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ORIGINAL ARTICLE

THE EFFECTS OF COMBINED ACTION OF LOW-INTENSITY ELECTROMAGNETIC RADIATION OF THE MILLIMETER RANGE AND COMPLEXES OF ESSENTIAL AMINO ACIDS IN TUMOR-BEARING RATS OF OLD AGE

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ABSTRACT

Purpose of the study. Amplifying the effects of low-intensity modulated electromagnetic radiation (EMR) of the extremely high frequency range (EHF) on the tumor and adaptational status of old tumor-bearing rats with the help of complexes of essential amino acids enriched with vitamins and microelements (AaVM).

Materials and methods. In experiments on 50 old white outbred male rats with transplantable sarcoma 45, the effects of EMR EHF and the combined effect of EMR EHF and AaVM were studied. For exposure to EHF EHF, the "Yav-1" medical device was used. The frequency modulation with 42.2 GHz as a center frequency was applayed. The duration of treatmaent was 4 weeks. We studied the dynamics of tumor size, adaptive status (according to hematological indicators of the character and tension of the general nonspecific adaptational reactions of the body), structural and functional changes in the tumor tissue, thymus and liver. In the statistical analysis of the results, student's t test and Wilcoxon-Mann-Whitney test were used.

Results. The anti-stress effect of EMR EHF on the organism of old tumor-bearing rats, accompanied by temporary inhibition of sarcoma 45 growth was shown. The combination of EMR EHF exsposure and AaVM (as an additional metabolic factor) leaded to a persistent pronounced antitumor effect in 60% of animals. Inhibition of tumor growth in 4 times or more, as well as individual cases of its partial regression were observed. At the same time, a higher adaptational status including more numerous signs of activation of the thymus and liver than in the cases of using only EHF EMR were noted.

Conclusion. The results indicate the promise of a combination of activation electromagnetic therapy and application of complexes of essential amino acids enriched with vitamins and microelements in the development of effective methods of accompanying and supportive treatment of cancer patients.

Keywords:
accompanying and supportive treatment, antitumor effect, adaptational status, electromagnetic radiation of an extremely high frequency range, essential amino acids, activation electromagnetic therapy.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ЭФФЕКТЫ КОМБИНИРОВАННОГО ВОЗДЕЙСТВИЯ НИЗКОИНТЕНСИВНОГО ЭЛЕКТРОМАГНИТНОГО ИЗЛУЧЕНИЯ МИЛЛИМЕТРОВОГО ДИАПАЗОНА И КОМПЛЕКСОВ НЕЗАМЕНИМЫХ АМИНОКИСЛОТ У КРЫС-ОПУХОЛЕНОСИТЕЛЕЙ СТАРЧЕСКОГО ВОЗРАСТА

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РЕЗЮМЕ

Цель исследования. Усиление эффектов низкоинтенсивного модулированного электромагнитного излучения (ЭМИ) миллиметрового или крайне высокочастотного (КВЧ) диапазона на опухоль и адаптационный статус крыс-опухоленосителей старческого возраста с помощью комплексов незаменимых аминокислот, обогащенных витаминами и микроэлементами (АкВМ).

Материалы и методы. В экспериментах на 50 белых беспородных крысах-самцах старческого возраста с перевивной саркомой 45 изучали эффекты ЭМИ КВЧ и комбинированного воздействия ЭМИ КВЧ и АкВМ. Для воздействия ЭМИ КВЧ использовали медицинский аппарат «Явь-1». Применяли частотную модуляцию с центральной частотой 42,2 ГГц. Продолжительность воздействий — 4 недели. Изучали динамику размеров опухоли, адаптационного статуса (по гематологическим показателям характера и напряженности общих неспецифических адаптационных реакций организма), структурно-функциональные изменения в ткани опухоли, тимусе и печени. При статистическом анализе результатов использовали t-критерий Стьюдента и критерий Вилкоксона-Манна-Уитни.

Результаты. Было показано антистрессорное влияние ЭМИ КВЧ на организм старых крыс-опухоленосителей, сопровождавшееся временным торможением роста саркомы 45. При комбинированном использовании ЭМИ КВЧ и АкВМ (как дополнительного метаболического фактора) стойкий выраженный противоопухолевый эффект был получен у 60% животных. Наблюдалось торможение роста опухоли в 4 раза и более, а также отдельные случаи её частичной регрессии. При этом был отмечен более высокий адаптационный статус, в том числе, более многочисленные признаки активизации тимуса и печени, чем в случае применения только ЭМИ КВЧ.

