South Russian Journal of Cancer 2023. Vol. 4, No. 1. P. 52-64
https://doi.org/10.37748/2686-9039-2023-4-1-6
https://elibrary.ru/iicmmc
REVIEW

MODERN APPROACHES TO GLIOBLASTOMA THERAPY

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ABSTRACT

Glioblastoma (GBM) is the most malignant and the most common primary tumor of the central nervous system. During the last several years GBM has been classified and managed according to the World Health Organization (WHO) criteria which subdivide it into primary and secondary GBM. As it is suggested, GBM originates from glial cells and has a diffuse growth pattern, but its etiology and pathophysiology are poorly investigated up to date. Its rapid progression and anatomical location in the brain often limits the effectiveness of therapeutic interventions. Despite all scientific and technological advances, GBM remains an incurable disease with a median survival of approximately 18 months. Standard treatment options involving maximal safe resection of the tumor followed with radiotherapy and chemotherapy do not provide satisfactory results.

Better understanding of the molecular pathology of GBM and its associated signaling pathways has opened up possibilities for new treatments for newly diagnosed and relapsing tumors. A multitargeted therapeutic approach using compounds capable of inhibiting more than one specific molecular target is a promising alternative to conventional therapies.

Currently, specialists study such innovative treatment options as small molecule inhibitors aimed at signaling pathway disruptions, immunotherapy, including checkpoint inhibitors, oncolytic vaccines, CAR T-cell therapy, and drug delivery systems. In terms of an innovative approach, the elaboration of targeted drug delivery systems is of particular interest, since this strategy looks the most promising due to its ability to increase the bioavailability and effectiveness of both standard and newly tested agents. This review discusses results of preclinical and clinical studies of innovative therapeutic approaches, their advantages and disadvantages. An interdisciplinary approach is expected to be able to combine the results of cutting-edge research in this area and to provide novel promising therapeutic strategies for patients with GBM.

Keywords:
glioblastoma, nanoparticles, immunotherapy, small-molecule inhibitors

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Funding: this work was not funded.
Conflict of interest: authors report no conflict of interest.

For citation:
Kuznetsova N. S., Gurova S. V., Goncharova A. S., Zaikina E. V., Gusareva M. A., Zinkovich M. S. Modern approaches to glioblastoma therapy. South Russian Journal of Cancer. 2023; 4(1): 52-64. https://doi.org/10.37748/2686-9039-2023-4-1-6, https://elibrary.ru/iicmmc

The article was submitted 08.06.2022; approved after reviewing 17.01.2023; accepted for publication 06.03.2023.

Южно-Российский онкологический журнал 2023. Т. 4, № 1. С. 52-64
https://doi.org/10.37748/2686-9039-2023-4-1-6
https://elibrary.ru/iicmmc
3.1.6. Онкология, лучевая терапия.
ОБЗОР

СОВРЕМЕННЫЕ ПОДХОДЫ К ТЕРАПИИ ГЛИОБЛАСТОМЫ

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РЕЗЮМЕ

Глиобластома (ГБМ) является наиболее злокачественной и часто встречающейся первичной опухолью центральной нервной системы. В течение последних лет ГБМ классифицировали и лечили в соответствии с критериями Всемирной организации здравоохранения (ВОЗ), которая подразделяет ее на первичную и вторичную. Считается, что ГБМ происходит из глиальных клеток, имеет диффузный характер роста, однако ее этиология и патофизиология не вполне изучены на сегодняшний день. Быстрое прогрессирование опухоли, её анатомическая локализация в головном мозге часто ограничивают эффективность терапевтических вмешательств. Несмотря на все научно-технические достижения, ГБМ остается неизлечимым заболеванием с медианой выживаемости пациентов примерно 18 мес. Стандартные схемы лечения, включающие в себя максимальное хирургическое удаление опухоли с последующим облучением и химиотерапией, не обеспечивают удовлетворительных результатов.

