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Perspective of Magnetic Fluid Hyperthermia (MFH) for the Treatment of Tumor

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Abstract

The localized heating of tumor in Magnetic Fluid Hyperthermia (MFH) enables it to be a superior way of treatment than other conventional treatment of tumors. In combination with chemotherapy, radiation therapy and surgery, better results have been achieved and thus made it clinically approvable. This article introduces recent advances of magnetic materials used in magnetic fluid hyperthermia, factors affecting the performances of these particles and the future of this therapy.

Keywords: Tumor; Chemotherapy; Magnetic fluid hyperthermia

Introduction

According to World Cancer Report, cancer has become a major health problem accounting for 8.2 million deaths in 2012. One defining feature of cancer is the uncontrolled creation of numerous abnormal cells, which can then invade surrounding tissues of the body and spread (metastasizes) to other parts of body, the latter process is the major cause of death from cancer. Still, after decades of research and several clinical trials most forms of human cancer are incurable. Over the past several decades, chemotherapy, radiation and surgery have been the key components of cancer treatment. In recent years hyperthermia therapy and immuno therapy have gained some success. These treatments have their own merits and demerits. Chemotherapy is the use of drugs to destroy cancer cells. It prevents cancer cells from growing and dividing to many more abnormal ones. But chemotherapeutic treatment is nonspecific thus resulting in side effects; the cytotoxic drug destroys healthy cells along with the tumor cells [1]. Along with chemotherapy, radiation therapy is also widely used in the tumor treatments. Here high energy radiations are used to kill tumor cells or prevent the reproductivity of the cells. In the case of treatment of tumors with radiotherapy special care has to be taken, as exposure of radiation can harm healthy cells around the tumor cells. Further the treatment is performed at tissue or organ level and not at cellular level, thus the chances of harming the healthy cells increases [2]. Surgery is another conventional treatment for the tumor cells. It is the removal of the tumor tissues during an operation. Surgical treatment of cancer is much successful but it is difficult to perform surgeries on every part of the body like certain internal areas of brain, liver etc. Further surgical oncology becomes difficult in the case of metastatic environment. All these conventional treatments have limited accessibility and lack of selectivity of tumor cells. There is a need of approach that specifically targets the tumor cells. However, combining these therapies gives better results in the treatment of cancer [3].

Hyperthermia

Hyperthermia has a long tradition in medicine as in the treatment of various diseases. Hyperthemia (HT) in tumor therapy uses an external heat source to increase tissue temperature and kills tumor cells or restricts their further growth or makes these cells more exposed to the effects of radiation or anticancer drugs. Here the target tissue is subjected to temperature in the range 42°C to 46°C. Tumor cells have low tolerance to sudden variation in temperature this affects the performance of the cellular structure and finally kills it. Hyperthermia treatments can be classified as local HT, regional HT, whole-body HT on the basis of heat distributed to localized, deep inner located and discrete malignancies, respectively. Different techniques involving laser, ionizing radiation, microwaves, ultrasound, etc. have been used in hyperthermia based treatment of tumor cells [4,5].

Still, HT is unable to get into main stream cancer therapy, the primary reason is its inability to target tumor cells directly, it effects nearby healthy cells around the tumor ones. It is also insufficient in understanding the mechanism of hyperthermia cytotoxicity. It is difficult in using HT in certain deep-seated parts of the body like brain, bladder, etc. The bones of skull shield certain tissues and these leads to thermal under dosage in targeted areas which results in recurrent tumor growth. Urothelial bladder cancers are difficult to be treated by HT [6]. Treating malignant cells via HT is difficult. There is a need for treatment at cellular level, allowing localized treatments that are target specific there by not damaging nearby healthy cells. Nanotechnology has come with a solution for this problem with the introduction of magnetic nanoparticles in the treatment of cancer.

