An Influence of Constant Magnetic Field on the Electrical Resistance of Blood Serum of Cancer Patients during the Treatment with Nanocomplex and Electromagnetic Irradiation

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***Abstract* — The article describes a study of electric resistance in blood serum of cancer patient during the treatment with magneto-sensitive nanocomplex and irradiation by inhomogeneous constant magnetic and alternating electromagnetic field. The kinetics of electrical resistance in blood serum of cancer patient with magneto-sensitive nanocomplex non-linearly depends on the magnitude of constant magnetic field. Nanoparticles of iron oxide and Fe^{2+} ions have different kinetics of electrical resistance during the influence of constant magnetic and electromagnetic field. The results can be used for the improvement of the technology of cancer magnetic nanotherapy.**

Keywords — magneto-sensitive nanocomplex; electro-magnetic radiation; electric resistance; cancer; blood serum

I. Introduction

Magnetic nanoparticle (NP) hyperthermia is a well-known thermotherapy that has been recently shown to be effective in the treatment of brain tumors. Magnetic NP injected into tumors have been heated, depending on the particle size distribution and frequency range used, by a combination of Neel and Browninan type relaxation under the influence of an external alternating magnetic field. By raising the temperatures of tumor tissues above 42 °C, apoptosis can be induced, whilst temperatures higher 45 °C can directly kill cells [1].

Induction heating of magnetic NP embedded in cancer tissue, also called hysteresis heating, results from the interaction of the magnetic moment of the NP with external alternating magnetic field. On the other hand, interaction of external alternating magnetic field with tissue can produce heat directly, as with any electrically conductive material. The mechanism that dominates this type of heating results from the production of (electric) eddy currents producing heat [2].

However, there are a number of limitations of magnetic NP hyperthermia such as: (1) therapy by NP in the temperature range 43–70 °C can be accompanied by the formation of drug resistance due to the induction of heat shock proteins, (2) the temperature above 45 °C may shut down tumor tissue perfusion, and (3) targeted therapy with magnetic NP is often not suitable for disseminated and abdominal tumors [3].

To overcome the above problems, we have developed a new technology of magnetic nanotherapeutics during moderate hyperthermia below 40 °C inside tumor. New technology based on the use of NP loaded with anticancer drugs, and sent to the tumor site to destroy it selectively in combination with electromagnetic excitation. The concept of new technology is based on the well-known effect of the cumulative increase and unbalance of reactive oxygen species known as oxidative stress, play a role in the carcinogenesis and subsequent tumor growth. Low and moderate levels of oxidative stress facilitate the initiation and promotion of the cancerous cell, whereas, high levels of oxidative stress can lead to their apoptosis or necrosis. Cancer cells are then particularly vulnerable to an oxidative assault and induction of high levels of oxidative stress in tumor tissue that has the potential to destroy or arrest the growth of cancer cells can be thought of as therapeutic strategy against cancer. Furthermore, one of the known mechanisms of antitumor activity of anthracyclines, like doxorubicin (DOXO), is the generation of free radicals [4]. The local combined action of inhomogeneous constant magnetic (CMF) and alternating electromagnetic field (EMF) with magneto-sensitive nanocomplex (MNC) of DOXO and iron oxide nanoparticles in tumor initiated the splitting of electron energy levels undergoes a redox-cycling reaction during which superoxide and hydrogen peroxide are produced. Subsequently, iron ions can catalyze the generation of hydrogen radicals from hydrogen peroxide by Fenton-type reaction, the formation of which can break mitochondria, lipids, proteins, DNA and other structures in tumor cells and finally lead to apoptosis or necrosis. Cancer cells sequester iron to aid in proliferation so overdosing cells with iron may be a mechanism to inhibit cancer progression [5].

Our early experiments have shown the relationship between peroxide oxidation and electrical resistance of blood serum for cancer patients [6]. In recent studies have shown that antitumor activity of magnetic nanotherapy nonlinear depends on the MNC parameters [7].

Known effect called magnetoresistance is the property of a material to change the value of its electrical resistance when an external CMF is applied to it. This effect, found in ferromagnets, depends on the orientation of the magnetization

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with respect to the electric current direction in the material at room temperature [8].