Значительные успехи в понимании молекулярной патологии ГБМ и связанных с ней сигнальных путей открыли возможности для новых методов лечения впервые диагностированных и рецидивирующих опухолей. Многоцелевой терапевтический подход, направленный на использование соединений, способных ингибировать более чем одну конкретную молекулярную мишень, представляет собой многообещающую альтернативу стандартным методам лечения. В настоящее время изучаются такие инновационные варианты лечения как применение низкомолекулярных ингибиторов, нацеленных на нарушение сигнальных путей, иммунотерапия, включающая ингибиторы контрольных точек, онколитические вакцины, CAR-T-терапия, использование систем доставки лекарств. С точки зрения применения инновационного подхода особый интерес представляет разработка систем адресной доставки лекарств, так как именно эта стратегия выглядит наиболее перспективной в связи с ее способностью увеличивать биодоступность и эффективность как стандартных, так и впервые тестируемых препаратов. В данном обзоре обсуждаются результаты доклинических и клинических исследований инновационных терапевтических подходов, их преимущества и недостатки. Ожидается, что реализация междисциплинарного подхода способна объединить результаты передовых исследований в этой области, привести к созданию новых обнадеживающих терапевтических стратегий в отношении пациентов с ГБМ.

Ключевые слова:
глиобластома, наночастицы, иммунотерапия, низкомолекулярные ингибиторы

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Финансирование: финансирование данной работы не проводилось.
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

Для цитирования:
Кузнецова Н. С., Гурова С. В., Гончарова А. С., Заикина Е. В., Гусарева М. А., Зинькович М. С. Современные подходы к терапии глиобластомы. Южно-Российский онкологический журнал. 2023; 4(1): 52-64. https://doi.org/10.37748/2686-9039-2023-4-1-6, https://elibrary.ru/iicmmc

Статья поступила в редакцию 08.06.2022; одобрена после рецензирования 17.01.2023; принята к публикации 06.03.2023.

INTRODUCTION

Glioblastoma (GBM) is the most malignant and common primary tumor of the central nervous system (CNS), accounting for 30 % of all CNS tumors [1]. It is believed that GBM originates from glial cells, has a diffuse growth pattern, and its etiology and pathophysiology have not yet been fully studied to date [2]. In recent years, GBM has been classified and treated in accordance with the criteria of the World Health Organization (WHO), which divides it into primary and secondary [3]. According to WHO, primary GBM occurs de novo, aggressive in nature, is characteristic mainly of the elderly (median age 62 years), while secondary develops through malignant progression from less aggressive tumors, such as diffuse astrocytoma (grade II) or anaplastic astrocytoma (grade III) and manifests itself in younger patients (median 45 years) [3]. Although GBM can occur at any age, it should be noted that the incidence increases with age, with the average age of diagnosis being about 65 years, the median overall survival is about 15–18 months, and the average time interval before relapse is about 7 months, with a 5-year survival rate of less than 10 % [4].

To date, the standard of treatment for patients with GBM involves maximum surgical resection followed by radiation and chemotherapy, temozolomide (TMZ) is used as a first-line drug [4]. Due to the high degree of invasiveness, radical resection of the primary tumor mass does not lead to a complete cure, since infiltrating tumor cells invariably remain in the surrounding tissues. In this regard, further stages of treatment in the form of radiation (LT) and chemotherapy (CT) are required to prevent the progression and/or recurrence of the disease [4; 5] LT is one of the ways to combat malignant neoplasms/ cells based on the use of ionizing radiation. Cell death is caused by two causes: cellular stress and DNA damage, represented as single-stranded and double-stranded breaks [5].

The chemotherapeutic stage is based on the use of TMZ, which belongs to the class of alkylating agents with the ability to overcome the blood-brain barrier (BBB). After absorption, TMZ undergoes spontaneous hydrolysis and turns into an active metabolite of 5-(3-methyltriazene-1-yl) imidazole-4-carbosamide, which is further hydrolyzed to the methyldiazonium cation and 5-aminoimidazole-4-carboxamide [6].

The mechanism of action of the drug is realized by transferring an electrophilic alkyl group to a nucleophilic DNA atom, methylation of the nitrogenous bases of DNA adenine (at position N3) and guanine (position N7) occurs. At the same time, various types of damage formed in DNA activate specific repair pathways that allow to eliminate damage and can contribute to resistance to radio and chemotherapy. In this regard, the efforts of researchers are aimed at developing various approaches to the treatment of GBM, aimed at new molecular targets that could be used as therapeutic alternatives. However, most of them fail during clinical trials [6–11]. These failures may be associated with compensatory mechanisms due to the activation of the DNA repair system, high systemic toxicity, insufficient stability of drugs and other factors.