Заключение. Полученные результаты указывают на перспективность сочетания активационной электромагнитотерапии и применения комплексов незаменимых аминокислот, обогащенных витаминами и микроэлементами, при разработке эффективных методов сопроводительного и поддерживающего лечения онкологических больных.

Ключевые слова:
сопроводительное лечение, противоопухолевый эффект, адаптационный статус, электромагнитное излучение крайне высокочастотного диапазона, незаменимые аминокислоты, активационная электромагнитотерапия.

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INTRODUCTION

Systemic disorders caused by the malignant process and aggressive methods of antitumor treatment determine the relevance of the issue of developing effective technologies for supporting and accompanying therapy of cancer patients [1]. As a means of such therapy, chemical and physical factors are used, including low-intensity electromagnetic radiation (EMR) of the millimeter (or extremely high-frequency, EHF) range [2–4] and various nutraceuticals [5, 6].

Previously, in vivo experiments showed antitumor effects obtained using weak EMR of various ranges used in activation therapy modes, even without the use of special antitumor agents [7–9]. Such effects affected the regulatory centers of the neuroendocrine and immune systems, activating processes that lead to an increase in non-specific antitumor resistance of the body. It is known that the effectiveness of regulatory actions largely depends on the metabolic resources of cells, their availability of biologically active substances that play an important role in maintaining tissue homeostasis and regulating systemic processes [7, 10]. It is advisable to use preparations containing complexes of essential amino acids, vitamins and trace elements as factors of biochemical support of activation electromagnetotherapy. These drugs are designed to compensate for protein, mineral and vitamin deficiencies that are characteristic of the body in conditions of malignant growth, especially in elderly and senile patients [11, 12]. In addition, it has been shown that the use of complex preparations of essential amino acids in antitumor treatment, as well as some enzymes involved in their metabolism, contributes to inhibition of growth and reduction of tumor metastasis, potentiates the action of antitumor monoclonal antibodies, improves the condition and increases the life expectancy of cancer patients and laboratory tumor-bearing animals [13–15].

The purpose of the study: enhancing the effects of low-intensity modulated EMR EHF on the tumor and adaptational status of senile tumor-bearing rats using complexes of essential amino acids enriched with vitamins and trace elements.

MATERIALS AND METHODS

The study was performed on 60 white outbred male rats of senile age (28–30 weeks) weighing 370–410 g with a 45-graft sarcoma (C-45) in compliance with international rules for the humane treatment of laboratory animals.

The tumor was transplanted according to the standard procedure [16]. After reaching the C-45 size of 0.8–1.2 cm^3, at which its spontaneous regression is considered unlikely, the treatment began. Low-intensity (10 $mW/cm^2/s$) modulated EMR EHF, complexes of essential amino acids, vitamins and trace elements (AaVM), and combined impact of EMR EHF and AaVM were used as active factors. Frequency modulation of EMR EHF was performed in the range 42.1–42.3 GHz using a sequence of signals of low biologically significant frequencies selected based on previous experiments or close to the frequencies of Schumann resonances [8]. Frequency modulation (as opposed to amplitude modulation) in electronic shifting of the radiation frequency in the range of 42.1–42.3 GHz at a rate determined by the modulation frequency. A medical device for EHF therapy "Yav-1" was used for exposure to modulated EMR EHF, as well as a modulator designed at the Rostov research Institute of radio communications based on a special-form signal generator G6–37. In accordance with the recommendations for EHF therapy [4], the impact was performed on the occipital region of the animal's head, which was in a plexiglass chamber, through an opening covered with a radio-permeable membrane (Fig. 1). Exposure varied in the range of 15–30 min according to activation therapy algorithms [8, 9]. The modulation algorithm and other parameters of the impact were described in more detail earlier [8].

