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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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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.

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

relative "large" size increases their immunogenicity and leads to their clearance by reticular endothelial system (RES). Nevertheless, the surface charges of these Nps should be considered for the toxicity profile, since high concentrations of anionic and cationic Nps can influence BBB integrity, meanwhile neutral and low concentration of anionic Nps do not have effect at this level.

Focusing on GBM treatment with Nps, a recent review has been published in 2015.[13] It shows a wide variety of formulations and multiple possibilities of conjugations with other compounds to increase their selectivity and effectiveness. Four ongoing clinical trials are collected in this review (NCT00734682; NCT02340156; NCT00769093; NCT00313599), but only one of them is in Phase II, while the rest are still in Phase I. The Nps studied are, respectively, Nanoliposomal CPT-11 (liposomal irinotecan), SGT-53 (complex of cationic liposome encapsulating a normal human wild type p53 DNA sequence in a plasmid backbone), Temozolamide (as chemotherapy agent), Ferumoxytol (an iron oxide nanoparticle) and Paclitaxel (as anti-tumor drug).

Of all these possibilities of formulations, we have chosen the study of the liposomal technology, given its potential application as a complementary therapy to hyperthermia.

3. Liposomes

Liposomes are early examples of cancer nanotherapeutics. They are vesicles made of an outer phospholipid membrane surrounding a water core. Its structure, very similar to those found in cell membranes, can carry lipophilic substances inside the targeted organ, like the brain.

Chemotherapeutic agents or radiosensitizers can be transported inside the liposomes, and various methods for the encapsulation of doxorubicin into liposomes have been described.[14] Since 1995, formulations with doxorubicin have been used for the treatment of Kaposi's sarcoma, breast cancer and refractory ovarian cancer,[15] and in the last 10 years its application has been extended to more cancer indications, as in the case of GBM.

Systemically administered liposomes are cleared rapidly and have poor therapeutic efficacy, so special preparations such as pegylated liposomes are needed to make the pharmacokinetic profile more favorable. To facilitate their transport through BBB, conjugated agents, such as coating of Nps with polysorbate (Tween) surfactants,[16] or transport by receptor mediated transcytosis and/or endocytosis,[17] can be used.

Human IL-13-conjugated liposomes enable specific binding to GBM-cancer cells overexpress the IL-3 receptor and uptake of the liposomes via endocytosis. The therapeutic potential and targeting efficacy of IL-13-conjugated liposomes carrying doxorubicin has been tested in vivo in a mouse model to find a significant reduction of the tumor volume compared with animals injected with non-targeted liposomes.[18] Another way to direct the liposome towards the tumor target is by labeling it with an antibody. The use of Anti-EGFR inmmunoliposomes has been tested in rats with GBM that overexpress EGFR and an efficient release of the targeted drug has been observed.[19] From these examples, it can be deduced that the possibility of labeling liposomes to new specific GBM markers offer a wide enough range to improve the specificity of anticancer drugs.

4. Thermosensitive liposomes (TSL)

Liposomal drug bioavailability can be improved by the heat-triggered release from thermosensitive lipid vesicles. These liposomes are able to remain stable in the bloodstream at physiological temperatures and to release the drugs they contain effectively in response to hyperthermia (HT).

Yatvin et al. proposed HT for drug delivery in 1978. They designed liposomes consisting of thermosensitive lipids DPPC (Dipalmitoilphosphatidilcholine) and DSPC (Distearoylphosphatidylcholine), undergoing gel-to-liquid phase transition at a temperature of around 44 °C, causing the releasing of entrapped hydrophilic drugs.[20] The first heat-triggered release formulation of doxorrubicina and low-temperature-sensitive liposomes (LTSL) with pharmaceutical development is called Thermo Dox®. Needham and Dewhrist developed its clinical application[21] and subsequently two clinical trials have been carried out (a Phase II trial in combination with local mild HT for patients with recurrent breast cancer of the chest wall,[22] and a Phase III trial combined with thermal ablation in patients with hepatocellular carcinoma[23]). Although the information provided by these studies is still limited, side effects have been observed in patients, including leukopenia, alopecia, asthenia, nausea, anorexia, and fever. The heat-induced release in the tumor region in combination with the intrinsic instability of LTSL formulation results in large quantities of LTSL-released free drug in bloodstream which is responsible for the occurrence of systemic side effects.

Thus, as mentioned above, they have studied thermosensitive liposomes conjugated with other substances (e.g. DPPGOG,[24] pegilations[25] or Brij-surfactants[26]) that enhanced its stability in the systemic circulation without compromising the rapid heat-triggered release in the tumor area.