Nevertheless, new approaches to the creation of optimized treatment methods related to the understanding of the complex biology of GBM are able to increase the survival rate of patients with this disease [7].

In this regard, the purpose of the review was to consider some options for new therapeutic strategies currently being developed, such as inhibition of pathological signaling pathways, immuterapeutic drugs, drug delivery systems, as well as to discuss their advantages and disadvantages.

1. Therapeutic targets associated with the p53 signaling pathway.

TP53 is one of the most frequently deregulated genes in terms of cancer. It encodes the protein p53, which is associated with invasion, migration, proliferation, prevention of apoptosis and the properties of GBM stem cells.

Normally, p53 exhibits suppressor activity by altering the expression of genes involved in cell cycle arrest, apoptosis, stem cell differentiation, and cellular aging. It is usually activated in response to DNA damage, genotoxicity, oncogen activation, aberrant growth signal transmission and hypoxia [8]. Under normal conditions, its activity is low and is controlled by MDM2 and MDM4 proteins through ubiquitination and subsequent degradation.

MDM2 and MDM4 act as oncogenic inhibitors of p53 suppressive activity against tumors. MDM2 negatively regulates p53, causing its degradation in the

proteasome. Thus, inhibition of MDM2/p53 interaction for reactivation of p53 function is a promising strategy for cancer treatment, including GBM [9]. MDM2 transcription is induced by p53, creating a negative feedback loop. MDM4, unlike MDM2, which is responsible for cleavage of p53, inhibits this protein by binding it to the transcription activation domain.

Amplification of MDM2 and MDM4 can inactivate p53, which leads to the loss of various functions of tumor suppressors: growth arrest, apoptosis, and aging [11; 12]. MDM2 and MDM4 genes have been shown to be amplified and/or overexpressed in several different types of cancer [10].

P53 and α5ß1 integrins also play an important role in cellular processes, being part of the convergence pathway that controls the apoptosis of malignant neoplasms, which encourages researchers to look for effective molecules that can regulate both targets simultaneously [11].

For example: idasanutlin (RG7388,) is an MDM2 inhibitor, has greater efficacy and selectivity [12]. It has been recognized as an attractive therapeutic strategy for reactivating p53 by inhibiting MDM2 and MDM4, negative suppressors of p53. However, acquired resistance and toxicity continue to limit the development of this MDM2 inhibitor as a clinical antitumor agent [13].

Nutlins belong to the cis-imidazoline group of molecules that were detected by screening a chemical library of molecules to study anti-cancer efficacy. Some studies on animal models have shown that nutlin treatment, in particular nutlin3, led to an increase in p53 concentration, increased apoptosis and decreased oncogenicity in cells [14].

Later, nutlin analogues RG7388, MI77301, CGM097, MK8242 and AMG232 were developed and tested in clinical trials. Among them, AMG232 (KRT-232) has been shown to be the most effective and selective oral MDM2/p53 inhibitor with favorable toxicological properties *in vitro* and *in vivo* [15]. AMG232 showed relative selectivity towards wt-p53 stem cells and was very effective in inhibiting the growth of three-dimensional tumor spheroids [16]. It is assumed that the molecule will have a low clearance rate and a long half-life in humans.

2. RTK inhibition.

Signaling cascades of receptor tyrosine kinases (RTK) coordinate intracellular signaling in response to growth factors, chemokines, and other extracellular stimuli to control biological processes [17]. In healthy cells, receptor activity is strictly controlled, and RTK signaling regulates cellular processes such as apoptosis, growth, survival, and translation. RTK activation is triggered by the binding of extracellular ligands, which leads to the oligomerization of receptors and autophosphorylation of tyrosine residues in cytoplasmic domains, which leads to further signal transmission, the result of which is a change in the expression of a number of proteins important for cell life [17; 18].

RTKs include more than 50 different human receptors, including platelet growth factor receptors (PDGFR), vascular endothelial growth factor receptors (VEGFR) and epidermal growth factor receptors (EGFR/HER/ERBB) [18]. It has been demonstrated that RTK mutations associated with the occurrence and progression of multiple malignancies, including GBM.

