ONCOLOGY

PROSPECTS FOR USING ULTRASOUND OF VARIOUS INTENSITY FOR THE TREATMENT OF PATIENTS WITH MALIGNANT BRAIN GLIOMAS

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ABSTRACT

Background. *Treatment for malignant brain gliomas includes surgery, radiation therapy, and chemotherapy with temozolomide. However, this complex treatment does not prevent tumor relapses and progression, which is caused by the activity of tumor cells and a high mutational burden. Researchers are experimenting with different intensity of focused ultrasound (FUS) in the treatment of glioblastoma (GBM). FUS has shown encouraging results in clinical studies.*

The aim of the study. *This review presents brief information on the history of the development of the studied method, the results of its application in experiments and clinical trials, as well as the main possible directions for its implementation in neuro-oncology, in particular, for the treatment of glioblastomas, depending on parameters, including frequency, power, pulse duration and duty cycle.*

Materials and methods. *We carried out an analysis and interpretation of existing publications; for the search, we used the PubMed database and the keywords "focused ultrasound, glioma, HIFU, LIFU", as well as Yandex and Google search engines and the same keywords in Russian.*

Results. *Low-intensity FUS can be used to temporarily open the blood-brain barrier (BBB), which limits the diffusion of most macromolecules and therapeutic agents into the brain. High-intensity FUS can cause tumor ablation due to a hyperthermic effect, and also stimulate an immunological attack of tumor cells, activate sonosensitizers to exert a cytotoxic effect on tumor tissue, and can increase the sensitivity of tumors to radiation therapy. Histotripsy causes tumor ablation through acoustic cavitation.*

Conclusion. *Focused ultrasound is a promising potential treatment for gliomas. Further study in the form of clinical trials should determine the optimal ultrasound parameters to achieve effective treatment for patients with malignant brain tumors.*

Key words: *oncology, focused ultrasound of various intensity, pediatric oncology, neuro-oncology*

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ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ УЛЬТРАЗВУКА РАЗЛИЧНОЙ ИНТЕНСИВНОСТИ ДЛЯ ЛЕЧЕНИЯ ПАЦИЕНТОВ СО ЗЛОКАЧЕСТВЕННЫМИ ГЛИОМАМИ ГОЛОВНОГО МОЗГА

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РЕЗЮМЕ

Обоснование. *Лечение злокачественных глиом головного мозга включает хирургическое вмешательство, лучевую терапию и химиотерапию с темозоломидом. Однако данное комплексное лечение не предотвращает рецидивы и прогрессирование опухоли, что обусловлено активностью опухолевых клеток и высокой мутационной нагрузкой. Исследователи экспериментируют с фокусированным ультразвуком (ФУЗ) различной интенсивности в лечении глиобластомы (ГБМ). ФУЗ показал обнадёживающие результаты в клинических исследованиях.*

Цель исследования. *В настоящем обзоре приводятся краткие данные об истории становления указанного метода, результатах его применения в экспериментах и клинических испытаниях, а также основные возможные направления его внедрения в нейроонкологии, в частности, для лечения глиобластом, в зависимости от параметров, включая частоту, мощность, длительность импульса и рабочий цикл.*

Методы. *Проведены анализ и интерпретация имеющихся публикаций, для поиска которых использовалась база данных PubMed и ключевые слова «focused ultrasound, glioma, HIFU, LIFU», а также поисковые системы Яндекс и Google и ключевые слова «фокусированный ультразвук, глиомы, HIFU, LIFU».*

Результаты. *ФУЗ низкой интенсивности можно использовать для временного открытия гематоэнцефалического барьера (ГЭБ), который ограничивает диффузию большинства макромолекул и терапевтических агентов в мозг. Высокоинтенсивный ФУЗ может вызвать абляцию опухоли за счёт гипертермического эффекта, а также стимулировать иммунологическую атаку опухолевых клеток, активировать соносенсибилизаторы для оказания цитотоксического воздействия на опухолевую ткань и может повышать чувствительность опухолей к лучевой терапии. Гистотрипсия вызывает абляцию опухоли посредством акустической кавитации.*

Заключение. *Фокусированный ультразвук является многообещающим потенциальным методом лечения глиом. Дальнейшее изучение в виде клинических испытаний должно определить оптимальные параметры ультразвука для достижения эффективности лечения пациентов со злокачественными опухолями головного мозга.*

