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# Recent Developments in the Use of Magnetic Fluid Hyperthermia on Glioblastoma Multiforme Disease

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**ABSTRACT**

The first evidence of the efficacy in the cancer treatment of hyperthermia, therapy focused on the heating of tumor masses to kill cells and tissues, went back almost a century and a half. One of the most promising techniques for increasing the cells and tissues temperature is based on the use of magnetic nanoparticles dispersed in concentrated colloidal suspensions and stimulated by an external alternating electromagnetic field, known as Magnetic Fluid Hyperthermia. Recently this technique has been used as coadjutant treatment of the most applied chemo and radio therapies in a series of different tumors, but in particular for Glioblastoma Multiforme till to clinical trials level. In this work, we report some of most significant progresses regarding the use of Magnetic Fluid Hyperthermia on Glioblastoma Multiforme disease published in literature during the last year, describing the more interesting outcomes for potential future clinical applications.

**Abbreviations:** HT: Hyperthermia, RT: Radiotherapy, EM: Electromagnetic, GM: Glioblastoma Multiforme, SAR: Specific Absorption Rate

## Mini Review

Hyperthermia (HT) is a therapeutic technique based on the heating of tumor cells and tissues up to temperatures between 40 and 45 °C [1] in order to kill them. At those temperatures a number of serious cellular events like protein denaturation [2], damages to the cytoskeleton [3], impairment of certain DNA repair processes [4], changes in cell membrane permeability and stimulation of the immune system [5] occur. It is well-know that temperatures above 4 °C can cause coagulation and vessels may collapse resulting in necrosis or apoptosis [1,6]. These effects are quite different from cell to cell and appear more pronounced in tumor cells and tissues mainly owing to their acidic microenvironment. Generally, cellular cytotoxicity induced by HT results strongly increased when cells suffer additional damages caused by chemo (CT) and Radiotherapy (RT). The synergy between HT and the more traditional cancer treatments has been extensively reported in literature [1,7].

Phases II and III clinical trials proved significant outcomes when HT was combined with RT [8-11]. As an example, a complete response increased from 38.1% with RT alone to 60.2% with HT and RT in locally recurrent breast cancer [9], from 39.6% to 62.5% in head and neck cancers [10], and from 48-58% to 72–83% in primary cervical cancer [11] has been reported. Magnetic Fluid Hyperthermia (MFH) is a quite recent kind of HT treatment based on the use of Magnetic Nanoparticles (MNPs) as agents able to release heat when activated by an alternating Electromagnetic (EM) field of appropriate frequency and amplitude. At this aim, generally stable colloidal suspensions of MNPs in liquid media [12] are commonly used. In principle, MFH offers advantages in comparison to the more traditional HT treatments. In fact, the huge number of MNPs present in the suspensions assures an excellent heat release power allowing MNPs to reach the tumor tissues directly by local injections or simply through the blood circulation [13] without surgery.

In recent years, many MNPs differing for magnetic properties and structure have been studied and characterized for MFH applications [14]. In particular, iron oxide MNPs, of magnetite ($Fe3O_4$) and/or maghemite ($\gamma$-$Fe_2O_3$), resulted very promising systems because of their biocompatibility, their heat release capability, their excellent magnetic properties and also the easily to be synthesized with sizes and shapes very well-controlled [15]. Here, we report on the more recent developments concerning the application of MFH therapy to the treatment of the Glioblastoma Multiforme (GM) disease, one of the most severe and dangerous cerebral tumor forms. In the past years, MFH has just been applied in clinical trials on GM suffering patients. Jordan and co-workers [16-18] proved the feasibility of MFH therapy from a technical point of view on GM patients operating with alternating magnetic fields of 2-15kA/m amplitude and 100kHz frequency and using 12nm magnetite MNPs coated with aminosilane directly injected in the tumor masses at high doses (ca. 30mg/$cm^3$ of tissue).