A large number of studies have shown that malignant neoplasms, including GBM, are characterized by active angiogenesis due to the secretion of regulatory growth factors, such as vascular endothelial growth factor (VEGF), platelet growth factor (PDGF) [19].

The platelet growth factor (PDGF) family is necessary for a wide range of physiological processes, such as migration and proliferation of pericytes, which contribute to the formation and proper functioning of blood vessels. The deregulated activity of PDGFR contributes to the occurrence of various pathological conditions, and, consequently, members of the PDGF/PDGFR family are important therapeutic targets [20].

There are three main approaches to inhibiting the PDGF/PDGFR pathway: 1) sequestration of the ligand with neutralizing antibodies, soluble extracellular parts of the receptors; 2) disruption of the interaction between the ligand and the receptor by blocking the receptor with receptor-specific antibodies or low molecular weight inhibitors; 3) using low molecular weight inhibitors to block the kinase activity of PDGFR [21].

Imatinib is one such drug that has an inhibitory effect on PDGFR. Although imatinib has activity against other malignancies, it has not shown significant activity against GBM during clinical trials. Tumor growth and overall survival remained unchanged

regardless of whether the drug was used in mono- or combination therapy [22; 23].

Tandutinib is another PDGFR inhibitor that has shown little therapeutic effect in clinical trials for recurrent GBM. AG1433 is another PDGFR inhibiting molecule that has proven its activity in preclinical studies on several HGG cell lines (gliomas of high malignancy) *in vitro*. In 2019, it was tested on 11 and 15 HGG cell lines with and without radiation therapy. It was found that the AG1433 molecule is effective, but the combination with irradiation does not increase its activity [23].

Vascular endothelial growth factor (VEGF) plays a crucial role not only in stimulating the growth of tumor vessels, but also in the formation of an immunosuppressive state. VEGF can inhibit the function of T cells, enhance the involvement of regulatory T cells (Tregs) and suppressor cells of myeloid origin (MDSC), and hinder the differentiation and activation of dendritic cells (DC) [23]. The VEGF family includes VEGF A, VEGF B, VEGF C, VEGF D and placental growth factor (PlGF). These ligands with different affinities bind to three endothelial receptor tyrosine kinases: VEGFR1, VEGFR2 and VEGFR3 [24].

VEGF promotes tumor angiogenesis by stimulating, proliferating and surviving endothelial cells, as well as increasing vascular permeability and recruiting vascular progenitor cells from the bone marrow. Unlike the formation of mature vessels under normal conditions, intra-tumor vessels are complex, disorganized, irregular and leaky, which leads to hypoxia and ineffective delivery of antitumor agents into the tumor microenvironment [24]. The combination of these factors makes it possible to consider an angiogenesis inhibitor as one of the options for antitumor therapy.

However, the absence of an antitumor effect when using a VEGF inhibitor, observed in some models of orthotopic GBM xenografts in rodents, may be due to a decrease in permeability and vasogenic cerebral edema. Several adaptive resistance mechanisms can neutralize the potential initial benefit provided by antiangiogenic therapy. Under conditions of inhibition of VEGF signaling, the tumor and its microenvironment release alternative proangiogenic growth factors to stimulate VEGF-independent angiogenesis, which is further enhanced by recruiting proangiogenic myeloid cells [24; 25].

One of the options for antiangiogenic therapy is bevacizumab, which is an antibody to VEGF. Although bevacizumab has become a standard part of the treatment of GBM relapses, numerous studies have shown that it nevertheless does not increase survival [25–27].

It is assumed that the simultaneous administration of low-molecular-weight VEGF and PDGF inhibitors may have a positive effect on the results of chemoradiotherapy. Sorafenib is a multipurpose RTK inhibitor that is active in VEGF (VEGFR-2 and –3) and PDGF (PDGF β and Kit). In a preclinical assessment on cells, U87 administered in monotherapy mode showed a significant improvement in survival, but there was no positive dynamics in clinical studies. Vatalanib (PTK787) is another of the low molecular weight inhibitors of VEGFR, PDGFR and c-Kit., which has demonstrated safety and tolerability during clinical trials for the treatment of GBM [26]. Vandetanib (ZD6474), a low molecular weight tyrosine kinase inhibitor of VEGFR, EGFR and RET 23, in combination with other chemotherapeutic agents in clinical trials in patients with GBM showed good tolerability, but the survival rate did not change significantly. An unsatisfactory result may be associated with a number of problems, such as heterogeneity, inability to overcome BBB [26].