The aim of this article is to study the effect of inhomogeneous CMF on the electrical resistance in blood serum with MNC of cancer patients during irradiation in vitro.

II. METHOD AND SUBJECT OF STUDY

In this work the electrical resistance was measured by the electrical circuit based on the Wheatstone bridge. Electrical resistance of 1 ml blood serum cancer patients with osteosarcoma (bone tumor) or other components was measured in the quartz cell at 20 °C consisting of the teflon holder and platinum electrodes to which was applied voltage 15 V [6]. The magnetic-dipole applicator was used for electromagnetic irradiation. It consists of the curved loop, magnetic flux dipoles (diameter - 2 mm, height - 40 mm and gaps between dipoles - 3 mm), permanent magnet and dielectric holder of the magnetic dipoles [9]. The first prototype of the apparatus "Magnetotherm" (Radmir, Ukraine) for medical treatment was used to generate alternating EMF producing eddy currents in serum blood with MNC [10]. The frequency of electromagnetic irradiation was 42 MHz with an initial power of 75 W (Fig. 1).

The MNC consisted of the NP Fe_3O_4 with KCl (International Center for Electron Beam Technologies of E.O. Paton Electric Welding Institute, Ukraine) with diameters in the range of 20–40 nm and antitumor drug doxorubicin (Pfizer, Italy) was processed in high precision magneto-mechano nanoreactor (NCI, Ukraine) [11]. The concentration of MNC in blood serum was 1.5mg/ml. Composition of MNC: DOXO – 0.5 mg/ml and Fe_3O_4 – 1 mg/ml.

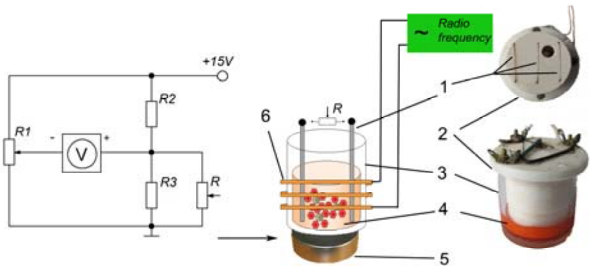

Fig. 1. The electrical circuit resistance measurement: 1 – platinum electrodes; 2 – teflon holder; 3 – quartz cell; 4 – blood serum with MNC; 5 – permanent magnet with magnetic dipole applicator; 6 – inductor; *R1* = 20 kOm, *R2* = 20kOm, *R3* = 100 kOm. *R* – resistance of blood serum in the quartz cell.

To differentiate the impacts of the effect of the NP and iron ions the iron (II) sulfate ($FeSO_47H_2O$) was used. The concentrations of iron (II) sulfate in blood serum was 1 mg/ml.

Kinetics of resistance can be approximated by an exponential function

$$R(t)/R_0 \approx 1 + \alpha\,(1 - e^{-t/\tau}), \quad (1)$$

where: cell resistance at the initial time for blood serum R_0 = 5.5 kOm; for distilled water - 9 kOm; for NaCl - 5 kOm; t – time (min); τ (min) and α (arb. unit) – parameters.

We used four types of the neodymium ($Nd_2Fe_{14}B$) permanent magnets (Table I) for localization of CMF in the blood serum. Spatially inhomogeneous structures of alternating and constant magnetic fields measured by magnetic sensor based on the Hall effect [12].

TABLE I. THE NEODYMIUM MAGNETS USED IN THE MAGNETIC-DIPOLE APPLICATOR

№	Adhesive force, kg	Diameter, cm	Height, cm
1	10	1.5	0.3
2	15	2.2	0.3
3	40	4.4	1.5
4	100	5,5	2.5

Constant magnetic field of magnetic dipole applicator was calculated according to the magnetostatic equations:

$$\mathbf{B} = \mu\mu_0\mathbf{H}, \quad (2)$$

$$\mathbf{H} = -\,\mathrm{grad}\,\varphi_m. \quad (3)$$

$$\mathrm{div}\,(-\mu\mu_0\,\mathrm{grad}\,\varphi_m) = 0. \quad (4)$$

where **B** is magnetic induction, **H** is magnetic field strength, which considered as potential field, φ_m is scalar magnetic potential, $\mu_0 = 4\pi\cdot10^{-7}$ N·A^{-2} is magnetic constant (Fig. 2).