In these studies, significant benefits on GM suffering patients were reported only when MFH was applied in combination with RT according to a well-defined protocol. In phase I and II clinical trials, Maier-Hauff and co-worker [19] studied the efficacy and tolerability of the MFH and RT combined treatment on patients suffering of recurrent GM disease using the same protocol proposed by Jordan and co-worker. In these studies, a median overall survival of 13.4 months in 59 patients was obtained, substantially longer than the typical six months median survival noted in such patients [20]. Moreover, the therapy was well tolerated without serious side-effects and post-mortem analyses noted that MNPs were mainly confined to areas of tumor necrosis [21].

## Basics and Limitations of MFH

The MNPs capability to release heat, after their activation by an external alternating EM field, is exploited in MFH therapy to reach hyperthermic temperatures in tumor cells and tissues. The MNPs energy absorption processes and thus their heating essentially depend on their electric permittivity ε and magnetic permeability μ that result to be strongly dependent on the applied frequency f and the field amplitude H. As a consequence, the external EM field parameters must be carefully chosen in order to optimize the MNPs heating performances and, at the same time, to preserve healthy tissues and patient comfort during the MFH treatment. Biological tissues are typically characterized by high electric permittivity values and so unwanted eddy currents, which released power is proportional to the square of (H·f·D) with D representing the eddy current loop diameter, can be generated in the tissues resulting in non-selective and uncontrolled heating.

The nanometer dimensions of MNPs allow to minimize these undesirable effects. In practice for the MFH clinical applications, limitations to EM field parameters, f and H, are also strongly advised. Typically, the frequency f is recommended to be in the range 50 kHz < f < 1MHz, because of increasing the frequency deleterious physiological responses, such as muscle stimulation, cardiac stimulation and arrhythmia [22] can occur. The EM field amplitude H must be also limited considering that the eddy current dissipation depends on the product H·f. Generally, H values under 15kA/m are recommended. In order to optimize the tumor cells and tissues heating processes and thus performing a more efficient MFH treatment, the magnetic properties of the MNPs must also be seriously evaluated. Ferromagnetic (or ferrimagnetic) nanoparticles, that exhibit a superparamagnetic behavior at physiological temperature and with dimensions below a critical size, typically few tens of nanometers (the so-called single domain size) are the most promising MNPs for MFH applications at clinical level.

In fact, these MNPs are characterized by a not persistent magnetization that relaxes to zero with a characteristic time, namely Neel relaxation time τN, depending on the ratio between the magnetic anisotropy energy of the system and the thermal energy. The heating mechanism to be considered is thus mainly due to the magnetic energy losses of the MNPs, occurring when the magnetization is not able to follow synchronously the external EM field orientation. The process efficiency results to be depending on the product between the effective relaxation time of the system, namely τeff defined as $1/\tau eff = 1/\tau N + 1/\tau B$ where τB represents the well-known Brownian relaxation time (depending on the MNPs hydrodynamic volume and on the colloidal suspension viscosity) and the external EM field frequency. The capability of MNPs to release heat can be directly measured by calorimetric experiments by means of the calculation of the so-called Specific Absorption Rate (SAR) parameter defined as: $SAR=(\Delta T/\Delta t)\cdot c$, where $\Delta T$ is the temperature increase measured in the time range $\Delta t$ and c the sample specific heat.

It is worth noting that, as above described, MNPs energy absorption is strongly related to the external EM field parameters. As a consequence, SAR values reported in literature often are hardly comparable to each other since they are calculated by experimental data obtained using different EM fields and frequencies.

## Very Recent MFH Applications on GM Disease

In 2020, some interesting studies concerning the application of MFH therapy to the treatment of GM disease, at preclinical level but potentially promising for future clinical applications, have been reported in literature. The more significant outcomes described in these works have been briefly reported in the following. Benyettou and collaborators [23] developed a novel nano-object (γ-SD/PLL) constituted by porous imine covalent framework (nCOFs) particles loaded with the anticancer drug Doxorubicin (Dox), coated with magnetic iron oxide nanoparticles and stabilized with a shell of

poly(L-lysine) cationic polymer (PLL) for synergistic MFH-CT applications. *In vitro* experiments demonstrated both an efficient cell-uptake ability and how the γ-SD/PLL pH responsivity allows Dox release selectively in acidic conditions (pH 5.0), mimicking the cancer cell environment, while limited drug release under physiological conditions is observed. Furthermore, γ-SD/PLL resulted to be a very efficient MFH agent. Temperatures till to 48 °C upon stimulation of an external alternating EM field were obtained, thanks to the nCOFs porous structure that facilitates the heat conduction.