The epidermal growth factor receptor (EGFR) plays a central role in cell division, migration, adhesion, differentiation, and apoptosis. When bound to ligands, EGFR is activated by homodimerization or heterodimerization on the cell surface, which leads to phosphorylation of its intracellular tyrosine kinase domain. Studies have shown that EGFR amplification and mutation are the most common genetic changes occurring in more than 50 % of GBM cases [26; 27].

Many EGFR inhibitors such as erlotinib, gefitinib and lapatinib have been widely evaluated in the clinic for the treatment of GBM. Gefitinib in neoadjuvant mode showed that its concentration in the tumor was 20 times higher than in plasma, but this discovery was not associated with inhibition of the downstream pathway. Thus, the drug effectively acts on the EGFR receptor, but does not affect the downstream targets of this pathway. The same conclusion can be made to erlotinib and lapatinib [27]. These studies show that first-generation EGFR does not effectively inhibit EGFR signaling in GBM, and the

above observation may be the reason for the failure of these drugs.

Another of the selective EGFR inhibitors is AZD3759, which effectively penetrates the BBB, has a free concentration in the blood, cerebrospinal fluid and brain tissues.

The main problems of modern EGFR targeting strategies are the lack of BBB permeability, the molecular heterogeneity of GBM and the need to increase the specificity of low molecular weight EGFR mutation inhibitors [27].

2.1. Therapeutic targets, related to the I3K/Akt/mTOR pathway.

Several studies has shown that, with GBM signal transmission is realized through PI3K/AKT/mTOR.

PI3K/AKT/mTOR, the central component of which is phosphatidylinositol-3-kinase (PI3K), as well as AKT and mTOR kinases, is considered one of the universal signaling pathways characteristic of most human cells. It is responsible for avoiding apoptosis, growth, cell proliferation, and metabolism. The PI3K/Akt/mTOR signaling cascade is considered as a promising target of modern combination therapy. A number of inhibitors targeting key components of this pathway are undergoing clinical trials.

2.1.1. PI3K inhibitors.

PI3K is involved in proliferation, differentiation, migration, metabolism and survival and is divided into three classes depending on their substrate specificity and homological sequence. A growing amount of preclinical and clinical data suggests that PI3K inhibitors offer promising treatment options for oncological diseases, including GBM [28].

One of the PI3K inhibitors buparlisib is promising for the treatment of GBM due to its ability to penetrate the BBB. In xenograft models, buparlisib demonstrated antitumor activity regardless of EGFR status. In addition, the synergistic activity of buparlisib in combination with TMZ was manifested in xenografts of mice. However, clinical results have shown insufficient inhibition of general signaling by tolerated doses in patients with relapse. The reason for the lack of efficacy is that the PI3K pathway cannot be completely blocked in tumor tissues. Recent studies have shown that buparlisib in combination with the PARP inhibitor rukaparib shows improved antitumor efficacy compared to monotherapy with these molecules [29].

It has also been shown that PQR309 (bimiralisib) is an effective PI3K/mTOR inhibitor with good BBB penetration. This molecule has a strong inhibitory effect on PI3K, rather than on mTOR. It has been confirmed that bimiralisib has antitumor activity against GBM *in vitro* and *in vivo*. In addition, the combination of this molecule with an AKT inhibitor shows strong activity against GBM in the LN-229 63 cell line xenograft model in BALB/c Nude mice [30].

Another PI3K and mTOR inhibitor with good pharmacokinetic parameters is GNE-493. However, its poor penetration into the brain limits its use as a treatment for GBM. This molecule was used as a starting compound to obtain its analogues with improved permeability, by reducing the number of hydrogen bond donors. One of such analogues is GNE-317. It was developed taking into account the aforementioned shortcomings, and is an effective brain-penetrating PI3K inhibitor [30; 31].

The PI3K/mTOR inhibitor voxtalisib showed good activity on GBM xenografts, both in monotherapy and in combination with conventional therapeutic agents [31].

