

Magnetotherapy in Experimental and Clinical Neuro-Oncology: A Review

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Abstract: The purpose of this publication is not to state the fact of the high antitumor effectiveness of the gold standard treatment of malignant brain tumors (surgical intervention with adjuvant chemoradiotherapy), but to consider the possibility of using alternative therapeutic options, in particular, magnetotherapy, as a component of the treatment of patients with this serious pathology, as well as a method of preventing a number of postoperative adverse reactions.

Keywords: Neuro-oncology, malignant brain tumors, treatment, magnetotherapy.

INTRODUCTION

An increasing number of the malignant brain tumors has been noted in recent years, which make up, on an average, more than 1.4% of all neoplasms detected in humans [1]. According to the World Health Organization, today there are more than 100 nosological forms of the malignant brain tumors, 42-50% of which belong to tumors of neuroepithelial genesis: astrocytic tumors (diffuse, fibrillar, protoplasmic Grade II, anaplastic Grade III astrocytoma, Grade IV glioblastoma, pilocytic astrocytoma Grade I, pleomorphic xanthoastrocytoma Grade II); oligodendroglial tumors (Grade II oligodendroglioma, Grade III anaplastic oligodendroglioma); mixed gliomas (Grade II oligoastrocytoma, Grade III anaplastic oligoastrocytoma), etc. Gliomas are the most frequent histological type of primary tumors of the central nervous system (CNS) [2]. More than half of the listed tumors (50-77%) are the most malignant (anaplastic and undifferentiated astrocytoma, glioblastoma, etc.) [3]. According to various authors, the standardized incidence rate of this pathology varies from 4.3 to 18.6 per 100,000 people [4], in the case of glioblastoma – on an average, 5 per 100,000 people [5].

Many authors put the problem of the treatment of the malignant brain tumors, especially glioblastoma, among the most difficult in neurosurgery and neuro-oncology. The main feature of the tumor process that determines the tactics of treatment of this category of patients is the presence of blood-brain and

hematotumoral barriers, which almost completely exclude the possibility of distant lymphogenic and hematogenic metastasis outside the central nervous system and act as an obstacle to the active transport of most drugs into the tumor. The spread of tumor cells occurs infiltratively, mainly through the membranes of the brain, cerebrospinal fluid pathways, as well as through perivascular and perineural spaces at a distance of up to several cm from the primary focus [6]. As a result, in most cases, the occurrence of local relapses is noted in the area of primary tumor growth and in the peritumoral tissue of the brain [7].

The main methods of treatment of the malignant brain tumors are surgical intervention with the adjuvant chemoradiotherapy (CR). Modern surgical methods and approaches are based on the use of ultrasound diagnostics and laser technologies, navigational endoscopic techniques and microsurgical manipulations, allowing to increase the radicality of the operation. Unfortunately, the majority of the malignant brain tumors are diagnosed with a degree of prevalence of the tumor process, when surgical treatment is not always radical due to the pronounced ability to infiltrate growth and involvement of functionally important parts of the brain in the tumor process, and the resulting neurological deficit does not allow surgical treatment to be prognostically justified. Even in the case of maximum removal of the tumor in the perifocal zone, 96% of patients have continued growth within a short period of time [8]. In order to prevent the occurrence of local relapses, adjuvant CR is used as a component of the complex treatment of the malignant brain tumors, aimed at damaging and destroying tumor cells and tissues that were not removed during surgery. From a certain point of view,

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the possibilities for treatment of the MBT were expanded with the inclusion of combined and complex treatment schemes by including photodynamic therapy, immunotherapy, brachytherapy, neutron capture therapy, genetic engineering. Despite the modern achievements of medical science and technology, along with the availability of a wide range of methods for the treatment of malignant gliomas, the survival rates from this severe pathology are disappointing. So, according to Roth P. and co-author (2017) 1-year survival rates in patients of the age groups «65-74 years» and «75 and over» are 28,7% and 12,1%, respectively. 5-year survival rates are 2,4% and 1,1%, respectively [9]. According to the data presented in the article by Yousuf A. *et al.*, the median progression-free time and median overall survival in patients with glioblastoma are 6,2-7,5 months, 14,6-20,5 months, respectively [10].

MAGNETIC FIELDS IN ONCOLOGY

In connection with the above, the question of optimizing treatment approaches in relation to this category of patients still remains open. Currently, there is a trend towards a wider use of physiotherapeutic factors in the treatment and rehabilitation of patients with malignant neoplasms. Current research areas in experimental and clinical oncology are the study of the possibilities of using laser and ultrasound technologies. Of particular interest is the study of the influence of the magnetic fields (MF) with certain parameters as a component of the treatment regimens of the malignant brain tumors, including those used to reduce the frequency of postoperative adverse reactions and complications of the CR.