As AaVM, polyvalent biologically active additives from the company "Kordea" were used, which contained native l-amino acids in free form, as well as basic vitamins and a number of trace elements, including selenium. AaVM diluted with boiled water was administered peros through feeding tube at a dose of 260 mg/kg after exposure to EMR EHF. Three different AaVMs were used in the experiments: "L–Lysine-Active Aviton", which contained 18 amino acids with a predominance of L-lysine

(37%); "Vita Active Amiton", which included 19 amino acids with the largest amount of glutamic acid, leucine, glycine, lysine and serine (44%); "Zinc Iron Copper Aviton", which included 18 amino acids, as well as zinc, iron and copper in a dose exceeding the daily requirement of the body for these metals under normal conditions. Each of the listed AaVM also included vitamins and trace elements ("F. Hoffman-LaRoche", Switzerland). On one day, the animals received only one complex out of three. At the same time,"L–Lysine-Active Aviton "was used 2 times more often than the other two AaVMs due to the known information about the pronounced immunomodulatory and antiviral effects of L-lysine and the antitumor effects of L-lysine-α-oxidase [15, 17].

Combined impact was performed 4–6 times a week for a total duration of 4.5 weeks. The study evaluated the weekly weight of each animal, the size of the tumors (calculating the volume by the formula of Shrek for ellipsoids) and hematological parameters, including differential blood count leucocytes (on 200 cells), leucocyte count and haemoglobin level in peripheral blood. Hematological parameters were used to determine the character and tension of General non-specific adaptational reactions of the body (AR) [7, 10, 18].

At the end of the experiment, animals were over-anesthetized and fragments of tumor tissue, as well as internal organs, thymus and liver were taken for histological and histochemical study. For review purposes, hematoxylin-eosin staining was used, Brachet staining was used to identify nucleoproteins, and complex staining was used to study structures including carbohydrate — containing biopolymers using the A. L. Shabadash method with Azur I and an acidic solution of basic brown using the Shubich-Lopunova-Mogilnaya method. At the same time, morphometric study of changes in the thymus was performed with the determination of indicators that reflected the activity of lymphoproliferative processes — the width of the cortical and medullary substance in the thymus lobules, as well as the stromal-parenchymal coefficient. Also the signs of interaction between tissue basophils and thymocytes were evaluated.

Due to the old age of animals, which caused age-related thymus involution and the development of degenerative changes in the thymus and liver, which can "mask" microstructural shifts associated with the tumor process when considered separately, we find it appropriate to use generalized characteristics of the state of the studied organs based on a semi-quantitative assessment of signs that reflected various structural and functional changes. At the same time, a number of indicators that characterized both positive and negative structural and functional changes in both organs studied were ranked according to their significance in the range from - 1 to +1.These indicators were evaluated in 10 fields of view (with magnification of 10x10, 10x40 or 10x90 – depending on the feature). In addition, if the ratio of the width of the cortical and cerebral layer of the thymus, as well as the size of the lobules, corresponded to the most favorable anti-stress AR or increased activation, the maximum positive score of "+1"was added. The picture typical for AR training was evaluated with a lower score — "+0.5". In the case of severe hypoplasia of lymphoid tissue and other signs that corresponded to AR stress, the maximum negative score was assigned — "-1". The simultaneous presence of signs characteristic of the stress response and anti-stress reactions in the organ micro imaging, indicating the development of tensioned anti-stress AR of low reactivity levels, was evaluated with a zero score. In addition, positive half points were added in the following cases:

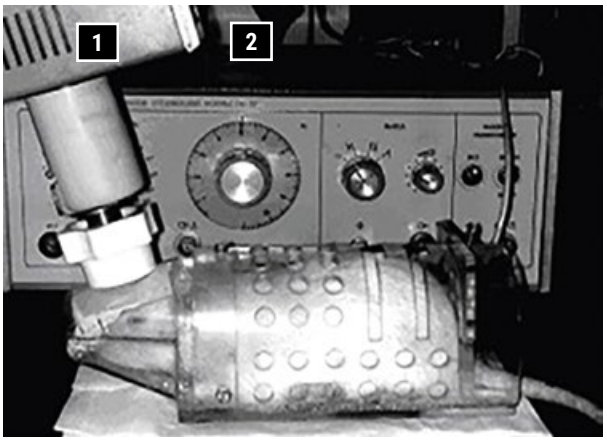


Fig. 1. Experimental setup for the impact of modulated EMR EHF on the occipital region of the head of a rat in a plexiglass chamber. Note: 1 – medical device for EHF therapy "Yav-1", 2 – frequency modulator (based on the G6-37 generator).

