The Evolution of Vievs of in vivo Use of Nanoparticles for Tumor Treatment

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ABSTRACT

The main aim of this study was to evaluate in animal model new minimally invasive techniques of antitumor treatment - using nanoparticles as thermosensibilisators when undertaking the Ultra High Frequences (UHF) therapy.

Experiment attempts are made to create prototype of therapeutic system containing nanodevices and several functional structures: acceptor, effector, navigational.

Use of magnetic nanoparticles as modificators of a sensitivity of cancer cells to hyperthermia may have the potentially significant impact on clinical cancer therapy.

The prospect of receiving of successfully functioning nanoparticles consists of a balanced combination of sizes, functions and disguise mechanisms of this device.

Keywords: antitumor, sensitivity, nanoparticles, hyperthermia

1 AIMS

The second goal of the project was to research whether the combined use of nanoparticles and local hyperthermia can provide a more effective method of curing tumors than existing ones.

2 ACTUALITY

The methods of site-specific delivery of antitumor agents without the general and system consecuences remain to be actual because the need to reduce the negative effects of antitumor treatment. The more specific medicine delivery system is, the higher dose can be used without surrounding healthy tissues damage. It is true for hyperthermia as well.

3 INNOVATION

During the last decade numerous reports about the use of temperature factors [1-4] in tumor treatment have been published. However, only little data regarding modification of a cancer cells sensitivity to those factors, Hyperthermia in particular, is available [3-4]. Nanotechnology allows accurate placement of an ingenious device (nanoparticles) in tumors that can be heated to very high temperatures, thus destroying the tumor.

In present study the experiment attempts are made to create prototype of therapeutic system containing nanodevices and several functional structures: acceptor, effector, navigational.

4 MATERIALS AND METHODS

4.1 Nanoparticles design

Nanodevices (see Figure 1 for structure details) were used as modificators of tumor sensitivity to UHF therapy.

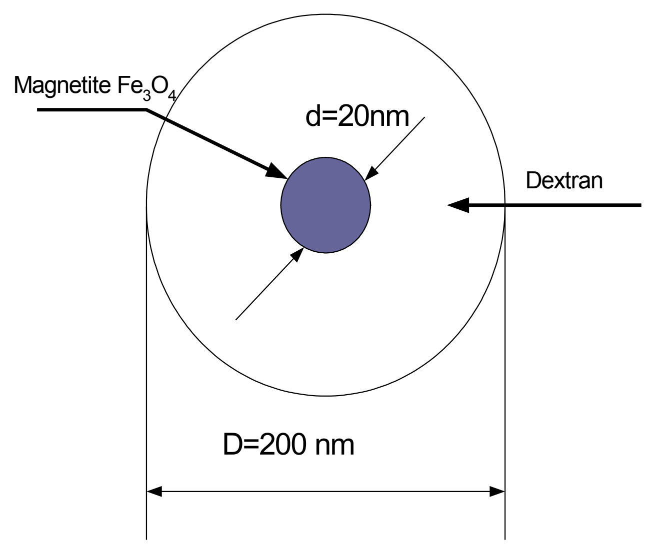

Figure 1. Structure of nanodevices used in study.

SPM image of the powder used can be seen on figure 2 [5]. The measurements were carried out in the air-operated SPM Solver P47 (NT-MDT, Zelenograd, Russia) using silicon cantilever as a probe for the sample surface testing. The cantilever parameters were the following: resonant frequency of 235 kHz, force constant of 11N/m.

The probe was scanned along the surface in a semicontact (tapping) regime and, during the scanning, both the relief and combined relief+ phase contrast signals were simultaneously registered.

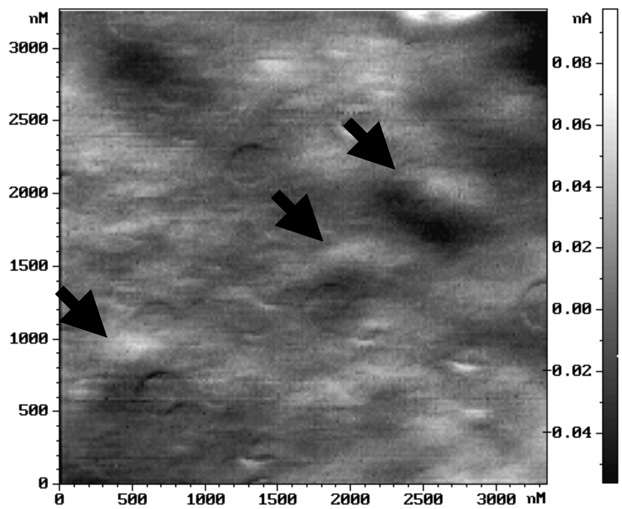

Figure 2. The 3.5×3.5 μm^2 SPM image of the sample surface registered in the combined (relief+ phase contrast) mode. Nanoparticles (marked by arrows) can be seen as protuberances with D=200 – 400 nm.

4.2 Preparation of the solution

The material explored was a dextran magnetite, which has a very low cyto-toxicity.