Ключевые слова: *онкология, фокусированный ультразвук различных интенсивностей, детская онкология, нейроонкология*

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INTRODUCTION

Gliomas of high malignancy in adults and children represent tumours with a high degree of lethality. As a result of the diffuse nature of the growth of the disease, surgical intervention is not always possible. Chemotherapy has low efficacy due to low blood-brain barrier (BBB) permeability. As a consequence of its low radiosensitivity, radiotherapy is mainly palliative. Unsatisfactory results of treatment of malignant neoplasms of the central nervous system (CNS) for many decades have forced researchers to search for alternative options to improve treatment outcomes [1, 2], some of which are immunotherapy, oncolytic virotherapy, and vaccine therapy. Immunotherapy is an emerging therapeutic field that uses many different techniques to stimulate the body's existing immune response to a tumour. This therapy has demonstrated remarkable success in haematological malignancies unresponsive to conventional therapies such as surgery, radiation and chemotherapy. A form of immunotherapy is chimeric antigen receptor (CAR) T-cell therapy, a new form of cancer treatment approved by the U.S. Food and Drug Administration (FDA). CAR is a modified surface receptor that adds specificity to T-cells to a pre-defined target antigen exhibited on tumour cells. These synthetic receptors are retrovirally or lentivirally integrated into patient-derived T-cells and re-injected into the patient: they thus represent a special type of personalised tumour therapy. Albeit CAR-T-cell therapy is making great strides in the treatment of haematological tumours, its efficacy remains unproven in the treatment of solid tumours such as glioblastoma (GBM) [3, 4]. Studies have shown that T-cells in the tumour immune microenvironment of glioblastoma are mainly T-regulatory (Treg) cells and depleted cytotoxic T-cells [5]. In summary, CAR-T has a natural immunosuppressive effect in the treatment of glioblastoma. The combination of CAR-T and immune checkpoint inhibitors such as PD-1 antibodies may be an effective solution strategy [6]. CAR-T cell therapy, however, can cause side effects such as immune autoaggression diseases, neurotoxicity and cytokine storm. Additionally, CAR-T-cell therapy also faces many challenges such as tumour heterogeneity, off-target effect and low tumour infiltration efficiency [7].

One of the promising directions in the search for innovative preparations for the treatment of oncological diseases is the use of oncolytic (natural or genetically modified) viruses (OVs) for selective action against tumour cells and their destruction, especially as part of combination therapy. Clinical trials of oncolytic viruses in this patient group have shown promising results, with patients achieving impressive long-term clinical responses. However, OV response rates remain low. This is thought to be due to the great heterogeneity of these tumours, both in terms of molecular composition and their immunosuppressive microenvironment, leading to variability in responses [8].

Vaccine therapy against cancer has shown great promise from both preventive and therapeutic perspectives [9]. Anti-cancer vaccines are designed to target tumour-associated antigens to induce an immune response against tumours. Considering that glioblastoma-specific antigens are rare, tumour-associated antigens are the targets. Current results from clinical trials of vaccines against high grade gliomas are not very promising, the lack of GBM-specific antigen and the high heterogeneity of tumours pose challenges for GBM vaccine therapy. Therefore, the study of DMST (Diffuse midline structures tumours) at the molecular genetic level is one of the urgent tasks in neuro-oncology. Unfortunately, these treatment options are experimental due to mixed results.

Nevertheless, advances in BBB disruption using focused ultrasound have opened up new ways to deliver chemotherapeutic agents, which we believe may be a promising method that could improve treatment efficacy by increasing the concentration of systemically administered medications in the brain parenchyma, thereby potentially increasing survival in this group of patients.

HISTORICAL BACKGROUND

The focused ultrasound (FUS) method itself is not particularly novel. It involves the machine emitting ultrasonic waves from different directions, with the waves converging on the area of interest, having the strongest effect there. Experimental study of the effect of high-intensity ultrasound on the animal organism was carried out by American researchers R.W. Wood and A.L. Loomis back in 1927 [10].

