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Current and prospective strategies in the management of Glioblastoma

Hanna Wołodkiewicz (HW)

Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

ORCiD https://orcid.org/0009-0000-5166-6855

Mail: hwolodkiewicz@gmail.com

Marta Wolszczak (MW)

Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

ORCiD https://orcid.org/0009-0005-6072-8524

Mail: wolmarta97@gmail.com

Jakub Szmit (JS)

Faculty of Medicine, Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

ORCiD https://orcid.org/0009-0000-0001-7425

Mail: s082739@student.wum.edu.pl

Abstract

Introduction and purpose:

Glioblastoma is the most common type of primary cancer in the brain, at the same time being the most aggressive one. In this review, we describe current and emerging strategies for glioblastomas, taking into consideration existing challenges and prospective solutions.

State of knowledge:

Standard treatment comprises surgery, radiotherapy, and primary and maintenance chemotherapy. Those treatments result in a mean overall survival of around 12 to 15 months. We summarize emerging advancements in the field of gene therapy, immunotherapy, viral (oncolytic) therapies, and anti-angiogenic drugs with a focus on key research findings and clinical trial outcomes.

Summary:

The unfavorable prognosis for GBM poses a pressing need for more effective treatments, resulting in prolonged progression-free survival and overall survival, but the difficult microenvironment and immunosuppressive abilities of glioblastomas pose a significant challenge for the emerging strategies. Fortunately, ongoing research proposes solutions to overcome these challenges, like convection-enhanced delivery (CED) to overcome the brain blood barrier or more efficient vectors. The most promising therapies are: DCVax-L (dendritic vaccine), CAR-T therapies targeted against IL13Rα2 and EGFRvIII, and oncolytic viruses: G47Δ (DELYTACT) and PVSRIPO. Future advancements in the management of GBM will focus on the combination of multimodal therapies.

Materials and methods: A comprehensive analysis of research papers available on PubMed was undertaken using the search terms encompassing the following keywords: “Glioblastoma standard treatment”, “Glioblastoma oncolytic virus” “Glioblastoma suicide gene therapy” “Glioblastoma emerging treatment”, “Glioblastoma CAR-T”, “Glioblastoma vaccine” “Glioblastoma VEGF” “Glioblatoma immune checkpoint inhibitors”, “Glioblastoma angiopoietin-2”. Relevant publications were analyzed. Only articles in English were considered. The review mostly focused on research papers from the last 5 years.

Keywords:

glioblastoma; suicide gene therapy; CAR-T; oncolytic virus; dendritic vaccine; immune checkpoint inhibitors

Introduction

Glioblastoma (GBM) is among the most aggressive cancer types, constituting nearly 50% of primary brain tumors. With rigorous standard treatment prognosis for patients with type IV gliomas remains poor with with a 5-year survival rate of only around 4–5% and overall survival of only around 12-15 months at best [1]. Incidence of glioblastomas rises with age, as the peak of diagnosis is observed at the age of 50 years. GBM is associated with a slightly higher prevalence in men than in women, with an average ratio of approximately 1.5:1. In some inherited disorders like Li Fraumeni Syndrome, Turcot syndrome, and Neurofibromatosis type 1, glioblastomas may occur more often. Additionally, there are known genetic mutations that may have an impact on the incidence of GBM, for instance, TP53, PTEN, EGFR, and NF1. The Stuppa Protocol is a current standard for the management of glioblastomas. The base of that treatment is a maximal resection af a tumor with subsequent radiotherapy of 60 Gy in 30 sessions in combination with chemotherapy. For chemiotherapy, a recommended compound is temozolamide (TZM), which is administered for 6 weeks with a dosage of 75 mg/m2/day and then followed by 6 cycles of maintenance TZM therapy. This approach was proven superior to surgery combined only with radiotherapy, with a mean OS of 14.6 months vs 12.1 months [2]. Evolution of biotechnology and immunological techniques led to the development of more sophisticated methods aiming at prolongation of overall survival in GBM, but the difficult microenvironment of the tumor and population of glioblastoma stem cells (GSCs) result in resistance to therapies and the ability to evade the immune system. That together poses a significant challenge for new emerging therapies [3]. Additional difficulties are associated with the blood-brain barrier that restricts the transportation and activation of immune cells in the central nervous system (CNS), which causes limited effectiveness of immunotherapies. There is ongoing research on overcoming this obstacle by introducing ultrasonic disruption (LIPU) and methods like intracranial infusions. The presence of two immunogenic types of tumors, called “cold” and “warm” types, and significant heterogeneity of tumor cells results in limited infiltration of T cells. The “cold” type of GBM is characterised by decreased antigen expression in addition to the presence of immunosuppressive cells. There are trials on transforming “cold” tumors into “warm” types [4]. In this review, we describe current and emerging strategies for glioblastomas, taking into consideration existing challenges and prospective solutions.