— in the presence of signs indicating the activation of interactions between thymocytes and tissue basophils as local regulators of tissue homeostasis, affecting the processes of maturation and differentiation of thymocytes;

— if there are signs of activation of hormone-producing epithelial-reticular complexes in the thymus (non-keratinized Gassal bodies).

In the analysis of micro imaging the liver of the experimental animals were evaluated as parenchyma and hemocirculation channel of the body. Positive points were assigned in cases of moderate fullness of the central and interlobular veins and preservation of the normal structure of the beams- "+1", uniform distribution and the absence of a pronounced decrease in the content of nucleoproteins and glycogen in hepatocytes — "+1", as well as in the presence of binuclear hepatocytes — "+0.5". Negative evaluations were carried out in cases of signs of hemostasis perivascular edema and disruption of the structure beams — –1, and in the presence of marked perivascular edema without disrupting the structure beams — "-0.5", and also in focal vacuolization of cytoplasm and lysis of chromatin in hepatocyte — "-0.5".

Statistical analysis of the experiment results was performed using the student's t-test and the Wilcoxon-Mann-Whitney test.

STUDY RESULTS AND THEIR DISCUSSION

Table 1 provides information on the dynamics of the size of sarcoma 45 within 4 weeks from the beginning of exposure. 2 weeks after the start of the treatment, tumor growth was inhibited in the group with EMR EHF and in the group with combined impact by 1.8 and 3.2 times, respectively. In the case of EMR EHF, the effect was unstable, whereas with combined impact, a marked decrease in the volume of sarcoma 45 compared to the control value was maintained until the end of the experiment. No anti-tumor effect of AaVM was observed (table 1). Therefore, the results obtained in this group were not considered in the course of further analysis.

An almost two-fold difference in the average tumor volume in the group with combined impact from the values of the indicator in the other groups after 4 weeks of treatment was obtained due to a significant antitumor effect in 60% of rats (12 out of 20). In these animals, tumor growth was inhibited by 4 times or more compared to the control group and male rats exposed to EMR EHF, and in some cases, partial regression of the tumor was noted. In the remaining 40% of the animals in the study group, the volume of the tumor at the end of the experiment did not differ statistically from the indicator in the other two groups (Fig. 2A).The impacts of the tumor tissue during inhibition of sarcoma 45 growth was characterized by a decrease in the density of growing malignated cells, a clear lymphocytic shaft, and a large amount of fibrin (Fig. 2B). In these cases, the proportion of viable tumor cells could be reduced to 1/8 of the field of view (at 10x40 magnification) ($p<0.01$). With partial regression of sarcoma 45, areas of tumor tissue replacement with connective tissue were observed. Thus, a pronounced antitumor effect was observed only with the combined action of EMR EHF and AaVM. In the future, we considered it appropriate to conduct a comparative analysis of the studied indicators in the order that only cases of effective influence of EMR EHF and AaVM (subgroup 1) should be taken into account in the group with combined exposure.

Table 2 provides information about the adaptive status of tumor-bearing rats during the entire experiment. As can be seen from the table, the effect of EMR EHF and combined impact on the growth of sarcoma 45 fully corresponded to the features of the adaptational status of animals in the studied groups. The adaptational status of rats that managed to achieve significant growth inhibition or even partial regression of sarcoma 45 was very different from the adaptational status of animals of the other two groups by the dominance of antistress AR without pronounced signs of tension. At the same time, in the case of EMR EHF, there was also a slight improvement in the AR characteristics compared to those observed in the control group. This was reflected in a more than twofold reduction in cases of AR stress (table 2).

Analysis of changes in the thymus and liver micro imagings allowed us to supplement the idea of the influence of the studied effects on