In 1942 William Fry, a veteran physicist in naval sonar research, and his brother Francis Fry began research at the Bioacoustic Research Laboratory (University of Illinois), where they developed a focused ultrasound device that focused ultrasound waves at 840 kHz (the first focused ultrasound device). They performed exposure of liver tissue to the FUS, obtaining an ablation effect. At the same time, when they attempted to irradiate the brain in animals, they failed to produce any significant damaging effect on its pathological tissue without applying the maximum possible power, which, among other things, was also accompanied by necrosis of the skin and bones of the skull. Two years later, however, they still managed to achieve selective impact of ultrasound on the brain by creating a trepanning window in the skull for its application. Already in 1950, they successfully succeeded in destroying a small focus in the human brain without damaging healthy tissue in a patient with Parkinson's disease [10].

In the 1950s the role of ultrasound as a possible method of treating tumours in humans and animals was actively studied by a research team led by Andrei K. Burov with the participation of a group of oncologists headed by Academician Nikolai N. Blokhin. In fact,

these researchers were pioneers in the use of high-intensity ultrasound in oncology. The results of their work are still known to specialists all over the world, they formed the basis for a number of subsequent studies. The ultrasonic wave sources they developed were characterised by high power: they used unfocused ultrasonic beams with a frequency of 1.5 MHz 200–500 W. Brown-Pearce carcinomas that had been transplanted into the testicles of rabbits were treated with such waves once. In 60–80 % of cases, the tumour either disappeared completely or underwent scar degeneration. Most notably, regression of not only the primary tumour but also its metastases, which were not affected by ultrasound, was observed, which could probably be explained by an immune mediated effect. In this case, repeated tumour grafting in experimental animals became impossible. The team headed by A.K. Burov also tested this method in the clinic: 10 people with terminal stage melanoma were treated, some of them showed complete disappearance of the tumour [10]. To date, Russian physicists are actively continuing research in this area. An example is the laboratory of industrial and medical ultrasound at the Department of Acoustics, Faculty of Physics, N.V. Lomonosov Moscow State University (headed by Oleg A. Sapozhnikov, Vera A. Khokhlova). One of the main directions of activity of this laboratory is the study of powerful focused ultrasound in therapy and non-invasive surgery, including modelling and measurement of nonlinear fields of medical ultrasound sources, investigation of the mechanisms of ultrasound effect on biological tissues, development of powerful multi-element phased arrays for ultrasound surgery [8].

It should also be emphasised that currently researchers from the Laboratory of Medical and Industrial Ultrasound at the Department of Acoustics, Faculty of Physics, N.V. Lomonosov Moscow State University, together with colleagues from the University of Washington (Seattle) as part of an international team are conducting studies aimed at the impact of focused ultrasound radiation on various tissues and organs inside the human body, non-invasively, i.e. without conventional surgical intervention. Meanwhile, this actively developing scientific trend has existed for about a quarter of a century and rather quickly moved from purely laboratory experiments to clinical use. For instance, in the last ten years it has become especially relevant as a result of the use of high-intensity FUS, in which researchers have learned to cause thermal necrosis of tumour tissues in the prostate, kidney, liver, breast and even in the brain, and the list is not exhausted [11].

In this regard, we would like to note the fact that the undoubted priority of domestic researchers in this area of medical science was signalled by the following international event. For her contribution to interdisciplinary research in biomedical and physical acoustics, V.A. Khokhlova was honoured in 2023 with the Helmholtz-Rayleigh Silver Medal of the Acoustical Society of America. With this award, the authoritative acoustics community recognised many years of successful studies by Vera A. Khokhlova and her associates concerning the use of nonlinear acoustic effects in medical applications of high-intensity ultrasound.

At the end of the XX century, namely in 1991, A. Gutkelch, K. Hininen, et al. reported about the treatment of malignant brain tumours with focused ultrasound hyperthermia and irradiation, and already in 1992 K. Hininen, et al. first proposed to use non-invasive focused ultrasound combined with magnetic resonance imaging (MRI) to control and monitor tissue damage. In doing so, the term MRI-guided focused ultrasound (MRgFUS) was first proposed. In 2001, the first International Society for Therapeutic Ultrasound (ISTU) was established to expand and disseminate knowledge of therapeutic ultrasound to the scientific and medical community. During the same year, G. Clement and K. Hininen demonstrated noninvasive focusing through the human skull using a phased array and a CT-based planning algorithm, and in 2006, M. Kinoshita, et al. demonstrated antibody delivery across the blood-brain barrier in brain tumours using MRgFUS [10].

Considerable experience in the use of ultrasound ablation for the treatment of neoplasms of different localisation: prostate cancer, breast cancer, liver cancer, bone tissue tumours, brain tumours has been accumulated in China [10, 12-14].