Despite this, further investigation on targeted thermosensitive liposomes and their specificity is needed. Several groups have started to design ways of targeting TLS to apply them with a heat trigger to enhance intracellular drug release to their molecular targets. In the article by Bilyana et al., they are classified into three groups: peptides attached to PEG, antibodies conjugated to PEG and cationc lipids in the lipid bilayer.

On the other hand, if the heated area is very extensive, it may promote the release of the drug into the blood or in areas far from the tumor. This can happen even if the liposome is well targeted because the rest of the drug, which is not bound to its receptor, may cause toxicity in healthy tissue, yet improving hyperthermia modalities to confine the heat in strategic points of the tumor could solve this problem. Oncothermia can be a good approach for this issue, as will be discussed below. But first, we are going to do a review of the characteristics of hyperthermia.

5. Hyperthermia (HT)

The concept of hyperthermia as a medical term refers to the increase in temperature in the human body as a cause or con-

sequence of suffering from a disease (fever). However, when we talk about hyperthermia in terms of anticancer therapy, it refers to the induction of an intentional increase in temperature in the organism seeking antitumor effects or radio-chemo enhancers in the tissue. William Coley was the first to find evidence of the relationship between a bacterial skin infection and cancer regression in sarcoma patients in 1891.[27] He tried to reproduce this phenomenon by inducing fever in the patient by administering a toxin (Coley's toxin) to produce antitumor response. Since then, safer and more effective types of hyperthermia have been developed either singly or in combination with conventional therapy.

Depending on the extent of the temperature rise in the body, it can be differentiated between whole-body, regional and local hyperthermia. Whole-body hyperthermia produces a temperature rise throughout the body, and it is often used in cases of metastatic cancer, being administered by the application of hot water blankets and thermal chambers. Regional hyperthermia consists in the perfusion with heated liquid or blood extracted from the patient and heated ex vivo into an artery supplying the tissue containing the tumor[28] (e.g. peritoneum or limbs). The disadvantages of these techniques are the low specificity of the treatment and the greater severity of adverse effects such as gastrointestinal disorders, myocardial ischemia, thrombosis and heart failure. In addition, regional hyperthermia is invasive and it can cause various complications such as secondary infections, tissue lesions, etc. regardless of the complexity of the technique to carry it out.

Conversely, local hyperthermia is focused on the tumor, so its selectivity increases and the side effects decrease. Depending on the invasiveness and the intensity of the heating, we can differentiate the thermoablative or sub-ablative modality. With thermoablation, the temperature rise is high enough and fast enough to cause immediate cell death, extensive cell necrosis mediated by protein denaturation and loss of function of other biological molecules, and tissue coagulation. It is a radical technique but, unfortunately, due to the difficulty of the precise control of hot spots within the tumor, the chances of a tumor remnant responsible for the subsequent recurrence are increased. By contrast, sub-ablative heating or mild hyperthermia results in increased temperature, usually to 40–45 °C, in the tumor and surrounding normal tissue where a series of chained subcellular processes occur, rendering the cells susceptible to various forms of damage leading to subsequent cell death.[29] Again, there are many ways to achieve this effect: one way is locating applicators within the tumor parenchyma, in which heat sources are introduced. Another way is placing metal antennas (small piece that absorbs radio-waves and consequently heats-up) in the tumor prior to submission to an external magnetic field, so the heat is generated inside the tumor and can be controlled easily by adjusting the strength of the magnetic field. These modalities are also invasive and produce a very heterogeneous heat distribution. Besides, the latter requires a large investment of money because of the requirements for special electromagnetically shielded rooms and compliance with other regulations.

External heating can be achieved either with electromagnetic (radiofrequency, microwaves, infrared) or acoustic waves (ultrasound), in which interferences of waves are exploited to enable heating of deeply located target regions and focus the heat to a predefined target volume. In the current clinical practice of hyperthermia, the most widely used method would be that of external hyperthermia using radioactive electromagnetic waves.

The cell death that occurs with the temperature rise in the range of 39–45 °C increases with the time of exposure. However, the use of hyperthermia as monotherapy is not a therapeutic strategy effective enough in clinical practice. The main benefit of mild hyperthermia is the enhancement of anti-tumor effects of radiation and chemotherapy without resulting in increased toxicity, which has contributed to a better control, cure and/or palliation.[30]

Thermobiological properties of hyperthermia[31] are (a) protein denaturation (nuclear proteins are the most sensitive), (b) increased sensitivity of hipoxic nutritionally deficient cells in low pH by increasing perfusion of tumors, (c) inhibition of DNA radiotherapy-induced damage repair, (d) sensitization of the "s" phase cells, (e) enhanced free radical production, (f) induction of the heat shock proteins HSP, (g) inmunomodulation. All these characteristics are excellent complements of conventional therapies, leading the tumor cell to mitotic catastrophe, induction of senescence, apoptosis, and necrosis.