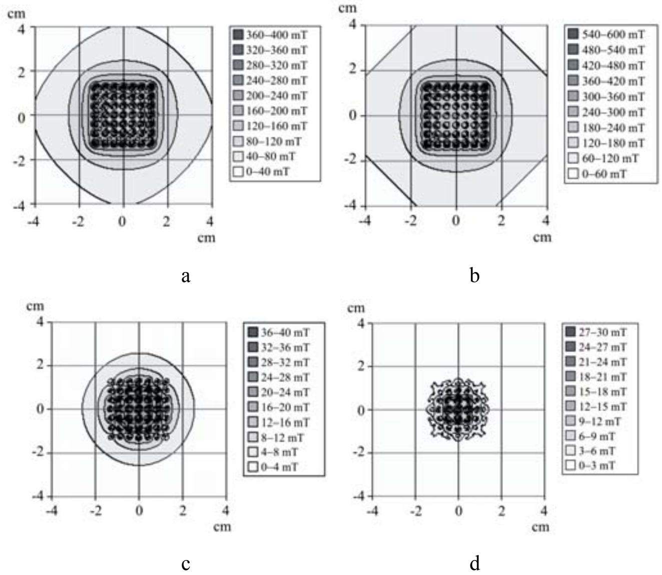

Fig. 2. The horizontal slice of static magnetic field for magnetic dipole applicator at a distance of 2 mm above the dipoles; permanent magnets: *a* –with adhesive force of 40 kg; *b* –with adhesive force of 100 kg; *c* –with adhesive force of 15 kg; *d* –with adhesive force of 10 kg.

A zero value of the magnetic scalar potential φ_m on the boundary of investigated region was chosen as boundary conditions. The problem in three-dimensional formulation was solved by the finite difference method using original software [13].

III. Influence of Inhomogeneous Constant Magnetic Field

The results of the influence of inhomogeneous CMF on the resistance of blood serum cancer patient with iron oxide nanoparticles and doxorubicin during electromagnetic radiation shown at Fig. 3 and Table II. Analysis of the results shows that maximum value of parameter τ = 7 min was observed when permanent magnet with adhesive force 15 kg was used, the minimum τ = 2.5 min was with magnet 100 kg. Magnets with adhesive force 15 and 40 kg have an intermediate value of the parameter. Parameter α changed similarly, but in the opposite direction. In general, it should be noted that the CMF influenced on the native state of electrical resistance within blood serum of cancer patient.

TABLE II. Changes in the resistance of blood serum for cancer patient under influency CMF+EMF+MNC

№	The adhesive force of neodymum magnet, kg	Parameters of the exponential function	
		α, arb. unit	*τ, min*
1	Without magnet	0.075	5
2	10	0.12	3.7
3	15	0.09	7
4	40	0.13	4
5	100	0.125	2.5

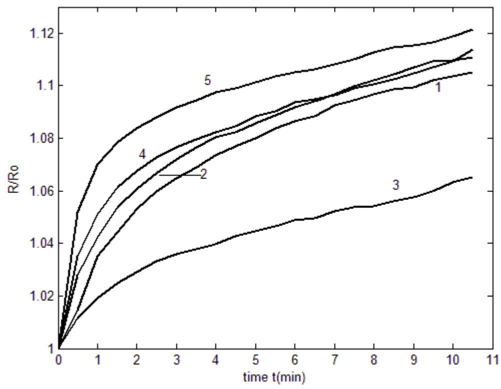

Fig. 3. The resistance kinetics in blood serum for cancer patient with MNC during electromagnetic radiation: 1– without magnet; 2 – 10 kg; 3 – 15 kg; 4 – 40 kg; 5 – 100kg.