EXPOSURE TO HIGH-INTENSITY ULTRASOUND

Currently, focused guided ultrasound under the control of MRI or ultrasound is used to ablate certain areas of the brain in the treatment of a number of neurological diseases: essential tremor, Parkinson's disease with predominant tremor, neuropathic pain - as well as for stopping bleeding, crushing kidney concretions. Additionally, thermal ablation with high-intensity ultrasound is officially approved in various countries for the treatment of malignant and benign tumours of the breast, prostate, liver, as well as uterine fibroids, primary and secondary tumour involvement of skeletal bones [15-20].

High-intensity ultrasound acts upon the tissues by warming them up. It penetrates through healthy tissues, causing a short-term, on the order of one second, temperature increase at the focal point by absorbing ultrasound waves and cavitation, sufficient for the development of coagulation necrosis [13]. In other words, the essence of such technologies using high intensity focused ultrasound (HIFU) is that the energy of the ultrasound beam penetrating into the human body from an external source is absorbed in the area of the affected organ, resulting in thermal denaturation [14]. In summary, without compromising the integrity of the surrounding tissue, high-intensity focused ultrasound allows to destroy of the tumour tissue, in other words to perform «non-invasive surgery».

To achieve this effect, sound waves with a frequency of 0.8–4 MHz and an intensity of 100–10000 W/cm^2 are used. The intensity of ultrasound used for therapeutic purposes is categorised into high (1000–10000 W/cm^2), medium and low (< 3 W/cm^2). As a comparison, in ultrasound diagnostics, the tissue exposure power ranges from 0.004 to 7.5 W/cm^2 [20, 21].

At the IV International Symposium dedicated to focused ultrasound in 2014, two cases were presented involving the use of the ExAblate Neuro 4000 device for ultrasound-guided thermodestruction of intracranial neoplasms – glioblastoma (in the thalamus region) and metastasis. In both observations, MRI after the procedure demonstrated partial destruction of tumour tissue [22]. Attempts to use brain tumour ablation in the clinic were reported earlier, in 1996–2010 [23], but these were only single cases or phase I trials on series of up to 15 patients, and these studies did not provide sufficient data concerning long-term follow-up, in particular, the dynamics of tumour size. As will be demonstrated below, the main focus of subsequent studies in this area has been focused on the application of low-power FUS rather than ablation.

As ablation with high-intensity ultrasound has been applied in several areas of oncology, certain disadvantages have been revealed, such as the risk of skin and bone burns in the path of the ultrasound wave to the focus, the difficulty in visualising the irradiated areas in real time using diagnostic ultrasound machines, and the possibility of damage to the bone and vessels around the irradiated area as a result of heat diffusion from the focus area. Consequently, alternative methods of mechanical tissue destruction, or histotripsy, have been proposed that overcome these disadvantages and also offer some other advantages. One of these methods is the so-called boiling histotripsy. A.P. Duryea, et al. [24] provide the following definition: histotripsy is a technology of pulsating focused ultrasound, when the initiation and control of acoustic cavitation allow for precise mechanical fragmentation of tissues. High-intensity ultrasound pulses of millisecond duration are propagated from the transmitter and focused inside a specific organ. Due to nonlinear acoustic effects, the wave profile becomes distorted as it propagates away from the transmitter, resulting in a shock front at the focus at each wave period. Absorption of the energy of such a nonlinearly distorted wave with a shock front results in rapid localised heating of the tissue at the focus, leading to its boiling during each pulse. This produces a vapour cavity measuring millimetres in size, noticeably larger than the volume of the superheated tissue area. The interaction of the shock wave with this cavity leads to the formation of an acoustic fountain and, consequently, to the fragmentation of the tissue into small fragments of subcellular dimensions. That is, it is the «fountain» that has the main damaging effect, and heating plays the role of only a «trigger», while eliminating the risk of damage to healthy tissues in the path of ultrasound [15]. As a result of the appearance of vapour cavities, the ablation site is easily visualised with ultrasound as a hyperechogenic area.

