OC-34: Ultrasonic Nanomedicine in the Aspect of Therapy of Oncological Diseases

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In this paper the authors develop the concept of using solid-phase inclusions in biological structures, as the concentrators of acoustic energy for ultrasound therapy of oncological diseases. Particular attention is paid to possibility of synthesis of these inclusions directly in the tumor tissue. The validity of the hypothesis of solid-phase sonosensitization has been confirmed in animal experimentations.

Studies in which nanoparticles (micelles, liposomes, nanoemulsion, bubbles, etc.), introduced into the bloodstream, are the means of delivering drugs to the tumor, and ultrasound is a factor stimulating drug release, can be attributed to the ultrasonic nanomedicine.

The method of ultrasonic nanotherapy of malignant tumors, developed in this study, differs from those described in the literature by two statements: (i) nanoparticles and their aggregates are formed immediately in the tumor from a nontoxic and non-medicinal substance introduced into the blood flow as a solution; (ii) the ultrasound exposure on a tumor containing nanoparticle aggregates causes effects leading to inhibition of its growth and, in some cases, to its total remission.

As a result of the metabolic atypia, physicochemical conditions in the tumor (decreased pH, an increased content of calcium ions in intercellular liquid, etc.) differ from conditions in normal tissues surrounding the tumor. These differences result in the possibility of solid phase formation mostly in the tumor. The solid phase segregates in the tumor after intravenous introduction of solutions of compounds whose calcium salts or acidic forms are insoluble under tumor conditions. Thus, the selectivity of the formation of nanoparticles and their aggregates mostly in the tumor can be achieved using the least specific, hence, most stable symptoms of its atypia.

The ultrasound-induced therapeutic effect on the biological systems modified by nanoparticle aggregates is achieved due additional acoustic energy release in regions where these aggregates are localized. This occurs due to the fact that aggregates locally change the ultrasound absorbance, increasing the heat release and intensity of cavitation processes (Nikolaev et al., 2009).

The above considerations were put into the basis of the development of the method of ultrasonic tumor destruction in the presence of solid nanoparticles and their aggregates. We called the phenomena underlying this method and associated with the presence of the solid phase as the solid-phase sonosensitization, and nanoparticles and their aggregates as solid-phase sonosensitizers (SPSs).

At the Blokhin Russian Oncological Scientific Center, Russian Academy of Medical Science, the experimental possibility of applying the solid-phase sonosensitization effect to ultrasonic therapy of oncological diseases is preclinically studied over several years (Nikolaev et al., 2010). The experiments are performed on animals with various tumor types, different therapy schemes, and include estimation of the therapeutic efficiency, harmlessness, and the effect on metastatic disease. These studies showed a high therapeutic efficiency of the method, i.e., tumor regression by 75-80% on average with an increase in the animal lifetime by a factor to 2, good exposure tolerance, and the absence of the effect on metastatic disease.

Figure 1 shows the tumor growth dynamics in several experimental series using octasodium salt of cobalt octacarboxyphthalocyanine (theraphthal), octasodium salt of zinc octacarboxyphthalocyanine (ZnPc), and gold nanoparticles as SPS. We can see in Fig. 1 that the time of tumor size doubling in the experiments using SPS (τ_{SPS}) increases ten times in comparison with the control group (τ_C) and five times in comparison with the case of only ultrasound exposure (τ_{US}). This means that the therapeutic efficiency of ultrasound exposure in the presence of SPS significantly increases. Similar results were also obtained for other tumor types (carcinoma Ca755, Ehrlich carcinoma, and Lewis carcinoma). In therapeutic efficiency, these results were comparable to the results of treatment using optimum chemotherapeutic schemes.