IV. Differentiation effect of some physical and chemical factors on the resistance of blood serum

In order to quantitatively compare the effect of some chemical components on the resistance, we have conducted studies with distilled water and a physiological sodium chloride solution (Fig. 4–6 and Table III).

The changes in the resistance of blood serum for cancer patient under the influence of some endogenous and exogenous factors can be seen in Table III. It should be noted that resistance of distilled water had a negative parameters α that is, the value of R/R_0 decreased during electrolysis. On the contrary, the kinetics of the resistance of NaCl and blood serum was growing. The introduction of NP and the effect of CMF + EMF reduced the value of the parameter τ and the parameter α decreased in physiological sodium chloride and blood serum cancer patient.

An analysis of the results is also showed that CMF and EMF exposure initiated an increase of the parameter α in blood serum resistance in experiments with $FeSO_4 7H_2O$ and NP.

TABLE III. Studies of Resistance Kinetics for Blood Serum with Distilled Water and Physiological Sodium Chloride*

Sample	Parameters of the exponential function							
	NP				*$FeSO_4 7H_2O$+ CMF + EMF*			
	Without influence		*NP + CMF + EMF*		*Without influence*		*NP + CMF + EMF*	
	α, arb. units	*τ, min*	*α, arb. unist*	*τ, min*	*α, arb. units*	*τ, min*	*α, arb. units*	*τ, min*
Blood serum of cancer patient	0.18	3	0.09	2.5	0.08	2.5	0.16	2.3
Physiological sodium chloride	0.1	7	0.06	2.5	–	–	–	–
Distilled water	–0.33	4.6	–0.14	0.6	–	–	–	–

*CMF initiated by the neodymum magnet with adhesive force of 40kg

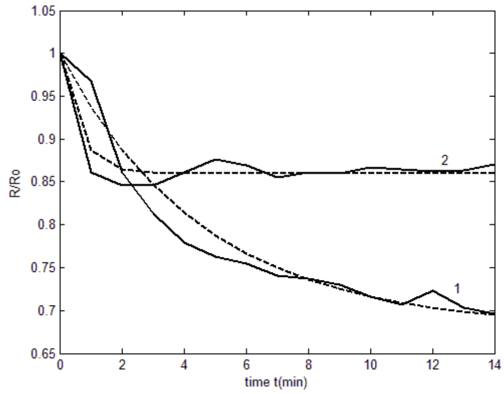

Fig. 4. Kinetics of resistance distilled water:1 – without influence, 2 – NP + CMF + EMF. --- approximated exponential function (2)

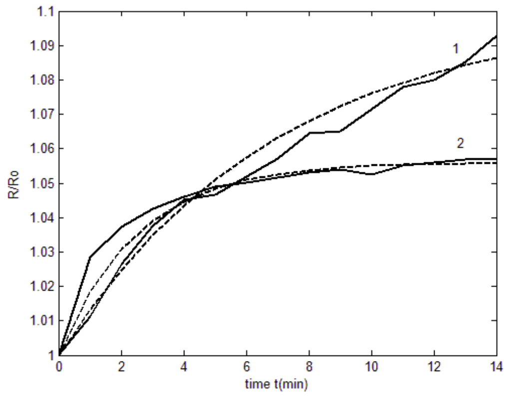

Fig. 5. Kinetics of NaCl resistance: 1 – without influence; 2 – NP + CMF + EMF. --- approximated exponential function (2)

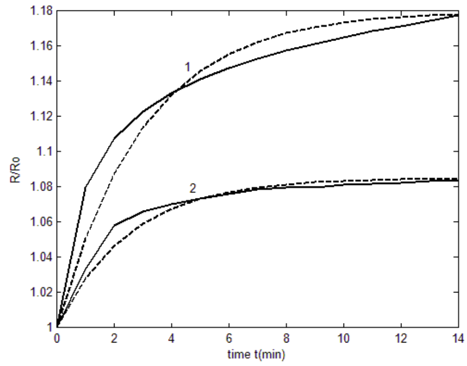

Fig. 6. Kinetics of resistance blood serum cancer patient: 1 – without influence; 2 – NP + CMF + EMF. --- approximated exponential function (2)

V. DISCUSSION

Based upon change of the resistance in blood serum of cancer patient under the influence of different inhomogeneous CMF during electromagnetic radiation we can suggest that the value of a constant magnetic field changes non-linear kinetics of resistance blood serum of cancer patient during magnetic tumor nanotherapy. The theoretical basis takes into account spin orbit coupling and band splitting [8]. Electromagnetic waves can change the electric resistance of the metallic NP and surrounding their molecules anticancer drug in the blood serum. Understanding the origin of the magnetic order and its coupling mechanism is essential for the development of new technological strategies to design magnetic nanotherapy suitable for spintronics applications.