There have been sporadic studies regarding the use of histotripsy in animals to date. For instance, the experiments with pigs managed to create necrosis zones in the cerebral cortex up to 1 cm in size without significant complications [25]. No significant complications were revealed in histotripsy of a mouse model of gliomas in the work of S.W. Choi, et al. [26]. Histotripsy using focused ultrasound in mice with glioblastomas leads to the release of tumour antigens and increases the number of immune cells in its microenvironment; in addition, in mouse models, histotripsy of liver, kidney, and pancreatic cancers, as well as neuroblastoma and melanoma, leads to a significant increase in animal survival [26, 27]. Clinical trials of histotripsy in brain tumours have not yet been conducted.

A relatively low ultrasound power is not used for ablation, but for implementation of various ways to improve drug delivery to the tumour zone [17, 21].

INCREASED BLOOD-BRAIN BARRIER PERMEABILITY

The presence of the blood-brain barrier, the function of which is to protect the brain from toxic substances, is considered as one of the reasons for the low efficacy of chemotherapy for brain high grade gliomas [28]. The BBB is formed by endotheliocytes, processes of astrocytes, pericytes, neurons, microglia macrophages, in addition, it includes extracellular matrix and glycocalyx [16, 29, 30].

It is known that the BBB is sometimes disrupted in glioblastomas (in the so-called «leaky» areas), as evidenced by the areas of contrast agent accumulation during MRI; however, in other parts of the tumour the BBB remains intact [31, 32]. This «diversity» of BBB permeability in glioblastomas is favoured by a variety of angiogenesis mechanisms [31]. The BBB within the tumour prevents most antitumour drugs penetration. Specifically, in the work of J. Portnow, et al. [33] has been demonstrated that in the brain of patients with glioblastoma or metastases of malignant tumours the average concentration of Temozolomide after its oral administration is approximately 5 times lower than in plasma.

One exception is Erlotinib (Tarceva), a HER1/EGRF epidermal growth factor receptor tyrosine kinase inhibitor used to treat brain metastases in non-small cell lung cancer. This preparation has a number of essential properties: it is fat soluble; it has no charge; its molecule is less than 500 D; there is no rapid elimination of this drug from the CNS [16]. Surgery and radiotherapy contribute to BBB disruption, but apparently this effect in malignant gliomas is not sufficient, considering the low efficacy of most chemopreventive agents [16]. Obviously, direct injection of an antitumour drug into

the tumour or intrathecal injections could be considered to overcome the BBB, but these techniques are associated with neurotoxicity and it is difficult to ensure prolonged exposure of the drug to the tumour tissue [34].

In view of the above problems, the technique of applying low-intensity focused ultrasound (LFUS) was established. Preclinical and clinical studies have revealed that this method can temporarily (for 24–72 hours) open the BBB without tissue damage, facilitating the penetration of antitumour drugs into the glioma area, and repeated sessions are possible. This technique involves the use of low-power ultrasound waves combined with intravenously administered microbubbles. When microbubbles travelling through the bloodstream are exposed to LFUS, they begin to periodically expand and contract. This process is called stable cavitation, it has a mechanical effect over the vascular walls, leading to reorganization tight junction proteins and increased drug penetration through the BBB. In this case, due to the mentioned cavitation phenomenon, less ultrasound power is required to disrupt the BBB, which ensures its safety, which has been evidenced in a number of experiments involving small and large animals. At the same time, LFUS slows down the elimination of anticancer drugs from brain tissue [16, 33, 35]. Besides, temporary disruption of the BBB during LFUS exposure can cause an acute inflammatory response leading to activation of immune system elements in the glioblastoma microenvironment [34].

In clinical studies, T1-weighted and dynamic MRI with contrast are used to assess the degree of BBB opening. It remains to be elaborated, however, how to confirm the increased drug accumulation in the tumour when LFUS is used locally [14].

In a review by J.W. Roberts, et al. [17] there have been 10 recently completed or currently ongoing clinical trials concerning BBB opening by ultrasound in the treatment of glioblastoma in adult patients, which are conducted in a number of countries: USA, Canada, South Korea, Taiwan, France, Switzerland, Belgium (NCT03712293, NCT03744026, NCT04417088, NCT04446416, etc.). This technique is used in them to improve the efficacy of the following drugs: carboplatin, temozolomide, pacitaxel, bevacizumab. One of these studies is NCT04614493 (France). In this phase I study of 19 patients with recurrent glioblastoma, ultrasound was delivered by an implantable device (SonoCloud-1; CarThera, France) before intravenous carboplatin administration.