The biological effect of the MF is determined by their interaction with the structures of the living system. Changes in cells under the influence of MP are realized at the molecular, cellular and tissue levels. In the monograph of Pletnev A.S. and Ulashchik V.S. (2016), the changes are systematized and analyzed [11]. Under the influence of the MF, an induced electric current is formed in biological structures, affecting ionic and polarization processes in tissues, enzyme activity (ATP-ases, protein kinase, monooxykinase), cellular metabolism, nerve conduction, which, as a result, contributes to improving microcirculation, reducing edema and the inflammatory process. Improvement of peripheral blood circulation and lymph outflow occurs due to normalization of the tone of blood and lymphatic vessels and due to improvement of rheological properties of blood [12].

The result of such multi-vector and versatile changes at all levels of the human body structure is the realization of the main effects of MF, which are an active and effective therapeutic factor. The main types of therapy using MF (magnetotherapy, MT) are permanent magnetotherapy (PMT), low-frequency magnetotherapy (LFMT), general magnetotherapy (GMT) and high-intensity pulsed magnetotherapy (HIPMT) [11].

PMT activates microcirculation, increasing vascular and epithelial permeability, enhances immunological reactivity, changing the content of T- and B-lymphocytes, increases the activity of redox processes in biological tissues. As a consequence, the main therapeutic effects of permanent magnetic field (PMF) are antiedematous, coagulating, sedative, local trophic, vasodilating, immunomodulatory and anti-inflammatory [11].

Under the influence of LFMT, the speed of the pulse along nerve fibers increases, their excitability increases, the function of the autonomic nervous system normalizes, increased vascular tone decreases, local blood flow is activated, blood supply and trophic of various organs and tissues improve, metabolism, regeneration processes and functions of endocrine organs are stimulated. The main therapeutic effects of LFMT are anti-inflammatory, trophic, vasoactive, antiedematous, hypotensive [11].

GMT increases the body's resistance to adverse factors, expands its compensatory and adaptive capabilities, normalizes and synchronizes the activity of many organs and systems, primarily the nervous and cardiovascular systems. The most characteristic therapeutic effects of GMT are antispasmodic, hypotensive, trophy-regenerative, anti-inflammatory, analgesic and metabolic effects [11].

High-intensity pulsed MF during HIPMT enhances local blood flow and microcirculation, stimulates metabolic processes in tissues and cell metabolism (trophic effect), and is able to stimulate the activity of internal organs. Due to various mechanisms, such MF have a pronounced antiedematous, analgesic, anti-inflammatory, trophico-regenerative and neuromyostimulating effects [11].

MAGNETOTHERAPY IN EXPERIMENTAL AND CLINICAL ONCOLOGY

According to a number of experimental studies on various cell lines and laboratory animals with

transfused tumors, MF leads to the development of local and general antitumor reactions [11]. The primary reactions develop in the zone of magnetic influence and manifest themselves in damage and destruction of tumor cells due to structural and functional violations of the integrity of their membranes, activation of microcirculation and oxygenation of tumor tissue, changes in antigenic properties and sensitivity to external influences of the tumor. The latter reactions are expressed in an increase in the functional activity of the hypothalamic-pituitary-adrenal system, a change in the intensity and direction of metabolic processes in the body, in the activation of various parts of the immune system, which contribute to the strengthening of antitumor resistance of tumor-bearing animals. Such changes contribute to the improvement of the results of antitumor therapy and, as a result, serve as the basis for the approbation and implementation of MT in clinical oncology [11].

Akbarnejad Z. and co-author. (2017), in an experiment on glioblastoma's cells cultures U87 and T98G, evaluated the antitumor efficacy of the combined use of the temozolomide and electromagnetic MP (100 Hz, 100 Gs). Based on the results obtained, the authors concluded that the proposed combination activates a cascade of apoptosis reactions by regulating p53, Bax, Caspase-3, Bcl-2 and Cyclin-D1. It was shown that the use of MP with these parameters led to an increase in the effectiveness of chemotherapy with temozolomide due to an increase in the production of reactive oxygen species in both cell lines and induced the expression of apoptic genes [13]. In another study by this team of authors, the EMF parameters (10-50 Hz, 10-100 Gs) and the duration of exposure up to 24 hours were changed to affect the cells of the U87 line. It was noted that in these modes, the use of MF significantly changed cell proliferation and the intensity of apoptosis [14].