Magnetic Fluid Hyperthermia

Magnetic Fluid Hyperthermia (MFH), is expected to be a new breakthrough in cancer treatment, this uses MNPs in combination with heat. This treatment can treat tumors located deep in body parts like skull (gliobastoma) or the pelvis (prostate and cervical carcinoma) [7]. Moreover the treatment can be carried at cellular level than at the tissue or organ level, thus superior over other conventional methods used in the treatment of tumors. Successful *in vivo* experiments using mouse xenograft models have been carried out for MFH [8]. Oliveira

et al. have studied the feasibility of applying MFH for treating bladder tumors [6]. In a recent study it has been seen that bortezomib (a drug approved by the US Food and Drug Administration) along with MFH results in greater tumor death unlike other conventional methods [9]. Thus MFH promises to be an effective therapy in the treatment of human tumor. MFH has gained clinical approval in the European Union. In the treatment of glioblastoma new product NanoTherm was introduced which uses aqueous dispersion of iron oxide particles that is injected into the tumor [10].

Super paramagnetic iron oxides (SPIO) have great potential in biomedical applications. Iron-oxide based nanocrystalline core shell has been studied where the core is of magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) and shell is generally a polymer of silica, dextran, etc. Transition metal ferrites like (MFe_2O_4), where M is divalent metal ion have been used to prepare MNPs [9]. Nanosized Mn-Zn ferrite materials have been extensively studied over last ten years for its high specific absorption rate (SAR). Recently Au/Co nanoparticles with core-shell has been studied [1,4,10-12]. Surface functionalization of these nanoparticles plays an important role in biomedical applications [13].

In MFH, the nanoparticles are adhered to cancerous cells and are subjected to alternating magnetic field (AMF) and the temperature is brought to 42–46ºC. Activation of these nanoparticles can be controlled by external oscillating magnetic field. This is described by Neel and Brownian relaxation. It is associated with hysteresis loss from MNPs. In continuous oscillating, the particles realign themselves matching the field; energy used for alignment is dissipated when magnetic moments return to equilibrium position. This energy dissipation increases the bulk temperature of the NPs and its surroundings; this principle is used in MFH. SPIO particles are super paramagnetic have no net magnetic moment until they are placed in external magnetic field and thus can be easily controlled by external field [3,8]. The saturation magnetization should be high and the material should generate best temperature range with least number of particles. The electromagnetic radiation used is in the range of radio frequency and can penetrate deep into the body and are not harmful [4,14].

Size of nanoparticles plays a crucial role in MFH. Blood brain barriers do not allow large size nanoparticles to accumulate on the tumor cells located in the brain. Thus the particles accumulate at the the periphery and cannot reach the interior of tumor cells. Similarly high blood perfusion in lungs also result in rapid heat dissipation before the nanoparticles reach the temperature range and hence resulting in incomplete treatment of tumor cells. It is noted that NPs (<20 nm) are excreted by kidneys. For critically small sized NPs aggregation phenomenon can take place and which is undesired. However, aggregation of particles in liver, spleen can be helpful in treating tumors in liver and spleen.

The physicochemical properties such as particle size, shape, surface charge, hydrophobicity/hydrophilicity, stability in physiological environment such as pH, rate of blood flow, etc. has to be studied [15]. Biocompatibility and nontoxicity are important parameters to be taken into account. The particles have to be non-toxic and coated with biomolecules, antibodies, polymer to stabilize and attach them to target surfaces. The ligands at the periphery of the nanoparticles should completely attach to the target sites. These modifications are also seen for nanoparticles used in drug and gene delivery. SPIO ferro fluid have large surface to volume ratio and thus easily aggregate at target tumor tissues. Polymeric coatings that are biocompatible, stable in solutions, and which are easily attachable to various biological ligands must be chosen [16]. Thus for MFH magnetic particles should have properties like nontoxicity, injectability, biocompatibility, effective absorption of AMF energies, high aggregation and adhering in tumor region.

In concluding, though many obstacles remain to overcome, MFH constitutes a promising therapy in localized treatment of cancer. Size of the MNPs plays an important role in determining the effectiveness of the HT. If the sizes of NPs are made manageable, MFH will be a promising therapy in treating brain and liver tumors. Surface functionalization of the NPs is also a challenge for nanotechnology; NP surfaces should be coated with tumor specific biomolecules and must be highly adherent to the tumors. Improved biocompatibility and nontoxicity of the particles can introduce magnetic hyperthermia in main stream of cancer treatment. MNPs should have higher saturation magnetization and must be used in least amounts. It can be combined with chemotherapy and radiation for better results. Magnetic hyperthermia definitely has potential to be used in clinical application.

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