State of knowledge

Gene therapy

The idea behind gene therapy is based on modifying gene composition by transferring and manipulating target genes to result in the termination of cancer progression, and additionally stimulating antitumor immune response [5,6]. Many approaches to introducing gene therapy are being taken into consideration, but the most promising ones are suicide gene therapy and tumor suppressor gene therapy [7]. Other, more experimental strategies are also tested by applying a genome editing tool. Those that have the most encouraging effect in bringing gene correction closer to reality are zinc finger nucleases, TALENS, and CRISPR [8,9]. In preclinical evaluation, CRISPR/Cas9 was used to target drivers of glioma growth and therapy

resistance, effectively knocking out oncogenes and sensitizing tumor cells to treatment. Although prospects of gene therapy are favorable, it remains an experimental field, as for now, no gene therapy has definitive proof of efficacy as a standalone treatment. Nevertheless, there is a rationale in combining gene therapy with standard treatment or with immunotherapy to eradicate residual infiltrative cells. Delivering newly established gene therapies is essential for their success. There are two main methods, one involving the deployment of viral vectors and the other using liposomes or polymer nanoparticles. The biggest advantage of non-viral techniques is avoiding the potential toxicity of viruses by lowering the immunogenicity and also their size limitation. On the other hand, viral carriers can spread throughout the tumor by conditionally replicating viruses, similarly to oncolytic virotherapy. New research is considering better vector options to enhance penetration and specificity to tumor cells [5].

1.1 Suicide Gene Therapy

Gene-Directed Enzyme Prodrug Therapy (GDEPT), also known as suicide gene therapy, facilitates the introduction of a gene encoding an enzyme into the tumor cell. The patient is given a non-toxic prodrug that the enzyme in the tumor cell can convert into the lethal drug, causing the apoptosis of the tumor cell. This approach enables to minimization of systemic effects of the oncolytic drug, as the drug is only in its active form in the tumor cell. This strategy is being broadly studied for multiple cancer types, including brain tumors and glioma. Several gene systems are being tested, the main ones being HSV-TK/GCV, CD/5-FC, and PNP/fludarabine. Preclinical studies of those systems mostly herald favorable results. However, its clinical translation faced difficulty in validating the findings further [5, 10, 11]. The HSV-tk/GCV system is composed of herpes simplex virus thymidine kinase and ganciclovir. This system enables the conversion of ganciclovir to ganciclovir monophosphate, which is then phosphorylated by cellular enzymes to produce cytotoxic ganciclovir triphosphate. Apoptosis of tumor cells is based on arresting the cell cycle in S and G2 phases, which leads to mitochondrial damage and activation of caspase-8 and Chk1 [10]. Primarily HSV-tk/GCV system exhibits promising results by increasing the overall survival in phase I/II when combined with surgery and chemotherapy [11]. Unfortunately, in the phase III clinical trial effects fail to corroborate previous results. Similarly, CD/5-FC system works by converting 5-fluorocytosine to cytotoxic 5-fluorouracil by cytosine deaminase. At first, in preclinical trials for high-grade gliomas, it demonstrated a positive safety profile, but those effects could not be translated into a phase III study. That tendency raises the assumption that the potential concept of gene therapy requires more study on optimizing delivery, enzyme expression, and prodigy activation as the microenvironment of the tumor remains a complex and crucial challenge [5, 12]. Newly researched systems are the PNP/fludarabine system that exhibited good long-term efficacy in preclinical models and neural stem cells expressing a suicide gene, but both need further investigation to confirm clinical application for nervous system tumors [10]. Other approaches to gene therapy include silencing gene expression, intracellular antibodies that block vital cellular pathways, and transgenic expression of caspases and DNases [11]. Effects of gene therapy are also associated with the “bystander effect”, which means that cells that weren’t infused with genes of the prodrug enzyme are also

