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Review Article

A Review on Drug Delivery across the Blood-Brain Barrier

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Abstract

Malignant brain tumors, particularly high-grade glioma (HGG) and glioblastoma multiforme (GBM), indicate a gloomy future despite significant progress in standard treatment and ancillary therapies like concurrent chemotherapy, radiotherapy, and surgery. The challenges of delivering drugs across the blood-brain barrier (BBB) and intrinsic factors associated with the protection of the GBM microenvironment are the primary barriers to effective GBM treatment. Nanomedicine's recent advancements have shown promise for overcoming some of these obstacles. The benefits and drawbacks of using nanoparticle (NP) drug delivery systems to boost the efficacy of targeted drug delivery for treating HGG are examined in this review. Late advances in nanomedicine-based drug conveyance systems that emphasis on immediate and double focusing on drug conveyances for beating the difficulties related with dangerous glioma are talked about. At long last, clinical interpretation of medication conveyance techniques, unsettled concerns, and prospects for future advancement to work with the compelling treatment of harmful glioma are introduced.

Keywords: Malignant glioma, Blood-brain barrier, Nanoparticle-based drug delivery

INTRODUCTION

Glioma, the most common cancer of the central nervous system (CNS), has a high rate of recurrence, mortality, and morbidity in adults. More than 80% of all brain cancers are caused by gliomas, of which 17% to 22% are low-grade gliomas (LGG) (WHO grades I and II), which have a median survival time of nearly 5.6 to 13.3 years. The most prevalent subtypes of primary malignant glioma in adults are high-grade gliomas (HGGs), which are WHO grades III and IV. Glioblastoma multiforme (GBM) (WHO grade IV), the most lethal HGG, has a median survival time of nearly 14.6 months. GBM is 16% of essential harmful HGGs, 54% of all gliomas, 45.2% of threatening CNS growths, and 46.3% of all the cerebrum cancers. GBM has a global age-adjusted incidence rate (IR) of 0.59 to 3.69 per 100,000 people, with a higher IR in men (3.97/100,000) than in women (2.53/100,000). There are primary and secondary subtypes, with the primary subtype affecting older adults (mean age = 64) and the secondary subtype affecting younger adults (mean age = 45) and developing from oligodendroglioma or astrocytom Enhanced prognosis makes it possible to complete and effective cure HGG despite advancements in treatment **(Chang RL et al.,1975)**.

After a recurrence, the average patient survival time is two to six months. For the treatment of gliomas in the brain that are malignant, no ideal treatment has been found. Increased doses of radiochemotherapy result in toxicity and the death of healthy tissues, not an increase in survival rate, To effectively manage malignant brain glioma, numerous advances in standard treatments or novel therapies based on the microenvironmental, developmental, phenotypic, and hereditary characteristics of the tumor are being proposed **(Takakura Y et al., 1990)(Yamamoto Y et al., 2003)** . New approaches are being implemented for using the blood-brain barrier (BBB) to enhance the delivery of targeted drug, while appropriately considering the pharmacokinetic characteristics, in order to attain a better drug concentration at the location of tumor. However, new therapies are also required for addressing long-term toxicity induced by the treatments administered to improve patients' quality of

life. Drug conveyance at cancer site is limited because of the presence of the BBB. The restriction could be circumvented in a number of ways. One of these methods is MR-guided focused ultrasound, but there are compatibility issues with it **(Kaneda Y et al., 2004)**.