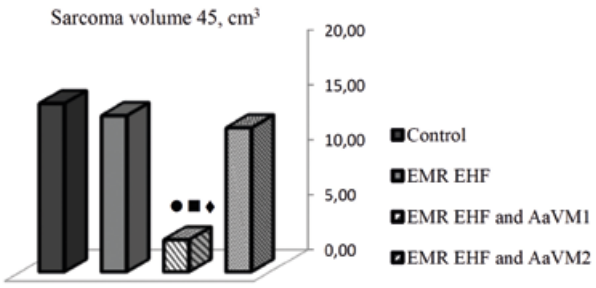
the adaptational status of senile tumor-bearing animals. Figure 3A shows the results of a score assessment of structural and functional changes in these organs, characteristic of animals of different groups. In the male rats of the control group, a clear predominance of negative changes was observed, indicating a decrease in functional activity and pronounced structural and functional disorders in the studied organs. This is reflected in the negative values of the corresponding scores (Fig. 3A). The thymus of these animals was dominated by signs of atrophy, a sharp predominance of stroma over parenchyma, cortical matter of lobules was weakly expressed, individual completely keratinized epithelial-reticular complexes were noted, and non-granulated forms of tissue basophils prevailed. The liver was characterized by a picture of hemostasis with perivascular edema and a violation of the structure of the beams, with a sharp decrease in the content of nucleoproteins and glycogen in hepatocytes and the practical absence of binuclear hepatocytes.

In contrast to the one observed in the control group, the results of morphometry and visual examination of the thymus micro imaging of animals of the two main groups even indicated some activation of lymphoproliferative processes in the majority of rats exposed to weak modulated EMR EHF (Fig. 3A).

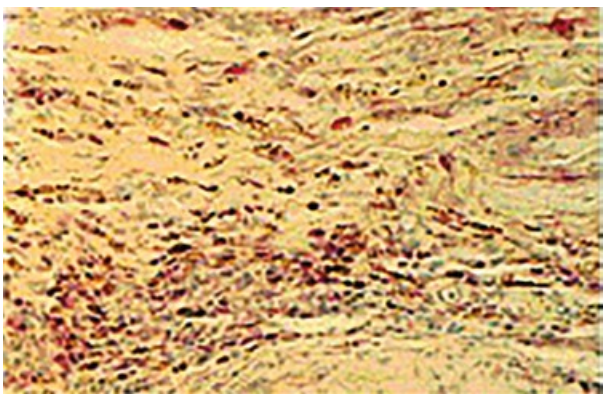
Table 1. Dynamics of sarcoma volume 45 (cm^3) under the studied impacts in white outbred male rats of senile age for 4 weeks

Stage of the study	Control *n*=15	EMR EHF *n*=15	AaVM *n*=10	EMR EHF + AaVM *n*=20
initially	1.41±0.25	1.14±0.26	1.40±0.32	1.30±0.25
week 1	2.66±0.64	2.54±0.40	2.70±0.54	1.63±0.19
week 2	6.30±1.04	3.49±0.81 ●	5.32±0.98 ■	1.98±0.24 ●▫
week 3	10.47±2.34	7.93±1.12	9.90±1.00	4.43±0.37 ●■▫
week 4	12.51±3.78	11.67±1.80	12.25±1.32	6.50±0.75 ●■▫

Note: EMR EHF – low-intensity modulated electromagnetic radiation of extremely high frequency range; AaVM-complexes of amino acids, vitamins and trace elements. Differs (p<0.05-0.01) from the control group – ●, rom EMR EHF – ■, from AaVM group – ▫. T-criteria.



A. Sarcoma volume 45 in the study groups at the end of the experiment



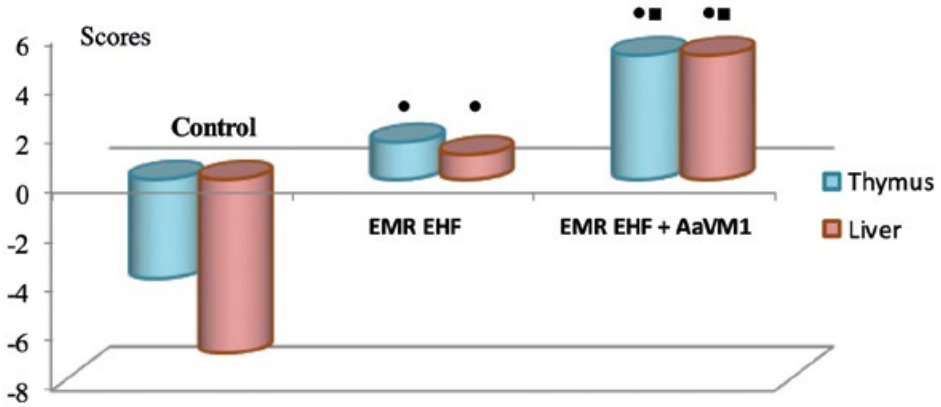
B. Changes in sarcoma tissue 45 under the influence of combined impact