*In vitro* tests on GM U-251 cells proved the γ-SD/PLL citotoxicity due to both Dox and MFH, while not significant effects were shown on HEK293 not cancerous cells. Finally, *in vivo* experiments on zebrafish embryos, during the early stages of development, a period of rapid cell division assimilated to tumor development, showed that γ-SD/PLL induced death, thus suggesting the potential of the novel developed nano-objects for MFH-CT treatments *in vivo* of GM and other diseases. Wang and collaborators [24] studied *in vitro* the effects of a combined MFH and CT treatment on GM U-87 and other cell-lines using previously developed and chemical and physical characterized dual pH and thermo-responsive superparamagnetic MNPs (MNC-DOX) coated with the P(DEGMA-co-PEGMA-b[TMSPMA-co-VBA]) polymer and loaded with the anticancer drug Dox. Histological assays and fluorescence microscopy images proved an efficient cell-uptake ability of the MNC-DOX nanocarriers.

Furthermore, without the stimulation of an external alternating EM field, the IC50 (half maximum Inhibitory Concentration) parameter of MNC-DOX resulted significantly higher than the one of free Dox MNPs thus indicating the potential to lower the systemic cytotoxicity in clinical applications. *In vitro* combined MFH and CT treatment on GM U-87 cells gave promising results, in fact, an almost complete cell death was observed. The MFH-Chemotherapy revealed significant synergistic effects that made the combined treatment much more effective than the CT alone. In the work, the effects of intracellular and extracellular MFH treatments have been also compared. Results showed that the MFH treatment after the MNC-DOX internalization is not required but preferable. The overall outcomes lead to the conclusion that the therapeutic efficiency observed, *in vitro* experiments, of the dual pH and thermo-responsive nanocarriers under the stimulation of an external alternating EM field, represents a first step towards *in vivo* and future clinical applications. Very recently, *in vivo* experiments aiming at evaluating the therapeutic effects of multiple (till to three) MHT treatments on a GM disease animal model have been carried out by Rego and co-workers [25].

The developed protocol consisted in the use of superparamagnetic, animosilane coated iron oxide nanoparticles (SPIONa) activated by an external alternating EM field. The EM field frequency and amplitude were been previously selected by the SPIONa heating potential determined by the SAR values calculated *in vitro* experiments on GM C6 cells. *In vivo* tests were performed on male Wister rats submitted to GM tumor induction. Bioluminescence, positron emission tomography and spontaneous locomotion evaluation techniques were used to assess the therapeutic effects of multiple MHT treatments. A slight tumor regression was observed after each single MHT treatment, but only after three MTH applications relevant and progressive improvements occurred and an almost total regression of the GM tumor was observed, paving the way for the use of this promising protocol in clinical trials.

## Conclusion

Recently MFH has been applied, mainly at a preclinical level, to the treatment of several tumor forms. A number of studies reported a significant therapeutic efficiency of the technique on different cancer cell-lines. Typically, the synergetic effects due to the combination of MFH with the more traditional cancer therapies, namely CT and RT, result in a treatment that is more successful than the sum of the single ones separately. Furthermore, clinical trials on patients suffering of different kinds of tumors such as prostate and breast cancers as well as GM have been carried out. At the present, some of them are still going on. Notwithstanding, MFH routine clinical adoption is still far to come, hampered by both practical and technical difficulties. In this work, we reported on very recent applications of MFH therapy to the treatment of GM disease, addressed mainly to the development, characterization and testing, at preclinical level, of novel and efficient agents for synergistic MFH-CT treatments potentially promising also for future clinical applications.

## Conflict of Interest

The authors declare no conflict of interest.

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