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Nanoparticles and nanothermia for malignant brain tumors, a suggestion of treatment for further investigations

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ABSTRACT

The current treatment for brain tumors, such as glioblastoma multiforme (GBM), has not been developed enough yet in order to fully heal them. The main causes are the lack of specificity of the treatments, the difficulty of passage of drugs through the blood–brain barrier, heterogeneity and tumor aggressiveness, and widespread dissemination in the brain. The application of nanoparticles (Nps) have been a breakthrough for both diagnostic imaging and targeted therapies. There have been numerous studies with different types of Nps in brain tumors, but we have focused on thermosensitive liposomes, which are characterized by releasing the chemotherapeutic agent included within its lipophilic membranes through heat. Furthermore, increasing the temperature in brain tumors through hyperthermia has been proven therapeutically beneficial. Nanothermia or modulated-electro-hyperthermia (MEHT) is an improved technique that allows to create hot spots in nanorange at the membrane rafts, specifically in tumor cells, theoretically increasing the selectivity of the damage. In scientific records, experiments that combine both techniques (thermosensitive liposomes and nanothermia) have never been conducted. We propose a hypothesis for further research.

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1. Background

Malignant brain tumors, such as glioblastoma multiforme (GBM), have a high mortality rate and poor survival odds. In Europe, about 45,000 people died from this cause, with an incidence of 57,000 new cases in 2012.[1] The treatment is based both on surgery, which eliminates the macroscopic tumor, and complementary radio and chemotherapy for the peripheral infiltrating part. The combination of trimodality reaches an average survival period of 40–50 weeks,[2] so it could be said there is no curative treatment for these tumors, despite the efforts of surgeons and oncologists. Some of the characteristics that confer this incurability are:

(1) Aggressive local dissemination and growth of residual tumor.
(2) Tumor location in which a complete resection cannot be achieved.
(3) The existence of the blood–brain barrier (BBB) and the blood–brain-tumor barrier (BBTB), restricting the distribution of many antitumor drugs into the cerebral nervous system (CNS). It is known that over 98% of small-molecule drugs and almost 100% of large-molecule drugs cannot cross those barriers.[3]
(4) Therapy-resistance of cancer cells caused by cellular heterogeneity, development of necrosis, aberrant angiogenesis and hypoxia.[4]

Surgery is the first approach, since a macroscopic and complete resection are related to a better prognosis. The large size of tumors and the close location to eloquent areas are the main limitations of a complete resection. Furthermore, the chances for a residual tumor to remain are high, so the complementary treatment with radiotherapy and chemotherapy becomes necessary.

Radiotherapy (RT) is the first treatment option for patients with inoperable or unmanageable brain tumors, but it is also administered after surgery in order to try to eliminate residual malignant cells. Radiation therapy acts mainly on cells with high replication, causing DNA damage directly or through free radicals such as reactive oxygen species. Aggressive growth and aberrant vessel formation cause necrosis and hypoxia, which confers resistance to the action of radiotherapy. However, thanks to advances in technology, it could be said that RT is one of the most individualized oncological therapies that exist in routine clinical practice. The photon fields are directed towards the target volume designed on CT and MRI of the patient. Despite that, since GBM usually has a wide local spread, the target area to be irradiated is usually large, covering a significant part of healthy tissue.

Concomitant chemotherapy can be used to make the tumor more radiosensitive, Temozolomide (TMZ) being the main drug for GBM. TMZ is an oral alkylating agent that exerts cytotoxic effects through DNA methylation,[5] and its application, along with RT, can improve the average survival rate by several months.[6] The pharmacokinetic barriers offered by brain tissue, such as the BBB, restricts the arrival of drugs at target sites.

Recently, new-targeted therapies have been incorporated into the usual clinical practice. Bevazizumab (BEV), a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), inhibits the formation of new blood vessels and, as a consequence, tumor growth. Unfortunately, current evidence suggests that such treatment produces favorable results in patients with recurrent GBM, but it is not associated with any benefits in newly diagnosed GBM and recurrent WHO grade III gliomas. The results of clinical trials on other antiangiogenic agents in patients with malignant gliomas were generally disappointing.[7]

Therefore, we need to find new treatments that are more effective in the treatment of brain tumors without damaging healthy tissue. In general, there are two synergistic goals that should be striven for to increase the efficacy per dose of any therapeutic formulation: to increase selectivity towards the tumor and to endow the agents comprising the drug with the means to overcome the biological barriers that prevent it from reaching its target.[8]

In this article, we intend to make a brief review of nanoparticles combined with electromagnetic hyperthermia. In addition, we suggest a possible future line of research in this field.

2. Nanotechnology and nanoparticles (Nps)

Nanotechology could be defined as a type of technology specialized in manipulation, manufacture and study of structures in a 1–1000 nanometre range[9]; that is, from a few atoms, to subcellular size.

Its use in cancer-related diseases include diagnosis (such as improvement in the detection methods of high-specificity DNA molecules and proteins in cancer cells[10]), imaging (as contrast agents for intraoperative imaging in the context of neuro-oncological interventions[11]), and drug or gene delivery (nanovectors).

Nanovectors can be classified depending on the preparation methods – as nanocapsules, nanospheres and nanoparticles – and the type of colloidal drug carriers from which they are made of – micelles, dendrimers, polymers, liposomes and emulsions. In this study we will only focus on the use of nanoparticles, and specifically on liposomes, due to their properties towards the treatment of brain tumors, including the avoidance of biobarriers and biomarker-based targeting.

Nanoparticles are solid colloidal particles made of macromolecular materials in which the active principle (drug or biologically active material) is entrapped or dissolved.[12] Some of the features of Nps that make them suitable for those tumors are its special size, the surface charge, and the possibility of making preparations in combination with certain substances to improve its treatment profile. Small size of Nps allows them to penetrate through the pores of small capillaries, cell's membrane and BBB; for example, it takes advantage of overexpression of fenestrations in GBM neovasculature to increase drug concentration at tumor sites. Paradoxically, its

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