Fig. 2. Antitumor effectiveness of the studied impacts.
A. sarcoma Size 45 in the studied groups of old male rats at the end of the experiment (4.5 weeks from the beginning of the effects). Notation – see table.1
Note: EMR EHF + AaVM1 and EMR EHF + AaVM2 are subgroups of animals with different severity of the combined effect of EMR EHF and AaVM.
Differs from the control group: ● – p<0.01; from the EMR EHF group: ■ – p<0.01; from the EMR EHF + AaVM2 subgroup: ♦ – p<0.05. T-test.
B. Changes in sarcoma tissue 45 under the influence of combined impact. Pronounced inhibition of tumor growth (EMR EHF + AaVM1). Reduction in the density of malignant cells. Lymphocytic shaft. Brachet. 10x6.3.

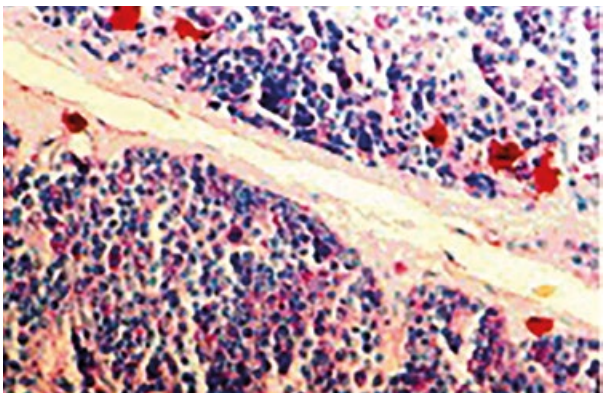
Table 2. Effects of the studied impacts on the tumor and the adaptational status of old male rats with transplanted sarcoma 45

Indicator	Control *n*=15	EMR EHF *n*=15	EMR EHF + AaVM1 *n*=12
Tumor volume, cm^3	15.3±2.6	14.2±1.8	2.9±1.3 ●■
AR stress	47	20 ●	0 ●■
Tensioned anti-stress AR	53	80	30 ■
Anti-stress AR without signs of tension	0	0	70 ●■

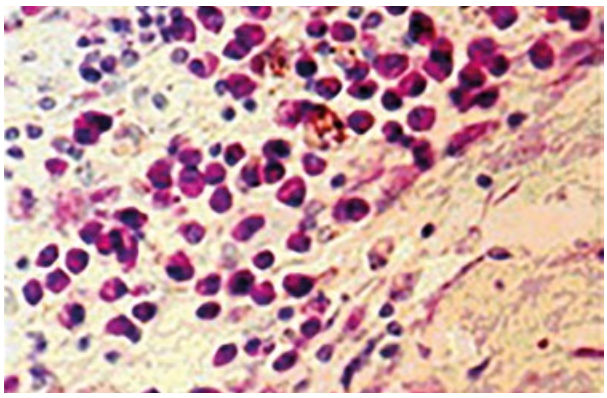
Note: AR-adaptational reactions. Differs from the control group: ● – p<0.05–0.01; from the EMR EHF group: ■ – p<0.05–0.01. T-criteria.



A. Indicators of the thymus and liver state



B. Signs of activation of interaction between thymocytes and tissue basophils.



C. Abundant infiltration of sarcoma tissue by 45 plasmocytes at pronounced inhibition of tumor growth.

Fig. 3. Changes in internal organs and tumors under effective combined action EMR EHF + AaVM1.

A. Relative (point) indicators of the morpho-functional state of the thymus and liver under the action of EMR EHF and effective combined action – EMR EHF + AaVM1. Differs from the control group: ● – p<0.05–0.01; differs from the EMR EHF group: ■ – p<0.05. Wilcoxon-Mann-Whitney Criterion.

B. An Increase in the number of degranulated tissue basophils in the immediate vicinity of thymocytes of the subcapsular zone of the cortical substance of the thymus lobes under effective combined action. Brachet. 10x40.

C. Pronounced inhibition of sarcoma 45 growth under the influence of combined impact (EMR EHF + AaVM1). Abundant infiltration of tumor tissue by plasma cells.