Multifunctional nanocarriers have emerged as one of the most promising systems for overcoming the challenges of clinical drug delivery through the BBB in this setting. Vesicular framework involving micropinocytosis, caveloae-interceded endocytosis, and clathrin-intervened endocytosis is utilized to intercede the NPs' intracellular vehicle. As a result, NPs form covalent bonds with specific ligands to traverse these pathways and deliver the drug to specific tumor sites via the BBB. Drug solubility, time-release delivery, stability, and toxicity are all improved by drugs encapsulated in NPs (10–200 nm), depending on the NP's shape and size and the chosen ligand **(Tsunoda S et al., 2004)**. Due to the improvement in lymphatic drainage and the relatively high penetration of endothelial cells in tumors, one of the primary mechanisms for the passive retention of NPs is thought to be the increased vascular permeability. Alternately, active targeting is a method in which a targeting moiety (a ligand, peptide, or coating) binds to the surface of the tumor to target specific modifications to the tumor's biological complexity. A few endeavors have been made to apply nanomedicine for the treatment of HGG, in request to cross the BBB's endothelium; endeavors have been made to utilize nanomedicine alongside standard medicines. Although many nanocarriers and NPs are still in the early stages of transformation, multifunctional nanomedicines based on BBB crossing have recently improved glioma treatment **(Cicek H et al., 1995)(Mi FL et al., 2002)**. The advantages and disadvantages of current treatments for malignant glioma, including HGG.

The precise and efficient delivery of drugs to the intended site is the focus of ongoing advancements in HGG treatment strategies. Despite the fact that the current standard treatments for malignant glioma are effective, improving their efficacy is still concerning **(Zhang Y et al., 2002)**. While combining the development of novel methods, devices, and materials for drug administration, some recent studies have deciphered the various issues associated with drug delivery for the treatment of malignant glioma. The most recent advancements in drug delivery strategies for treating malignant glioma are discussed in this section. Direct intratumoral drug administration, including the most recent devices for facilitating drug delivery to the brain, is the subject of the first subsection. Following that, recent studies on improving systemic drug delivery to the brain for effectively treating malignant gliomas are discussed **(Abraham GA et al., 2003)**. In the treatment of malignant gliomas, direct drug delivery refers to the local administration and direct injection of anticancer medications into the tumor site. For the purpose of treating malignant glioma and extending the half-life of therapeutic molecules within the brain, various nano formulations have been investigated. For instance, paclitaxel formed to mind entering NPs were created to treat GBM by conveying drug straightforwardly to the cerebrum. PEG-coated NPs may alter the therapeutic efficacy of targeted drug delivery within the GBM tissue, as PEG-polymerized NPs demonstrated 100 times higher ex vivo diffusion rates than uncoated NPs.

Convection-improved conveyance (CED), a sort of direct methodology of conveying intratumoral drug, has been broadly examined to upgrade drug dispersion into the mind tissue utilizing NP suspension. CED delivers a drug and creates an external pressure gradient in the brain through the use of a catheter with a diameter of 0.70–1.30 mm and a motor-driven pump. As a result, conventional intratumoral injections can improve drug diffusion at the targeted tumor site. Moreover, CED doesn't rely upon the atomic load of medications; As a result, CED could be used to deliver nucleic acids, proteins, toxins, and antibodies **(Calandrelli L et al., 2002)**. The pressure gradient also prevents the drug from backflowing during delivery. Be that as it may, existing clinical examinations, which have portrayed the protected and all around endured utilization of CED, neglect to lay out stamped improvement in the pace of endurance.

CONCLUSION

To combat tumor heterogeneity and high mutation rates, it is necessary to combine various therapies in addition to translating novel drug delivery strategies into clinical models. For instance, the standard treatment for GBM was found to be more effective. Nanoformulations and hydrogels for the treatment of malignant glioma, for example, require further development in the design of approaches that combine various clinical therapies and combine various fields. However, in order to maximize positive outcomes, it is necessary to have a deeper comprehension of each therapy. Encapsulated materials, devices, and methods should be the subject of additional research. Additionally, developing nanocarriers that are capable of targeting both cell-expressing proteins (such as EGFR) and ligands that are overexpressed on the BBB may prove to be effective delivery systems. Patients' survival may be enhanced by filling such nanocarriers with potent therapeutic molecules. Nanocarrier-based targeted drug delivery strategies could be a step toward effective treatment for malignant glioma, despite the aforementioned concerns. These strategies must be further considered.

DECLARATION OF COMPETING INTEREST

None

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