Among the well-known MT methods, the most recognized and widespread in clinical oncology to date has been GMT using vortex MF. In addition to vortex MF, various other options for the use of variable and constant MF are being tested as a component of complex therapy of tumors. So, in order to improve the immediate results of complex treatment of patients with malignant gliomas, Atmachidi D.P. proposed to combine CR with the effect of variable (PeMP) and constant (PMP) MP of medium intensity (PeMP, 0.8-5.0 MT, 0.03-3.9 Hz, 1-7 min + PMP, 20 MT, 15 min) on the brain (hypothalamus area and surgery area). The author reported that CLT with the effect on the brain of

these MP is an effective component in the complex treatment of patients with the MBT. The use of these MF allows to achieve a direct clinical effect in the 93.3% of cases (in the control group without the use of the MF – 40.0%, $p < 0.05$). Progression of the disease was noted in 6.7% of patients of the main group and in 46.7% of the control group ($p < 0.05$). The use of adjuvant CR with the effect of MF on the brain in treatment of glial tumors led to an improvement in patient survival rates: an increase in the overall 2-year survival rate from 16.7% to 40.0% ($p < 0.05$) and 2-year relapse-free survival from 3.33% to 20.0% ($p < 0.05$).

It is equally important that the developed method of the CR with the local exposure to MF was characterized by good tolerability, favorably differing from the traditional method of treatment (CR) by fewer and a lesser severity of adverse reactions (hematological toxicity: 13.3% vs. 42.2%; dyspeptic syndrome – 13.3% vs. 30.7%; peripheral neuropathy: 10.0% vs. 19.2% of cases).

It should also be noted that the use of the CR in combination with MT in the treatment of malignant gliomas led to a decrease in the severity of symptoms of neurological toxicity compared with the control (CR in a single mode): general cerebral symptoms – by 24.0%; motor disorders – by 26.9%; sensitivity disorders – by 16.7%; speech disorders – by 10.7% and disorders of higher nervous activity – by 13.9%. In the next observation period, it contributed to better dynamics of the general somatic status and Karnovsky index (9.3% vs. 2.6%, respectively) compared with the control (CR, $p < 0.05$). The obtained results gave the author grounds to recommend patients with malignant gliomas after surgery to use the effect of MP on the hypothalamus region (PeMP, 0.8–5 MT) and on the area of surgery (PMP, 20 MT) as an adjuvant component of therapy. According to the author, the effect of MP on the brain as a component of the complex therapy of the MBT is relevant and necessary, since it is based on the effect on perifocal glia, having a cytostatic, decongestant, anti-inflammatory effect, increasing the effectiveness while reducing the toxicity of CR. It is also important that MF affects the hypothalamus, realizing the systemic effect of increasing the nonspecific and antitumor resistance of the patient's body [15].

In the study of Popov I.A. in experiments on human glioblastoma T98G cell culture, the author found that the combination of ionizing radiation in a single focal dose of 10 Gy with a MT of frequency 0.3-3.0-9.0 Hz

and induction of 15 mT contributes to an increase in the number of dead cells to 17.9% compared with the control (5.7%; $p < 0.05$) and a decrease in the mitotic index to 3.5% compared with the control (6.6%; $p < 0.05$) [16, 17, 19]. The use of the programmed mode of MT developed by the author as a factor of accompanying treatment in assessing the neurological status on the NIHSS scale after radiation therapy testified to the relief of neurological symptoms in 84.0% of patients with magnetotherapy and without magnetotherapy – in 48.0% ($p < 0.05$). The use of MF contributed to the restoration of cognitive functions (according to the MoHS scale), which was observed more often 3.4 times before radiation therapy and 4 times after its completion relative to control. Similar positive dynamics was noted when testing on the Bartel scale ($p < 0.05$), as well as the Karnovsky scale at the level of 90 points in the main group – $60 \pm 7.1\%$, versus $27.3 \pm 9.5\%$ in the control group ($p < 0.05$), which reflected functional neurological and cognitive savings and improved the quality of life of patients with MBT (glioblastoma) [18, 19]. The authors also reported that in the early postoperative period it led to a decrease in the ratio of the average values of the tumor volume (from $6.7 \pm 2.4 \text{ cm}^3$ in the control to $2.3 \pm 0.7 \text{ cm}^3$ in the main group, $p < 0.05$) and the average values of the volume of perifocal edema (from $2.7 \pm 0.5 \text{ cm}^3$ to $1.43 \pm 0.34 \text{ cm}^3$; $p < 0.05$). After the end of the course of radiation therapy in combination with magnetotherapy, there was a continued regression of edema to values 3.8 times less than the initial ones. When accompanying magnetotherapy was included in the complex treatment of patients with GBM, a statistically significant increase in the 6- and 12-month overall survival of patients in the main group relative to the control group was revealed, respectively, 100% vs. $88.8 \pm 8.7\%$, and $68.5 \pm 10.4\%$ vs. $52.0 \pm 7.5\%$ ($p = 0.001$) [18, 19].

CONCLUSION

In conclusion, it is worth noting that the search and testing of new modifying approaches that potentially increase the antitumor effectiveness of the use of traditional methods of treatment in neuro-oncology are relevant. The search for publications on the issue under study indicates that the scientific works that take place are isolated, however, they fully reflect the fact of significant prospects for the use of MF in experimental and clinical neuro-oncology.

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