The preparation of the solution consists of 3 steps:

- a fabrication of the magnetite particles colloidal solution with beforehand given size;
- a fixing of dextran shells on colloidal particles of the magnetite;
- a fabrication of the solution (the pulp of dextran magnetite nanoparticle with mean size about 200 nm in polyglukine).

4.3 Stages of the experiment

For undertaking the studies electronic device "Metatom" was used (Fig. 3). The device referred has property of exciting UHF oscillations. The oscillations are conducted from the generator chassis through flexible cable to an antenna placed percutaneously into the tumor.

Five rats with tumors, inoculated on lateral surface of femur, by mass 150-200 g were used as a biological model.

All the rats were anaesthetized with droperidol and ketamin. The solution prepared (see section 4.2 for details) was injected into soft tissue (muscles of femur) in dose of 2 ml. Exposure time before antenna installation was 5 minutes.

Hereinafter antenna was entered into place of injection on depth about 3 centimetres and the session of hyperthermia was undertaken (Fig. 4). Duration of the session was 5 minutes, the temperature was increased to 45 - 55 degrees, the power delivered – 20 watts.

For control purpose we injected the same volumes of physiological salt solution into the contralateral extremities of the animals. The hyperthermia sessions on these extremities were conducted the same way as on the limbs affected by tumors.

All the animals were sacrificed and the tissues involved were subjected to standard histological investigations.

Figure 3. Electronic device “Metatom” – tool for intratumoral UHF hyperthermia.

Figure 4. Antenna is inserted into the rats limb. UHF hyperthermia in progress.

4.4 Mechanism of the action

UHF hyperthermia provides the heat at the site of the tumor invasively by applying an external alternating magnetic field to the magnetic particles at the tumor site. UHF oscillations produce electrical currents inside magnetite nanoparticles. The particles heat up and conduct the heat to the tumor cells.

The cells near the particles will be "burnt" by the heat produced by them.

4.5 Results of the histological investigations

Histological investigations were performed for all the rats after treatment. Figures 5-6 show the difference between UHF hyperthermia and UHF hyperthermia, modified by nanoparticles.

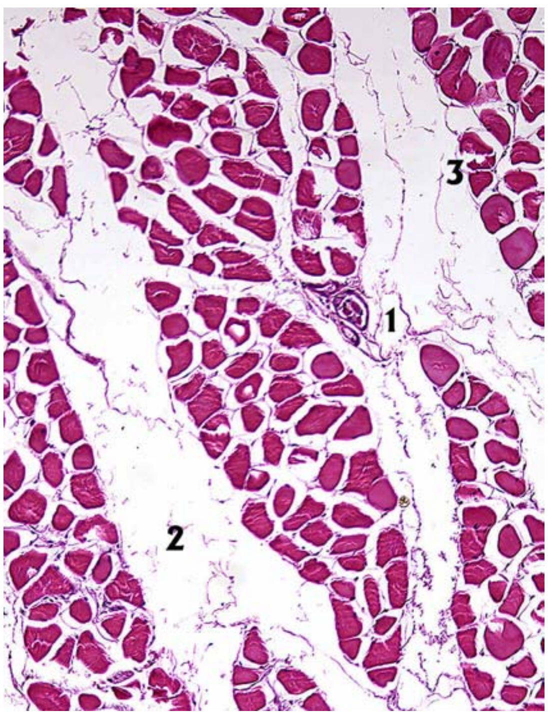

Figure 5. Histology of tissue after nanoparticles modified UHF therapy. Signs of irreversible damage. 1 – thrombosis capillaries; 2 - edema of interstitial connective tissue; 3 – muscle cell deterioration.

Histological investigations of tumorous and muscle tissues of animals which were subjected to nanoparticles injections before UHF hyperthermia showed the enormous edema of interstitial connective tissue (up to cystoid cavities formation), partial thrombosis capillaries in zone of lesion, hydropic swelling of a cells, necrosis of some muscle cells and loss of transverse striation. The structure of muscle fibers is seriously deteriorated by interstitial edema.

When compared to tissues impregnated with physiological salt solution these injuries are much more expressed.

Figure 6. Histology of tissue after UHF therapy without modification. No signs of irreversible damages.

5 CONCLUSIONS

The present work has demonstrated that:

- there is a sensitizer effect of magnetic nanoparticles probably caused by a significantly higher level of preferential heat induction into tumor tissue as compared to normal tissues not injected with pulp of dextran magnetite nanoparticle;
- the prototype system developed is capable of repeatedly and reliably administering focused thermotherapy targeting only tumor without damaging normal tissues.

Therefore, use of magnetic nanoparticles as modificators of a cancer cells sensitivity to hyperthermia may have the potentially significant impact on clinical cancer therapy.

6 PERSPECTIVES

The principal ability of dextran magnetite nanoparticles creation is proven. The combination may be injected into tissues and can control and modify the intra-tissue UHF hyperthermia. It is necessary to continue R&D activities to vary the sizes and characteristics of composite nanoparticles that will allow to intensify their antitumor action.

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