The results show the effect on the change of electrical resistance of chemical and physical factors such as the distilled water and physiological sodium chloride solution with NP during irradiation by CMF and EMF. This is illustrated by well-known phenomena – reduction of conductivity for distilled water and increase in physiological sodium chloride solution. Conductivity is linked directly to the total dissolved solids [14].

In the study was shown the difference between the impacts of the effect of NP of iron oxide and iron ions Fe^{2+} on electrical resistance in the blood serum. We believe that this is due to the large size of NP and their increased redox activity.

A high-gradient spatially inhomogeneous CMF and EMF were used for cancer magnetic nanotherapy. The magnetic flux density was focused onto the region of the tumor by special electromagnetic localizers that were placed in contact with the surface of the tumor. The localizers initiated the attractive force exerted on magnetic NP in a blood vessel by a spatially inhomogeneous CMF during drug targeting. Attractive magnetic force $\mathbf{F}_{mag}$ can be evaluated by the equation:

$$\mathbf{F}_{mag} = (\chi_2 - \chi_1)\, V/\mu_0\, \mathbf{B}(\nabla B), \qquad (6)$$

where χ_2 is the volume magnetic susceptibility of the magnetic particle, χ_1 is the volume magnetic susceptibility of the surrounding medium, μ_0 is the magnetic permeability of free space, V is particle volume, B is the magnetic flux density, ∇B is CMF gradient. It is clear from this equation that in order to generate a force on the magnetic particle, the CMF must have a gradient. In the presence of a homogeneous field, the particle will experience no force [15].

Usually magnetic resonance relies on the counterbalance between the exceedingly small magnetic moment on a proton, and the exceedingly large number of protons present in biological tissue, which leads to effect in the presence of CMF and EMF. If a sample is placed in a non-uniform magnetic field then the resonance frequencies of the sample's nuclei depend on where in the field they are located. The effectiveness of magnetic resonance can depends on the magnitude of magnetic field gradient. Note that the electron spin magnetic moment is opposite to the electron spin while the proton spin magnetic moment is in the direction of the proton spin. During of magnetic resonance in water for ^{1}H protons Larmor precession frequency corresponds to a radio frequency field with $\omega_0/2\pi$ = 42.57 MHz. At 0.5 T resonance frequency for proton spins difference in water and fat is very small –73.5Hz [16].

NP are selectively taken up by the reticuloendothelial system, a network of cells lining blood vessels whose function is to remove foreign substances from the bloodstream. It is also notable that tumor cells do not have the effective reticuloendothelial system of healthy cells. This has been used, for localization in malignant lymph nodes, liver and brain tumors. MNC after internalization in cells establishing a substantial locally perturbing dipolar field which can leads to local magnetic resonance.

Tumor transplanted animals was subjected to irradiation of permanent magnetic and electromagnetic fields. The highest antitumor activity and survival rate of animals were observed after the treatment by MNC with larger magnetic moment of saturation, square of the hysteresis loop and lower coercivity. Intratumoral temperature does not exceed 38 °C. Inhibition of growth tumors according to the authors was result of influence of free radical reactions and electron transfer processes in the electron transport chain mitochondria on the basis of magnetic resonance effects in tumor tissues [7]. However, if NP is antiparallel, each spin polarization will scatter by the same amount, since each encounters a parallel and antiparallel once. The total electrical resistance is then higher than in the parallel configuration (small current) [8].