HSP deserves a special mention. They are ubiquitous proteins involved in general cellular stress response and they play an important role as an antineoplastic in the extracellular medium and inside the tumor cell, having a protective effect stabilizing the damaged proteins. They are involved in immunomodulation induced by hyperthermia and in their contribution to the production of inflammatory cytokines which activate CD8+lymphocytes and macrophages, besides shuttling immunogenic peptides onto major histocompatibility complexes (MHCs) for presentation to T cells.[32] Immunomodulation produced by HT occurs because it induces to immunogenic cell death, tumor phenotype and modification of the microenvironment, and inducing then to the activation of the immune system to produce a systemic response through the abscopal effect. Vasodilation and increased blood perfusion facilitates the passage of immune cells to the tumor site increasing contact with the tumor antigens.

6. CNS malignancies and HT

In 2014, William Lee did a review about the outcomes from human HT experiments in brain tumors.[33] It has been tested in some case reports, case series and in eight published trials.

A clinical trial conducted by researchers at the University of California, San Francisco, randomized 79 patients who received surgery, external radiotherapy and brachytherapy, with or without interstitial hyperthermia. The overall survival time was statistically significant in the "heat" arm (from 31% to 15% in 2 years).[34]

The conclusion drawn is that the application of thermotherapy in brain tumors is still in its infancy. Although it seems to be effective in combination with RT and QT, we must be careful with the interpretation of these results, since the wide variability of HT modalities (from implanted catheters to infusion of magnetic nanoparticles) used means that the mechanism of action is not well understood. In

addition, these studies have been limited in their scope and some have reported complications in some patients (e.g. increased intracranial pressure and necrosis).

7. Modulated-electro-hyperthermia (mEHT; trade name: Oncothermia®)

In electromagnetic hyperthermia, not only heating process by temperature increase occurs, but also the energy absorbed has electromagnetic effects. The physiologic regulations of blood flow, lymph network, and nerve system depend on the temperature. It has been shown that increasing the temperature can cause vasoconstriction in certain tumors, leading to decreased blood perfusion and heat conduction while causing vasodilatation in the healthy tissues leads to increased relative blood perfusion and heat conduction in this region, providing an effective heat trap,[35] which is responsible for the chemo- and radiosensitization of the tumor.

The absorption of energy by the tissues varies according to the frequency of the wave, due to the heterogeneity of structures and interconnected materials of which it is composed. The most commonly used frequency (the medical standard) is 13.56 MHz; it especially selects the lipids membranes, transmembrane proteins and rafts.[36] In this way, the radiofrequency currents could create hot-spots in nanorange at the membrane rafts, which could be heated high quickly. These spots heat up the complete cell, which heats up the tumor itself at a mild temperature.

Modulated-electro-hypertermia is a new technology of HT which benefits from the differences between malignant and healthy cells, delivering in consequence the required energy in a more accurate way. The selection is made by (1) the concentration of ionic metabolites (Warburg effect),[37] (2) dielectric constant (cellular connections) in the immediate vicinity of the malignant and healthy cells (Szentgyorgyi effect),[38] (3) frequency dispersion specialties of cellular membranes (Schwan effect),[39] and (4) structural differences between the malignant and healthy tissues (fractal physiology).[40]

As in the case of conventional hypertermia, Nanothermia kills the cells by apoptosis and induces a damage associated molecular pattern by the apoptotic bodies.[41] The action on the membrane rafts causes the release of Calreticulin and HMBB1, the membrane expression of HSP70 and HSP90, and the expression of the DR5 death receptor. This pattern leads to immunogenic cell death, which could lead to the bystander and abscopal effect.[42]

Nanothermia has multiple clinical studies, mainly in the Phase II category. Some special results are published for gliomas.[43–45] with good results and a low toxicity profile. However, none of them has been tested using nanotechnology to enhance the result.

8. Discussion and conclusions

GBM remains a challenge to its therapeutic management because there is no curative treatment available. It is necessary to keep looking for a more definitive therapy along with the development of current therapies, such as the improvement of drugs-delivery methods. Most of them are tested in two types of animal models, with brain tumors implanted intracranially or subcutaneously. This may not reproduce well the results in the clinic for human patients, but at the very least, they can establish the bases for the future clinical trials in human patients.

The main problem of treatment of GBM is the difficulty of penetration of drugs through the BBB, the heterogeneity and wide tumor spread, and the formation of aberrant vessels that generate hypoxia and, therefore, chemo-radioresistance.