2.1.2. AKT/mTOR inhibitors.

In addition to PI3K, such components of this signaling as AKT and mTOR also contribute to the development and progression of GBM. It has been shown that an increase in the level of activated phosphorylated AKT, as well as hyperactivation of mTOR, contribute to uncontrolled growth of GBM cells and a decrease in survival, and therefore they can be considered as possible therapeutic targets [32–34].

In particular, GDC-0068 (ipatasertib) is a highly selective ATP-competitive inhibitor of pan-AKT, which leads to increased antiproliferative activity in cell lines with PI3K/AKT activation. Preclinical data have shown that ipatasertib can enhance the antitumor activity of classical chemotherapeutic drugs [35].

Among the mTOR inhibitors sirolimus, temsirolimus and everolimus are approved by the FDA. Sirolimus, a well-studied drug with antifungal, immunosuppressive and antitumor effects, is a macrolide antibiotic. Sirolimus is known for its ability to inhibit the mTOR signaling pathway and has been extensively studied for its therapeutic potential [36].

Palomin 529 (P529) is a dual mTORC1/2 inhibitor that can increase the effectiveness of radiation therapy by delaying the DNA repair mechanism [37]. P529 penetrates well into the brain, which provides support for further evaluation of its use in the treatment of GBM. AZD2014 is also a dual inhibitor of mTORC1/2, which enhances radiosensitivity both *in vitro* and in orthotopic conditions *in vivo*. It is assumed that a dual mTORC1/2 inhibitor may be a suitable radiosensitizer for the treatment of GBM [38].

Rapalink-1 is a third-generation mTOR inhibitor, which consists of sirolimus and MLN0128. It showed good inhibitory activity in mice with intracranial xenografts U87MG, was well tolerated and significantly improved survival.

Currently, there are a large number of targeted drugs targeting the PI3K/Akt/mTOR pathway that are undergoing preclinical or clinical trials. However, targeted GBM therapy has not yet demonstrated significant clinical survival benefits. Currently there are several possible reasons for the limited effect: 1) BBB, therefore targeted drugs cannot reach effective concentrations; 2) heterogeneity of GBM [39].

3. Immunotherapy.

For a long time, based on experimental data, the central nervous system was considered as an "immunoprivileged" system due to a small number of antigen-presenting cells (APC) and limited penetration of lymphocytes through the BBB. Currently, some studies have refuted this postulate and demonstrated the penetration of activated T-lymphocytes through the BBB, thereby showing that the central nervous system interacts with the immune system [40]. With a variety of pathological processes, there is a change in the permeability of the BBB due to anti-inflammatory cytokines. As a result, a large number of lymphoid and myeloid immune cells penetrate into the tissues of the central nervous system.

However, in comparison with other solid tumors, GBM is characterized by low infiltration of NK and T cells, nevertheless, various immunotherapy strategies for malignant brain tumors are currently being actively developed. The basic principle is that the host immune system can destroy the tumor provided the effector function is enhanced, this leads to the elimination of cancer cells by improving the recognition of tumor agents [41]. Immunotherapy is based on such strategies as immunomodulatory cytokine therapy, anti-cancer vaccines, checkpoint inhibitors, CAR-T therapy.

3.1. Cytokine therapy.

Cytokine therapy uses mediators of immune activation and proliferation, such as interleukins, interferons and granulocyte-macrophage colony stimulating factor, to create a broad antitumor response. Interleukins activate lymphocytes to initiate innate and adaptive immune responses. Interferons induce immune cells and inhibit angiogenesis in cancer immunotherapy [42].

However, the administration of cytokine therapy to patients with GBM is ineffective due to the short half-life and limited ability to overcome BBB. To solve these problems, high doses of cytokines should be administered, which in turn can lead to cytokine storms, autoimmune reactions and systemic side effects [43].

3.2. Immune control checkpoints inhibition.

Immune checkpoint inhibitors (ICIs) are molecules that reduce the activity of regulatory pathways that limit the activation of T cells. These inhibitors are aimed at interacting with cellular proteins that prevent the cytotoxic effect of T-lymphocytes [44]. The most studied molecules for cancer immunotherapy using ICI inhibitors are CTLA-4 receptors (cytotoxic T-lymphocyte-associated protein 4), PD-1 (Programmed cell death 1) and its PD-L1 ligand (Programmed death-ligand 1).