killed by the diffusion of toxic metabolites or immune activation [13]. There is also a pressing need to develop delivery systems in a manner that emphasises safety and efficacy in managing brain tumors [11].

1.2 Tumor Suppressor Gene Therapy

Tumor formation is often associated with the inactivation or mutation of tumor suppressor genes that are crucial in the regulation of tumor cell growth. Restoring the function of those genes potentially can lead to inhibition of tumor growth and angiogenesis, apoptosis, and cell cycle arrest. Most commonly targeted genes for brain tumors in that strategy are TP52, CDKN2A, which encodes p16, and PTEN [14]. Also, in that therapy, a bystander effect can play some role in inhibiting the progression of tumorigenesis [15]. Preclinical trials of restoring the function of the p53 gene and p16 gene exhibited favorable effects in animal models of glioma, causing inhibition of glioma growth and invasion. Also, some research suggests a potential link to radiosensitivity. Again, clinical studies have shown limited results in patients with relapsing high-grade gliomas [10]. However, the p53 gene was a well-tolerated treatment and, for some subset of patients who were immune to other treatments, showed a favorable response [15]. Another therapy that was being researched was PTEN gene therapy, which proved results in inhibiting angiogenesis and proliferation. Additionally, enhancing sensitivity to standard treatment [10]. Other approaches are focusing on genes that are responsible for enhancing the immune attack on the tumor. As an example, cytokine genes like interleukin-12 or interferon-beta transfected into the tumor can cause an immune response [5]. The main difficulty in achieving expected efficacy is reaching a sufficient level of functional protein expression, possibly associated with difficulty in effective delivery of the gene [14]. However, a multidimensional approach utilizing different therapeutic modalities, including tumor suppressor gene therapy, can bring synergistic benefits. Nevertheless, there is a pressing need for broader clinical trials on effective delivery systems [15].

Immunotherapy

The prerogative standing behind immunotherapy is to promote endogenous immune cells in the patient's body to recognize and destroy tumor cells, and as a result, stop the progression of a tumor. This transformative approach includes several strategies like therapeutic vaccines, sensitized lymphocytes, and monoclonal antibodies, which are able to target tumor antigens or specific proteins and modulate immune checkpoints. Many other approaches are still under investigation. Transportation of immune cells into the brain faces unique challenges that are a result of the blood-brain barrier (BBB). A specific challenge is associated with the lack of fenestration in endothelial cells of the BBB. The cells are tightly connected by the junction to

prevent the movement of several particles. On the other hand, some research suggests that this barrier is compromised in some tumors like glioblastoma, which holds a promise for favorable results of this treatment in patients diagnosed with this severe type of brain tumor. Another challenge of immunotherapy is the pressing need to prevent excessive inflammation and, by that, to avoid possible brain edema in a limited space within the brain and cranial vault [16, 17].

