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NANOMEDICINE AS A THERAPEUTIC WINDOW FOR THE TREATMENT OF BRAIN CANCER: RECENT DEVELOPMENTS AND FUTURE PROSPECTS

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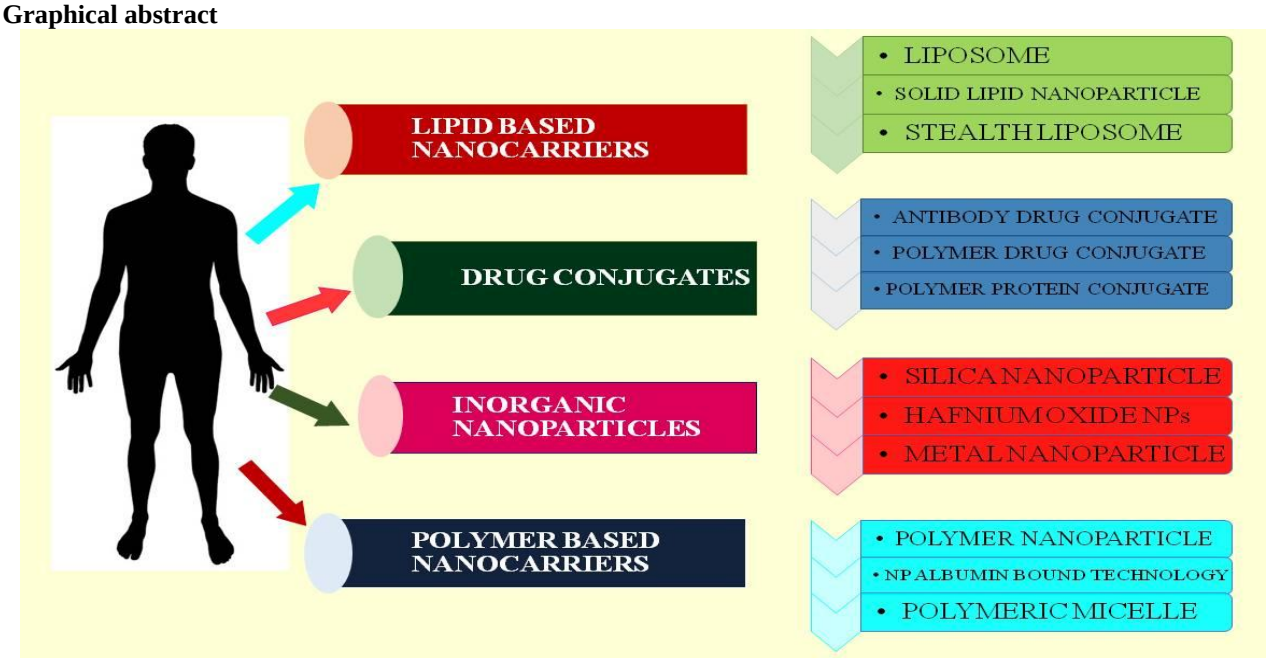
ABSTRACT
Malignant brain cancer treatment is limited by a number of barriers, including the blood-brain barrier, transport within the brain interstitium, difficulties in delivering therapeutics specifically to tumor cells, the highly invasive quality of gliomas and drug resistance. As a result, the prognosis for patients with high-grade gliomas is poor and has improved little in recent years. Nanomedicine is a way in order to address these needs. The way through which cancer development and targeting therapy can be understood is detection of somatic mutations in tumors. The screening for BRAF V600E mutation is employed in clinical practice in Libya for its prognostic and potentially predictive role in patients with metastatic colorectal carcinoma (mCRC). This review elaborate the obstacles that come in route of treatment, also it tell us about different ways nanomedicine have been used to overcome them with a focus on liposomal and polymeric nanoparticles.

KEYWORDS: Brain tumor, Doxorubicin, Glioblastoma, Nanomedicine, Nanoparticle, Paclitaxel.

Graphical abstract



INTRODUCTION

Brain metastases are the most frequently occurring neurologic complications of cancer in adults, with 9–17% of all cancers resulting in brain metastasis and brain metastasis occurring in 8–14 per 100,000 in the general population.[1] **Nanomedicine** is defined as the application of nanotechnology to medicine. Interdisciplinary research on **nanomedicine** formulations, on disease diagnosis and on disease treatment has brought about a number of efforts to combine diagnosis and **therapy** within a single **nanomedicine** formulation. Primary brain tumors, on the other hand, are relatively rare, and comprise about 1.4% of cancers.[2] Brain metastases are associated with