CTLA-4 and PD-1 are expressed on the surface of T cells. Tumor cells, evading the immune ones, express PD-L1. However, despite the positive results obtained during preclinical trials, some clinical studies using ICI inhibitors (anti-PD-1 and anti-CTLA-4, separately and in combination) in GBM showed no improvement in patient survival [45–47]. These and other studies have revealed the reasons for the low effectiveness of these inhibitors: BBB, low infiltration by tumor T cells and multilevel immunosuppression by elements of the tumor microenvironment [47].

3.3. Vaccines.

Vaccines are known as a means to stimulate immune effector cells and enhance their infiltration into tumors. They are divided on the basis of nucleic

acids, neoantigens, peptides and cells. Therapeutic vaccines contribute to the determination of antigens expressed by tumor cells for further detection and destruction of the cancer focus by the immune system.

Nucleic acid-based vaccines are injected as a segment of genes, DNA or RNA encoding tumor antigens and causing an immune response. Vaccines containing RNA have certain advantages over those containing DNA, this is due to the direct translation of antigenic proteins and higher safety. However, one should not forget that "pure" RNAs are susceptible to nucleases and can be destroyed before APC transfection [48].

Neoantigenic vaccines are new epitopes resulting from mutations in the genome of tumor cells. They have high specificity, antigenicity and safety [48]. At the stage of the first clinical trials is a personalized combined vaccine GAPVAC-101, containing neoantigen and unmutated antigen targeted against GBM.

Cellular vaccines are mainly created using dendritic cells (DC), which are responsible for activating adaptive immunity and stimulating B and T lymphocytes. In this type of immunotherapy, DC is isolated from the blood of patients to stimulate antigen-presenting properties *in vitro*, and then injected back into the patient to activate effector cells [49]. The advantages of therapy with this type of vaccine are the induction of an antitumor T-cell response, an increase in tumor immunogenicity due to the strengthening of antigen-presenting functions of DC and the ability to link innate immunity with adoptive immunity. This is important, in particular for low-immunological tumors, such as GBM [50].

3.4. Chimeric antigen receptor T cells (CAR).

Adaptive T-cell immunotherapy is an antigen-specific approach based on the transformation of the patient's own immune cells. T-cells obtained from patients with tumor diseases undergo modification outside the human body. As a result of modification, the T-lymphocyte acquires a tumor-specific chimeric antigen receptor (CAR) to provide more effective target recognition [51].

One of the barriers affecting the effectiveness of CAR-T-cell therapy in solid tumors, such as GBM, is the high heterogeneity and diverse expression of tumor antigens. The creation of CAR T cells targeting multiple antigens by expressing multiple CAR on T cells is considered as an approach to overcoming this limitation [37].

4. Alternative drug delivery systems.

The search for alternative effective treatment methods is associated not only with the emergence of new therapeutic agents, but also with the development of drug delivery systems. Systemic drug delivery is seen as a promising and universal prospect that can overcome the failure of systemic drug administration. In this area of research, there are a number of materials that can be used to increase the absorption of chemotherapeutic drugs by cells. In some works, the results of work in the field of application of nanostructures of various sizes, physico-chemical properties and forms for the treatment of oncological diseases were demonstrated. They may include lipid and/or polymer materials that are capable of generating structures such as liposomes, micelles, exosomes, polymer and inorganic nanoparticles, polymer conjugates. In this regard, their properties depend on the components used, which determine their further function [52].

Each nanostructure should be carefully studied and designed to achieve maximum therapeutic effect with minimal possible side effects on the body. Most of them can be modified so that they respond to various internal or external stimuli, which is an advantage for controlling the release of encapsulated therapeutic substances. The design of drug delivery systems must be specific in order to successfully target the affected area without affecting the surrounding tissues [53].

Nanoparticles (NPS) are transport systems ranging in size from 1 to 100 nm. Their use can provide such advantages as prevention of premature degradation of drugs in the bloodstream, improved penetration into cells, targeted delivery of immune drugs and enhanced absorption [54]. Also, LPS are used to overcome BBB, which is known to be one of the main reasons complicating the delivery of therapeutic molecules into the brain, thereby limiting their effectiveness. To overcome this limitation, modern therapeutic agents are loaded inside polymer or lipid nanostructures that have the ability to penetrate through the BBB.