2.1 Vaccines

For the treatment of glioblastoma, many models of vaccines were considered, like peptide vaccines, DC vaccines, and heat-shock protein vaccines. Dendritic cells (DC) served as an example for the engineering of cancer vaccines. DCs of the patients are harvested, and tumor antigens are loaded onto the cells. Those antigens can comprise EGFRvIII, WTq, and lysates. Injected back into the patient's body, dendritic cells are supposed to stimulate a T-cell response [18]. The technology of cancer vaccines has to overcome a challenge associated with immune suppression induced by a tumor, which leads to decreased therapeutic effectiveness. One of the ideas for addressing this problem is to target components of the tumor microenvironment and, at the same time, minimise adverse effects [19]. Clinical translation of the primary effect of cancer vaccines has had contradictory results. Rindopepimut is a vaccine targeting EGFRvIII proven to be effective in combination with standard chemotherapy for newly diagnosed patients with glioblastoma, but the result could not be repeated in the recurrent setting [18]. A promising outcome has been recently yielded by the phase III study of DCVax-L, which is a dendritic cell vaccine loaded with lysate of GBM. Encouraging effects of DCVax-L were also exhibited in the 331-patient prospective externally controlled cohort trial. For patients with newly diagnosed GBM mean survival was 19.3 months in comparison to the placebo group, where it survival time was 16.5 months ($p=0.0020$). Similarly, favorable results were observed for patients with recurring GBM. Patients who received the vaccine has a prolonged survival of 13.2 months versus the placebo group were mean survival time was 7.8 months ($p<0.001$). In both groups, the reduction of risk of death and long-term survival exhibited favorable results. Additionally, the treatment was well tolerated, and the side effects experienced by patients were minimal, making it a promising treatment for GBM [20]. A different type of vaccine is the heat protein approach. The most broadly researched compound is a HSP-peptide complex vaccine (HSPPC-96), which includes tumor-specific antigens joined with HSP gp-96 protein. This vaccine was tested in a group of patients with recurring GBM and resulted in an expanded lifespan of study as a standalone treatment. On the other hand, a combination of HSPPC-96 and bevacizumab, a monoclonal antibody used in recurring GBM, did not exhibit any alteration in the survival of the patients [4]. The field of cancer vaccines is an active investigation area that has expanded

in recent years. Many phase I and II clinical trials have been conducted, despite some promising results. As for now, further research is crucial to determine other factors playing a role in the efficacy of cancer vaccines. The main challenge for the fields of glioblastomas is the ability of GBM to induce immune tolerance, some measures are taken to overcome this obstacle by combining different treatment modalities and using a cancer vaccine as an adjunctive treatment [4, 21].

2.2 Sensitized lymphocytes

A different approach to overcoming the difficult microenvironment of GBM is the adoptive cell therapies, where the patient's T lymphocytes are engineered to recognize a specific tumor antigen, enhancing immune response and promoting tumor regression [22]. There are two main strategies embodying this idea, which are tumor-infiltrating lymphocytes (TILs), chimeric antigen receptor T-cell therapy (CAR-T), and NK cell therapies. CAR-T cells are genetically modified to express receptors binding to tumor antigens like EGFRvIII, IL13Rα2, and B7-H3. Preclinical trials showed favorable results, leading to attempts to use it in humans. For example, CAR-T therapy targeted against IL13Rα2, which is an interleukin-13 receptor that is often overexpressed in GBM, induced significant regression of recurrent GBM, but these findings are still in the early phase. Clinical trials of EGFRvIII resulted in patients achieving durable responses and prolonged survival, which gives hope for new emerging treatments. Use of CAR-T therapy targeted against B7-H3 is still under investigation in preclinical trials, but preliminary findings can shed new light on CAR-T therapy in GBM. On the other hand, the safety profile of CAR-T therapy can be a significant obstacle, as commonly experienced side effects were neurotoxicity, cytokine release syndrome (CRS), and on-target, off-tumor toxicity. Those side effects can have severe consequences, even resulting in the patient's death. Median overall survival of patients after CAR-T therapy varied between 5.5 to 11.1 months in the review analyzing cases of 151 GBM patients, which is not substantially better in comparison to standard treatment in GBM [3, 23]. The difficulty in achieving a durable effect of CAR-T therapy can be associated with a few things, like antigen loss and the immunosuppressive tumor microenvironment. New strategies for overcoming these issues are implemented, for example, targeting multiple antigens simultaneously, enhancing T-cell persistence, and combining CAR-T cells with checkpoint inhibitors or other immunomodulators [22, 24]. Despite these challenges, there is some hope as CAR-T therapy improves prognosis in other CNS malignancies like pediatric diffuse intrinsic pontine gliomas and certain lymphomas. This can lead to the assumption that with the right targeted antigens and microenvironment, the therapy can have positive results [3]. Ongoing trials are also investigating the advantages of allogenic CAR-T cells to surpass limitations related to manufacturing issues resulting in delays in introducing the treatment and high costs of autogenic therapy [25].