The severity of signs of lymphoproliferative activity was generally similar in these groups. At the same time, with effective combined use of EMR EHF + AaVM in the subcapsular zone of the thymus lobes, a more significant number of degranulating tissue basophils was observed in the immediate vicinity of thymocytes, which determined higher scores in this group (Fig. 3B). The described difference could indicate more active intercellular interactions in the organ and, as a possible consequence, a higher functional potential of T-lymphocytes under combined impact. Similarly, in the case of effective use of EMR EHF + AaVM, more pronounced signs of liver normalization were noted than with the action of EMR EHF alone (Fig. 3A). This applied both to the morphological characteristics of hemodynamics in the organ, and to the signs reflecting the level and uniformity of the distribution of nucleoproteins and glycogen in hepatocytes, as well as the number of binuclear hepatocytes in the hepatic parenchyma.

Inevitably, the question arises about the mechanisms of antitumor effect of combined impact. As a rule, when using non-specific factors that do not have a direct damaging effect on the tumor, we can talk about activation of immune processes that lead to inhibition of tumor growth or even elimination of tumor tissue [19]. In the case of inhibition of sarcoma 45 growth under the influence of combined impact, such a feature of microstructural changes in the tumor tissue as its pronounced infiltration by plasmocytes was noted (Fig. 3C). Taking into account the literature data on the fundamental possibility of changing the activity of B-lymphocytes under the influence of T-lymphocytes [20], it can be assumed that the effectiveness of combined action of EMR EHF and AaVM is associated with increased intercellular interactions in the thymus, leading to activation of T-lymphocytes, which in turn contribute to the mobilization of plasmocytes involved in the effector mechanisms of tumor cell damage. At the same time, we cannot exclude some contribution to the effects of the combined impact of direct damage of tumor tissue, due to the influence of L-lysine-α-oxidase (activated by the receipt of L-lysine), which, in particular, is associated with release of cytotoxic hydrogen peroxide effect on β-adrenergic receptors and proteins responsible for the adhesive properties of cells [15].

CONCLUSION

In contrast to the results obtained in some other experimental models [4, 8, 19], in old white outbred male rats with sarcoma 45 under the influence of low-intensity modulated EMR EHF presented in the activation therapy mode, only a temporary effect was observed — unstable inhibition of tumor growth two weeks after the start of exposure. Antistress changes caused by EMR EHF were not sufficient to activate effective antitumor mechanisms and achieve stable inhibition of tumor growth. A pronounced antitumor effect in more than half of the animals was obtained by combined use of activation electromagnetotherapy and AaVM as an additional metabolic factor. In these animals, there was a 4-fold or more inhibition of tumor growth, as well as some cases of partial regression. At the same time, a higher adaptational status was noted, including more numerous signs of activation of the thymus and liver, than in the case of using only EMR EHF. The results obtained indicate that the combination of activation electromagnetotherapy and the use of complexes of essential amino acids enriched with vitamins and trace elements is promising for the development of effective methods of accompanying treatment of elderly cancer patients.

Authors contribution:
Zhukova G.V. – concept, research design, conducting research, analyzing results, text writing.
Shikhlyarova A.I. – participation in the analysing of the results, scientific editing.
Loginova L.N. – participation in research and analysing of the results.
Protasova T.P. – participation in research, technical editing.

References

1. Recommendations for maintenance and supportive therapy RUSSCO. (In Russian). Available at: https://rosoncoweb.ru/standarts/suptherapy/2019/

2. Chissov V.I., Kabisov R.K., Pletnev S.D., Betsky O.V., Faykin V.V. A method of treating cancer patients with electromagnetic radiation of the mm range. Invention patent RU 98 102 380 A, 27.01.2000. Application: 98102380/14 from 1998.01.23. (In Russian).

3. Kolmatsui NB, Levitskii EF, Golosova OE, Pyzhova IB. The application of UHF therapy for the prevention of complications of specific antiblastoma therapy in the patients presenting with III-IV stage lung cancer. Questions of balneology, physiotherapy and therapeutic physical culture. 2013;90(2):4–7. (In Russian).

4. Betskii OV, Lebedeva NN. Biological effects of low intensity millimeter waves (Review). Biomedicinskaya radioelektronika – Biomedicine radioengineering. 2015;(1):31–47. (In Russian).