Lipid nanocarriers are divided into categories depending on the physicochemical properties and methods of creation. The main lipid – based carriers include: 1) niosomes, which are lamellar self-assembling structures consisting of nonionic surfactants and cholesterol; 2) transferosomes, similar to niosomes and liposomes, consisting of a lipid bilayer created from a lipid matrix stabilized by various surfactants; 3) liposomes, which are spherical vesicles created by a lipid bilayer of phospholipids; 4) solid lipid nanoparticles consisting of a solid lipid core and 5) nanostructured lipid carriers whose core contains a liquid lipid phase inside a solid lipid phase [55–58].

Solid lipid nanoparticles are one of the newly developed groups of lipid-based nanocarriers. They have the ability to efficiently deliver both lipophilic and hydrophilic drugs, as well as other therapeutic molecules, to numerous affected tissues. They reduce the toxicity of the therapeutic molecule they carry, while protecting them from clearance by the reticuloendothelial system. Their inherent ability to dissolve poorly in water leads to a controlled and delayed release of drugs, long-term stability allows them to be used for a long period of time. Against the background of many advantages, solid lipid nanoparticles have a number of disadvantages: displacement of the encapsulated therapeutic agent, tendency to gelation and low encapsulation efficiency. The low encapsulation efficiency is due to the internal structure of the lipid nucleus, which does not create empty spaces during crystallization, which makes it difficult to retain the potentially encapsulated substance inside the solid phase [56–59].

Polymer nanoparticles are stable structures that provide controlled and delayed release of the drug and can be modified in such a way as to respond to external or internal stimuli. In the literature, most nanoparticle delivery systems that have been used to treat brain diseases consist of synthetic polymers such as polyethylene glycol, polylactide, chitosan, poly(L-lactide-co-glycolide) (PLGA), polyacrylic acid (PAA), polylactide (PLA), polyvinyl alcohol (PVA). Their chemical composition affects stability, biodegradability, biocompatibility, bio-distribution, cellular and subcellular fate. They can be modified to package and deliver therapeutic agents to the desired site of action or to respond to certain physiological and external stimuli [57; 58]. One of the conditions for the development of polymer nanoparticles for medical applications is their biodegradability, which should depend on the therapeutic application, target sites (organs, tissues, cellular or subcellular organelles) and the route of administration.

This system has a negative impact on humans: low solubility and decomposition in acidic by-products is a limitation for their use in brain diseases. In addition, the use of organic solvents to produce most of these nanoparticles is another disadvantage that can cause problems of increased toxicity [58].

Metal nanoparticles (MNPs) are a nanomaterial for targeted therapy and visualization of malignant brain tumors. Conjugation of peptides or antibodies with the surface of MNCs allows direct targeting of the surface of tumor cells and potentially disrupting active signaling pathways. Most MNCs are being developed as contrast agents for magnetic resonance imaging (MRI) and computed tomography (CT) probes [59]. However, most of these studies are only preclinical.

Among MNPs, only iron oxide nanoparticles (IONP) are approved by the FDA for preclinical and diagnostic studies. Their unique properties, such as low toxicity, biocompatibility, superparamagnetic properties, excellent solubility in water and catalytic behavior, make them promising candidates for biomedical applications [59].

Medicines created thanks to the development of nanotechnology have been widely used in the biomedical field in the last decade. These compounds can be inorganic or organic, of various shapes and sizes. The combination of different materials gives these nanostructures their universal properties and makes them so attractive in nanomedicine.

CONCLUSION

Up to the date, an obvious need to develop new effective methods of treating GBM still remains. The solution of this difficult biomedical problem is greatly facilitated by the pronounced progress of interdisciplinary research and the promising results obtained during them. One of the priorities in this area is the development of low-molecular-weight inhibitors of signaling pathways associated with the development of this disease. Also, the poten-

tial possibility of using immunotherapeutic strategies aimed at strengthening the functions of the immune system in the aspect of recognizing tumor cells and their subsequent destruction deserves close attention. From the point of view of applying an innovative approach, the development of drug delivery systems is of particular interest, which can increase the bioavailability and effectiveness of both already approved antitumor drugs and new promising compounds. It is expected that ideas that can combine the most outstanding results of individual research areas can lead to the creation of new promising therapeutic approaches for patients with GBM.

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