On the basis of earlier and described here studies in which is shown the principal possibility of influence of the CMF on the electrical resistance in the blood serum of cancer patient we propose hypothetical mechanism of electron and proton transport chain regulation in tumor tissues with MNC by constant magnetic field during electromagnetic irradiation (Fig. 7).

The anisotropic magnetoresistance effect in 3d transition metals depends on the orientation of the magnetization with respect to the electric current direction in the material. Since an electron's spin is directly coupled to its magnetic moment, its manipulation is intimately related to applying external magnetic fields. Generally, an electron current contains both up and down spin electrons in equal abundance. When these electrons approach a magnetized ferromagnetic NP, one where most or all contained atoms point in the same direction, one of the spin polarizations will scatter more than the other. If the ferromagnetic NP is parallel, the electrons not scattered by the first layer will not be scattered by the second, and will pass through both. The result is a lower total electrical resistance (large current).

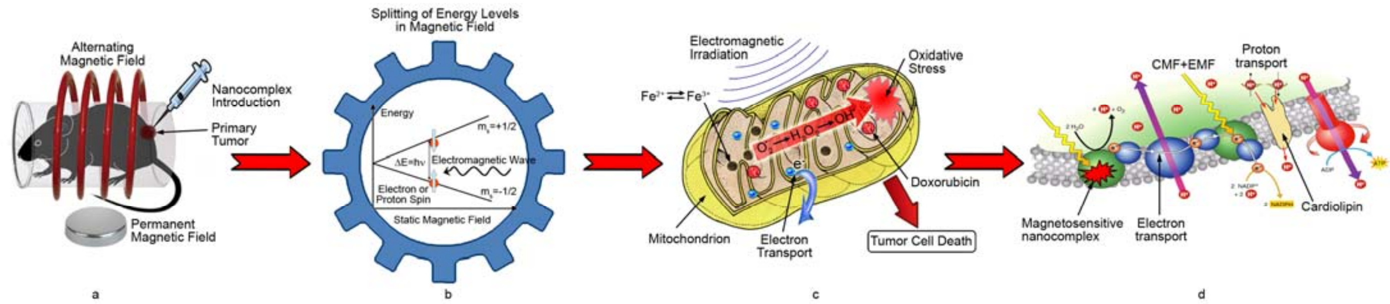

Fig. 7. Fig.7.Hypothetical mechanism of electron and proton transport chain regulation for the mitochondria in cancer cells with MNC by constant magnetic field during electromagnetic radiation: a – the local combined action of constant magnetic and electromagnetic fields and MNC in a tumor; b – magnetic resonance; c – oxidative stress; d –electron and proton transport deregulation

The electron and proton transport chain in cells consists of a spatially separated series of redox reactions in which electrons are transferred from a donor molecule to an acceptor molecule. The underlying force driving these reactions is the Gibbs free energy of the reactants and products. The function of the electron transport chain is to produce a transmembrane proton electrochemical gradient as a result of the redox reactions [17].

During CMF and EMF treatment of tumor with MNC irradiation can lead to a change of electron and proton transport in mitochondria and next could cause increased superoxide anion radical $O_2^{\bullet-}$ and H_2O_2 production initiating uncoupling activity in tumor cells and finally lead to apoptosis or necrosis [5].

CONCLUSION

Kinetics of electrical resistance of blood serum for cancer patient with magneto-sensitive nanocomplex non-linearly depends on the magnitude of constant magnetic field during electromagnetic radiation. The lowest growth dynamic of the blood serum resistance was observed under influence of magnet with adhesive force 15 kg. The kinetics of electrical resistance growth in blood serum under influence of magnets with adhesive force of 10kg and 40 kg was similar and slightly higher than without magnet. The highest growth dynamic of the blood serum resistance was observed under influence magnet with adhesive force 100 kg.

The serum, water and the physiological sodium chloride solution with nanoparticles during the influence of constant magnetic and electromagnetic fields have different kinetics of electrical resistance.

Nanoparticles Fe_3O_4 and ions of iron (II) sulfate also have different kinetics of electrical resistance during influence of constant magnetic and electromagnetic fields.

These results can be used for the improvement of the technology of cancer magnetic nanotherapy.

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