In those 11 patients who achieved clear BBB disruption according to MRI, survival rates were slightly higher than in those with no or minor disruption: overall survival was 12.9 and 8.6 months, and progression-free survival was 4.1 and 2.7 months, respectively. In general, the FUS procedure (so-called sonification) was tolerated satisfactorily; 2 cases of swelling in the tumour area were observed, the manifestations of which were controlled with steroids [35]. The results of the other mentioned studies have not yet been published. Apart from that, preclinical testing of the effect of low-intensity FUS aimed at increasing BBB permeability in midline gliomas for drugs from the group of small molecules and monoclonal antibodies is being carried out at the Princess Maxima Centre for Children's Oncology (Utrecht, the Netherlands) [36]. In this group's study involving a mouse model of pontine glioma, a more than 5-fold increase in Olaparib bioavailability due to the opening of the BBB by means of FUS was revealed, which slowed tumour development during radiotherapy, although it did not lead to increased survival of the animals. The authors conclude that preclinical studies should be continued [37].

SELECTIVE ULTRASOUND EFFECTS ON TUMOUR CELLS

Undoubtedly of interest is the work of D.R. Mittelstein, et al. [38], conducted *in vitro* using cellular models of breast cancer, colon cancer and leukaemia, which demonstrated that the use of low-intensity ultrasound < 5 W/cm^2, with a frequency of 0.5–0.67 MHz, pulse duration > 20 ms leads to selective damage to the cells of these malignant tumours without significant effect on healthy immune cells or erythrocytes. Physical experiments have revealed that acoustic standing waves and cavitation lead to cytoskeletal disruption, increased expression of apoptosis markers and death of tumour cells. The selectivity of the effect against the tumour cells, according to the authors, advantageously distinguishes this technique from ablation with high-intensity ultrasound. The methodology needs further validation.

INCREASING THE EFFECT OF RADIATION THERAPY USING FOCUSED ULTRASOUND

Moderate hyperthermia of tissues under the influence of FUS can lead to an increase in their oxygenation and perfusion, thus increasing their sensitivity to radiotherapy [39, 40]. The world's first clinical study involving the use of FUS for radiosensitisation in glioblastoma is currently being conducted in Taiwan [17].

SONODYNAMIC THERAPY

So-called sonodynamic therapy (SDT) is now being developed, in which FUS locally converts a substance inactive against the tumour into an antitumour drug. As a sonosensitizing agent, for example, 5-ALA and Fluoroscein are used. These drugs selectively accumulate in tumours such as glioblastoma and are now being used to improve tumour imaging during neurosurgery as they are activated not only by sound but also by light. Ultrasound by not quite clear mechanisms, interacting with these drugs, leads to the formation of reactive oxygen species that cause apoptosis. Two

clinical studies (one in the USA, one in Italy) concerning the use of sonodynamic therapy in malignant gliomas are now being conducted [17]. Most accredited theories include the effects of cavitation, generation of reactive oxygen intermediates (ROIs), induction of apoptosis in cancer cells, improvement of anti-tumour immunity, inhibition of angiogenesis and induction of hyperthermia [41].

1. Cavitation effect

The cavitation mechanism involves the formation and expansion of microbubbles filled with gas or liquid medium. Bubbles are usually formed from gases dissolved in the medium or from pre-existing nuclei, such as microbubbles injected as ultrasound contrast agents. The negative «rarefied» components of ultrasonic waves allow the expansion of small stabilised gas-filled «cavities» or bubbles within a liquid medium [42]. Under the influence of ultrasound pressure, these bubbles commence to oscillate, causing vibrations of the cell membrane or, if higher intensity ultrasound is applied, strong shock waves, compressing and thereby causing mechanical damage to the surrounding tissues. This phenomenon favours the breakdown of water molecules and the subsequent formation of hydroxyl radicals and hydrogen atoms

2. Reactive oxygen intermediates generation

The scientific basis of SDT relies heavily over the generation of ROIs through the simultaneous combination of low intensity ultrasound, molecular oxygen and sensitising drug [42]. The generation of ROIs in SDT appears to be closely related to the cavitation effect: the maximum expansion of gas bubbles and the subsequent rapid implosion release significant energy, leading to an increase in temperature and pressure in the surrounding microenvironment. It has been suggested that these extreme temperatures and pressures at the time of explosion act as a «sonicochemical» reactor capable of generating ROIs in the presence of water and oxygen; these unstable molecules, if formed intracellularly, can exert strong cytotoxic effects such as oxidative stress, DNA damage and apoptosis, and can induce lipid peroxidation if formed near the cell membrane. ROI formation in this process is mainly attributed to sonoluminescence and pyrolysis mechanisms.