In this scenario, nanotechnology has given new hope to the treatment of these tumors as it achieves improvements both in the diagnosis and in drug-delivering, as we have detailed throughout the article.

We have focused on reviewing studies on the combination of nanoparticles, such as thermosensitive liposomes and the electromagnetic mild HT. The thermo-labile liposomal chemotherapeutic agents could help in reducing the generalized toxicity of the chemotherapy drugs by selective drug delivery at the tumor site. Also, nanoparticle mediated hyperthermia could be effective against cancer stem cells, since both its radio- and chemoresistant condition are key factors to the potential tumor cure.

In the literature there is little knowledge about those combined treatments for brain tumors, and most of them are related to the use of metallic nanoparticles under a magnetic field as HT production. As mentioned above, the use of magnetic fields requires a large investment of money due to the need of special electromagnetically shielded rooms and compliance with other regulations. In the area of patients belonging to my hospital, the chances of accessing this type of treatment are practically nonexistent, since I do not know of any facilities with such equipment. However, a new oncothermia clinic has opened in Granada, so the accessibility is much higher and hence my interest in the study of electromagnetic mild HT.

Regarding the publications that fit the search criteria described above, the oldest one was published in 1996, where the authors investigated the antitumor effect of thermosensitive liposomes containing cisplatin (CDDP) combined with HT on rat malignant glioma.[46] Brain tumor heating was administered by means of a radiofrequency antenna designed at their institute, reaching the temperature above 41 °C. After a 15-minute heating period, CDDP–liposome or free CDDP was injected into the rat via the tail vein at a dose of 6 μg/g; heating was continued for an additional 15 min. They concluded that the treatment is very effective in direct thermal killing of tumor cells and targeting of CDDP–liposomes to the tumor site and effective release of liposomal CDDP (with greater activity than when free CDDP was injected) while the surrounding normal brain tissue remains intact.

Two recent articles published in 2014[47] and 2016[48] by researchers at the University of Taiwan have found that focused ultrasound hyperthermia (UH) enhances the delivery and therapeutic efficacy of pegylated liposome doxorubicin (PLD) for brain metastasis of breast cancer in a murine model. They defend that the UH not only could heat brain tumors but also could make BTB more permeable for the PLD delivery into the sonicated brain tumor region.

Regarding these articles, it seems that nanotechnology is a very helpful device for treatment of the CNS-related diseases. Beyond the traditional effects of hyperthermia, nanoparticle-mediated hyperthermia can improve effectiveness in cancer therapy (from disruption of microvasculature to sensitization of recalcitrant cancer stem cells to radiation). Accordingly, the quick addition of this therapeutic modality to the oncologist's repertoire should be considered as a priority.

However, in the review conducted by William Lee about thermotherapy gliomas, it appears that no trials have been executed combining radiofrequency mild HT with nanoparticles such as TSL. None of the publications reviewed combine Nps, HT and RT. Until the coming studies show a good release profile of the drug specific and adequate toxicity profile, caution should be exercised when using these combinations.

It is true that, despite the potentiality of HT as a therapeutic weapon in the hospital, it has not been adequately exploited clinically. There are several reasons for this: historical methods of achieving global hyperthermia were cumbersome, non-standardized and nonspecific. There is a great variability in the modalities of application of HT so its mechanism of action is not well established. In addition, some of them are invasive, expensive and difficult to access techniques.

Since the beginning of this century, there has been a resurgence in hyperthermia with a renewed interest in redefining the biological rationale of hyperthermia, immunomodulation at higher temperatures along with the availability of better hardware and software permitting safer and more effective hyperthermia treatment delivery.[49] These developments make hyperthermia a potent and viable complement to the existing treatment modalities in future oncology management.

As in other treatment modalities, such as chemotherapy and radiation, hyperthermia is most effective when confined to the tumor. In this sense, MEHT is a new technology which provides high specificity towards tumor cells versus healthy ones, as commented.

Therefore, a new hypothesis arises from this knowledge, namely that the combination of highly selective hyperthermia, such as MEHT, in combination with nanoparticles, like TLS, should improve the effectiveness and toxicity profile in the treatment of brain tumors by increasing their accuracy in the tumor tissue.

In conclusion, the objective of this article is to encourage researchers to start a new line of research relating MEHT and TLS, since their development could represent an essential breakthrough in the fight against cancer.

Conflict of interest

None declared.

Ethical approval

The study has been approved by the provincial Biomedical Research Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. For this type of study formal consent is not required. Details that might disclose the identity of the subjects under study have been omitted.

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