Tumor growth inhibition and its complete remission in certain cases probably result from destruction of tumor cell membranes and cellular organelles. Figure 2 compares the electron micrographs of mitochondria of melanoma B16 tumor cells unexposed and exposed to ultrasound (0.88 MHz, 1 W/cm^2 + 2.64 MHz, 2 W/cm^2) in the presence of SPS nanoparticles (theraphthal). The experiment was performed on BDF1 mice. In the micrograph of tumor exposed to ultrasound, we can clearly see mitochondria with destructed membrane structures (cristae). Similar

defects of mitochondria were almost absent when using the same ultrasound exposure parameters without theraphthal.

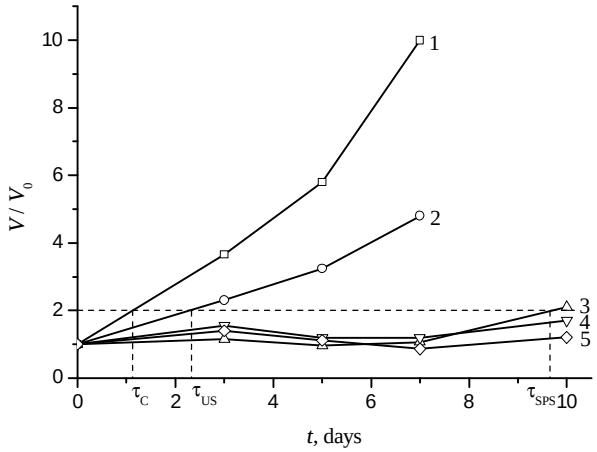

Fig. 1. Growth dynamics of tumors containing SPS after ultrasound exposure for BDF1 mice and melanoma B16 tumor. Conditions: simultaneous exposure to ultrasound of two frequencies: 0.88 MHz, 1 W/cm^2 and 2.64 MHz, 2 W/cm^2; the exposure time is 10 minutes at 40 °C; V_0 is the tumor volume to the beginning of ultrasound exposure, t is the time of observation of tumor volume V growth after ultrasound exposure. (1) control; (2) ultrasound; (3) theraphthal, 30 mg/kg + ultrasound; (4) gold nanoparticles, 7 mg/kg + ultrasound; (5) ZnPc, 12 mg/kg + ultrasound.

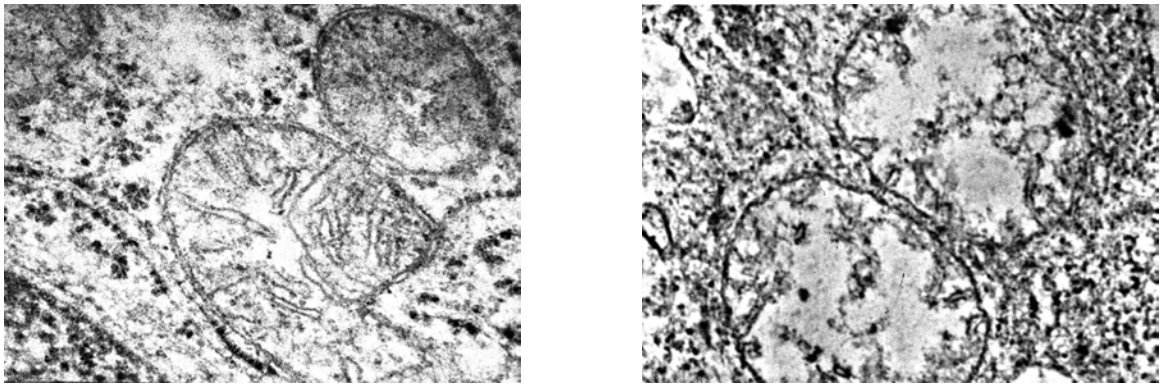

Fig. 2. Electron micrographs of mitochondria of melanoma B-16 tumor cells. Control (left) and ultrasound exposure in the presence of theraphthal nanoparticles (right).

Analysis of the results shows that nanoparticles of non-medicinal substances synthesized immediately in the tumor or injected intravenously are effective "amplifiers" of antitumor action of ultrasound.

References

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