3. Induction of apoptosis in cancer cells

Under normal conditions, cells are able to clear a certain number of ROIs as they are normally produced in the body during respiration; however, during SDT, excess ROIs are generated that cannot be immediately excreted and cause oxidative stress within the cells. Oxidative stress affects mitochondrial membrane potential, which may eventually lead to apoptosis [42].

4. Improved anti-tumour immunity

Generally, the effects of SDT by targeting the tumour microenvironment and tumour cells (both immune infiltrating and tumour cells) may increase tumour immunogenicity.

5. Angiogenesis restriction

Even if this mechanism is still not evident, the anti-angiogenic effects of SDT with 5-ALK were observed by V Choi, et al. both *in vitro* and *in vivo*; in particular, they observed that SDT using low-intensity ultrasound significantly inhibited endothelial cell proliferation and migration *in vitro*, as well as the ability to form capillary networks; consequently, in an *in vivo* study on a rodent model of human tongue cancer xenograft they showed that the expression of vascular endothelial growth factor, a critical proangiogenic factor, was significantly reduced after SDT treatment compared to subjects receiving only ultrasound or a control group [42, 43].

6. Hyperthermia induction

In some preliminary studies, ultrasound-induced hyperthermia has been demonstrated to enhance the effect of SDT, although the exact mechanism of this effect is still not evident [41].

FOCUSED ULTRASOUND AND LIQUID BIOPSY

Y. Meng, et al. [44] after exposure to low-power FUS at the tumour areas in 9 patients with glioblastomas observed an increase in the blood of brain and tumour biomarkers, in particular, extracellular circulating DNA, the methylation profile of which indicated its possible origin from the tumour. The authors attribute this effect to the temporary opening of the BBB as affected by ultrasound. Previously, similar effects were observed in animal experiments [45, 46]. Proceeding from these data, it can be concluded that FUS is a promising method for increasing the informativeness of liquid biopsy in malignant gliomas of the brain.

CONCLUSION

These literature data evidence that focused ultrasound of different intensities is considered by researchers in a number of countries as one of the promising ways to improve the effectiveness of treatment in oncology, particularly in brain tumours. However, it should be emphasised that studies in this area have so far been conducted mainly in the form of basic physical research and experiments on cellular models and animals. Clinical trials are still very few and have not exceeded in general the Phase I. Nevertheless, one cannot ignore the fact that in our country there is a well-defined basis for conducting studies related to the application of FUS in clinical terms. At the same time, the substantial experience of a number of Russian clinics in the treatment of malignant tumours of the CNS using modern conventional high-tech antitumour methods both in adults

and children, as well as the availability of modern equipment for MRI and ultrasound diagnostics, including liquid biopsy, and, along with this, the availability of original developments of Russian physicists allow not only to continue, but also to intensify the studies aimed at a deep understanding of the exact mechanisms involved, in particular, in focused ultrasonic disruption of the BBB.

Studies involving the use of sonosensitisers and ultrasound for sonodynamic treatment of gliomas, however, are currently at a very early stage. That said, before FUS becomes a routine treatment option for CNS tumours, studies are needed to confirm the sonodynamic effect in other preclinical glioma models besides the most commonly used rat C6 glioma cell line. More importantly, further studies to determine the optimal ultrasound wave parameters required for induction of sonodynamic effects in malignant cells without causing damage to healthy brain tissue are also a priority. Overall, the results obtained in such experiments may be invaluable for planning further *in vivo* preclinical studies and, in the future, clinical studies.

Concurrently, the preliminary clinical data published to date appear to offer the exciting prospect of a new method for the specific treatment of glioma that may be selective to malignant cells and at the same time practically non-invasive, which will allow its future use primarily in paediatric patients, as well as its repeated application in case of disease recurrence, especially after previous radiotherapy.

Conflict of interest

The authors declare the absence of apparent and potential conflicts of interest related to the publication of this article.

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Authors' contribution

Regentova O.S. – conception and design of the study; data collection and analysis; final approval for publication of the manuscript.

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Antonenko F.F. – collecting and analysing information.

Zelinskaya N.I. – collecting and analysing information.

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