median survival times of about 3–25 months, and a 5-year survival rate of 1.8%.[3] Treatment modalities employed for brain metastases include: surgical resection, whole brain radiation therapy, radiosurgery and chemotherapy.[4] The choice of treatment would usually be based on several considerations. These include: histopathology of the primary tumor, status of systemic disease, patient's performance status (general well being and lifestyle activity level), age of the patient, number and sites and precise location of the brain metastases (such as proximity to sites of vital brain function), coexisting morbidities and symptoms.[2, 4] Glioblastoma multiforme (WHO Classification astrocytoma Grade IV), a metastatic primary brain tumor, accounts for 12–15% of all brain tumors and is the most common primary brain tumor in adults.[5] Glioblastoma is an aggressive metastatic astrocytoma with a median survival of 14 months and <5% of patients survive for 3 years.[6] This tumor is difficult to diagnose early as the tumor is usually asymptomatic or presents with symptoms which are difficult to associate with GBM, for example, symptoms associated with a high intracranial pressure (headaches, nausea, vomiting and cognitive impairment).[7] A major contribution to the poor survival rates is the insufficient transport of therapeutic molecules across the blood–brain barrier (BBB).[8] The current standard of care comprises surgical resection to the maximum possible extent, followed by concurrent radio chemotherapy and adjuvant chemotherapy with temozolomide. This treatment regimen became the standard of care for newly diagnosed glioblastoma patients after the results of the 2004 European Organization for Research and Treatment of Cancer 26981–22981/National Cancer Institute of Canada Clinical Trials Group CE3 randomized Phase III trial demonstrated a 20.7% improvement in the median survival as well as 27.2% 2-year survival rates in glioblastoma patients, who had received postsurgical concomitant and adjuvant temozolomide (known as the Stupp regimen) compared with 10.9% 2-year survival rates with postsurgical radiotherapy alone.[9] For recurrent glioblastoma on the other hand, there is currently no standard treatment regimen, and thus patients frequently receive investigational agents in clinical trials.[10]

Therapeutic nanomedicine

Nanomedicines are advantageous over standard low-molecular-weight drugs in several different regards. They e.g. I) reduce renal excretion and/or hepatic degradation, leading to prolonged circulation times; II) reduce the volume of distribution, leading to less accumulation in healthy non-target tissues ('site-avoidance drug delivery'); III) improve the ability of drugs to accumulate at pathological sites ('site-specific drug delivery'); and IV) improve the therapeutic index of drugs, by increasing their accumulation at the target site and/or reducing their localization in potentially endangered healthy organs. In addition, nanomedicine formulations assist low-molecular-weight (chemo-) therapeutic agents in overcoming several additional barriers to efficient drug delivery to pathological sites.A large number of nanotherapeutics have been designed and evaluated over the years, relying e.g. on liposomes, polymers, micelles, nanoparticles and antibodies as carrier materials. The vast majority of these formulations have been used for drug targeting to tumors, and rely on EPR-mediated passive drug targeting. Regarding the former, it is important to note that in recent years, increasing numbers of efforts have been initiated in which therapeutic nanomedicines are used for drug targeting to non-cancerous disorders, including e.g. rheumatoid arthritis and atherosclerosis.[11] As mentioned above, also inflammatory diseases are characterized by leaky blood vessels, and the accumulation of long-circulating nanotherapeutics within such lesions (via 'site-specific drug delivery'), together with their ability to attenuate localization in healthy non-target tissues ('site-avoidance drug delivery'), enables the use of potent anti-inflammatory agents, such as corticosteroids, at much higher i.v. doses, thereby providing a clear rationale for novel inflammation-targeted nanotherapeutic treatments.

The blood–brain barrier

The treatment of brain tumors (or more generally, CNS tumors) is particularly challenging, mainly because of their intracranial location.[12] Intracranial tumors are effectively 'shielded' from the effects of most systemically administered cytotoxic agents. The brain parenchyma and most (but not all) intracranial tumors are protected by the intact BBB, which maintains the brain microenvironment by serving as a physical and metabolic barrier regulating the access of molecules to the brain. The physical barrier is formed by the tight junctions between the adjacent endothelial cells (which prevent blood-borne substances from crossing into the brain parenchyma), a lack of capillary fenestrations, very low pinocytotic activity and the metabolic barrier is formed by degradative enzymes, specialized transport receptors and endothelial cell efflux pumps.[13]

Other brain tumor treatment barriers

Another barrier thought to restrict access of systemically administered therapeutic agents to tumor cells is the brain tumor–cell barrier (BTB; a barrier caused by the efflux activity of tumor cells).[14] Other challenges associated with effective brain tumor treatment are: dose-limiting toxicity, mainly myelosuppression and tumor resistance to alkylating agents; the latter mediated mainly by MGMT.

CONCLUSION

Glioblastoma and brain metastasis are still areas of unmet medical need and several nanoparticle formulations are showing promise in glioblastoma rodent models of the disease with a few even transitioning to clinical testing. The leaky vasculature in brain tumors has been exploited to concentrate drug-laden nanoparticles at the tumor site, following intravenous

injection. Brain cancer research and medical practice have advanced over the past decades, but progress, while significant, has been incremental and slow. The use of nanoparticles in this field has been fueled by a lack of current solutions to many of the barriers that impede further progress. Clinical translation of these technologies, in particular, has been slow, as few related studies have reached clinical trials and fewer still for applications in the brain It remains to be seen if the promising rodent data are indeed translated to approved clinical therapies and attention will need to be turned to the issue of manufacturability if the ligand-targeting systems are to transition into clinical products.

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