increase the amount of drug that the cells will uptake and therefore an improvement in treatment effectiveness as shown by the use of tamoxifen as MDR proteins inhibitor in the mentioned PAMAM dendrimers.[22]

Ultimately, these new systems seek for higher efficacy and tolerability of the therapy, together with a reduction of the hard side effects that sometimes the patients need to pass through.

Nanotechnology-based drug delivery systems

In recent years, several approaches using nanocarriers such as liposomes, micelles or nanoparticles have been employed for brain delivery of therapeutic drugs with the aim of protecting them from degradation or loss of therapeutic effect. Although, the description of all these systems is beyond the scope of this review (formulation, pros and cons, etc.), a brief description of these drug vehicles will be provided assuming that they will be constantly referred over the text. An extended description of all these systems is reported elsewhere.[23,24] See Table 1.