5. Heyland DK, Weijs PJM, Coss-Bu JA, Taylor B, Kristof AS, O'Keefe GE, et al. Protein Delivery in the Intensive Care Unit: Optimal or Suboptimal? Nutr Clin Pract. 2017 Apr;32(1_suppl):58S-71S. https://doi.org/10.1177/0884533617691245

6. Kostyuchenko LN, Kostyuchenko MV, Kuzmina TN, Lychkova AE. Strategy of accompanying nutritional and metabolic therapy of patients with colorectal cancer. Russian Medical Journal. 2019;(6):37-44. (In Russian).

7. Garkavi LK, Kvakina EB, Shikhliarova AI, Kuz'menko TS, Barsukova LP, Mar'ianovskaia GI, et al. Magnetic fields, adaptation reaction and self-organization of live systems. Biofizika. 1996 Aug;41(4):898–905.

8. Zhukova GV, Shikhlyarova AI, Barteneva TA, Barsukova LP, Kostrovitskiy YV, et al. Some strategies of activation therapy using radiations of microwave ranges in experiments on tumor-bearing animals. Cardiometry. 2015 Nov 27;(7):47–57. https://doi.org/10.12710/cardiometry.2015.7.4757

9. Zhukova GV, Shikhliarova AI, Soldatov AV, Barteneva TA, Goroshinskaya IA, Petrosian VI, et al. Some approaches to the activation of antitumor resistance mechanisms and functional analogs in the categories of synergetics. BIOPHYSICS. 2016 Mar 1;61(2):303–315. https://doi.org/10.1134/S0006350916020251

10. Kit Kit OI, Shikhlyarova AI, Zhukova GV, Maryanovskaya GY, Barsukova LP, et al. Activation therapy: theoretical and applied aspects. Cardiometry. 2015 Nov 27;(7):22–29. https://doi.org/10.12710/cardiometry.2015.7.2229

11. Vettore, L, Westbrook RL, Tennant DA. New aspects of amino acid metabolism in cancer. British Journal of Cancer. 2020 Jan;122(2):150–156. https://doi.org/10.1038/s41416-019-0620-5

12. Lieu, EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. Exp Mol Med. 2020;52(1):15–30. https://doi.org/10.1038/s12276-020-0375-3

13. Al-Mahtab M, Akbar SMF, Khan MSI, Rahman S. Increased survival of patients with end-stage hepatocellular carcinoma due to intake of ONCOXIN®, a dietary supplement. Indian J Cancer. 2015 Sep;52(3):443–446. https://doi.org/10.4103/0019-509X.176699

14. Dzhugashvili M., Pokrovsky V. S., Snegovoy A. V. Novel approaches for the correction of micronutrient deficiency in patients with malignant tumors. Malignant Tumours 2016;2:55–65. https://doi.org/10.18027/2224-5057-2016-2-55-65

15. Pokrovsky VS, Lukashev EV, Chernov NN, Treshchalina EM. Experimental study of the effectiveness of L-lysine-α-oxidase Trichoderma CF. AureovirideRifai on human tumor xenografts models in bestimus mice and evaluation of synergy with cisplatin or topoisomerase inhibitors. Journal of Oncology Issues. 2017;63(3):497–505. (In Russian).

16. Konoplev VP. Perepisnye of the tumor. In: Models and methods of experimental Oncology. M: Medgiz., 1960, 144-162 p. (In Russian).

17. Zhang C, He Y, Shen Y. L-Lysine protects against sepsis-induced chronic lung injury in male albino rats. Biomed Pharmacother. 2019 Sep;117:109043. https://doi.org/10.1016/j.biopha.2019.109043

18. Selye H. Thymus and adrenals in the response of the organisms to injuries and intoxication. Brit. J. Exp. Path. 1936;(17): 234–248.

19. Zhukova GV, Shikhlyarova AI, Barteneva TA, Bragina MI, Gudtskova TN, Petrosyan VM, et al. The pattern of the immune processes during activation therapy with the use of microwave electromagnetic radiation. Cardiometry. 2017;(11):35–45. https://doi.org/10.12710/cardiometry.2017.11.3545

20. Bishop GA. B cell-T cell interaction: antigen bridge to antigen presentation. Nat Rev Immunol. 2016;16(8):467. https://doi.org/10.1038/nri.2016.82

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