2.3 Immune checkpoint inhibitors

One of the strategies used in immunotherapy is monoclonal antibodies that are engineered to target tumor-specific antigens or to halt the inhibitory pathways that restrain immune cells.

Immune checkpoint inhibitors are an example of used successful and standard treatment for many cancers not related to brain malignancies. This approach also appeared successful in the treatment of brain metastases, especially from melanoma or lung cancer. A combination of ipilimumab and nivolumab was used in patients with melanoma, which causes the blockade of CTLA-4 and PD-1, respectively. The results were positive, leading to intracranial response rates and prolonged survival in melanoma patients with brain metastases. That brings the immune checkpoint inhibitors to routine use in that indication. There are also attempts to use this method in the treatment of GBN. Unfortunately, they are mostly disappointing in the case of the overall survival of patients. The reasons behind that could be the immunosuppressing activity of GBN, blood blood-brain barrier, and often a need for corticosteroids to control brain edema, which can lead to weakened immune response. For glioblastomas, many different binding sites were investigated, like PD-1, PD-L1, or CTLA-4. Nivolumab is an anti-PD-1 antibody that was tested for primary and recurring GBM, but failed to prolong mean survival time in most trials. Only one trial managed to exhibit a promising result with the use of nivolumab and IL-12 gene therapy (veledimex) at a dose of 10 mg. This treatment resulted in a mean survival time of 16.9 months. It is worth noting that those effects weren't present when the dose of veledimex was 20 mg [26]. There were also attempts to combine nivolumab with bevacizumab, a VEGF-neutralizing antibody, but with no satisfactory result in mean survival time [27]. There was also a trial investigating the neoadjuvant use of pembrolizumab in patients with recurring GBM. Pembrolizumab activates peripheral T cells, which then infiltrate the tumor and expand, causing antitumor toxicity. Additional effects of pembrolizumab are attributed to the induction of IFN-γ-related gene expression changes in monocytes and tumor-associated macrophages (TAMs). That is why current research mainly focuses on neoadjuvant use and therapeutic combinations that enable further understanding of the tumor microenvironment [26]. Other antibodies against TIM-3, IOD1, and anti-EGFR are still under investigation, like cetuximab and nimotuzumab. TIM-3 is a surface receptor expressed on T cells, and IOD1 is an intracellular enzyme. Both are important molecules playing a role in the exhaustion of T cells in GBM [18]. Even though immunotherapy became a breakthrough for many cancers, glioblastomas require a more comprehensive approach combining different modalities of treatment to achieve expected results. Those combinations and appropriate dosage still need more clarification in future research [4].

Oncolytic virotherapy

Oncolytic virotherapy is a promising field in the treatment of glioblastomas. The rationale behind this strategy is based on genetically engineered viruses that selectively infect tumor cells and induce cell apoptosis. Additionally, the release of tumor antigens can trigger an immune response, which is another pathway of inducing the regression of GBM. Viruses can also act as a vector in viral transfection techniques by delivering therapeutic genes into the tumor, as the mutation of genes is a primary reason for metastasis. The main concern for oncolytic virotherapy was possible induction of a brain infection via transferrin viruses in the CNS, but that was resolved by depriving viruses of their neurovirulence. Many types of viruses have been considered and trialed for the management of GBM, like herpes simplex

virus (HSV), adenovirus, poliovirus, and measles virus. Many others are still undergoing clinical trials to prove their efficacy and safety for broader use, like Toca 511 and G47Δ [28]. Moreover, new techniques are being developed to facilitate the transmission of the viruses into the CNS, overcoming the limitation of the BBB. The new sophisticated technique is the convection-enhanced delivery (CED), in which a catheter with a pressure gradient is used to expedite viruses into the interstitial spaces of the CNS. The efficient way of transportation of therapeutic compounds is crucial for the successful result of the therapy, but the difficult environment of the CNS led to intertumoral delivery as the primary way, even though the best way of delivery into metastatic tumor sites [29]. HSV is a broadly used model for oncoviral therapies. Many different molecular binding sites were tested, with the most promising models being G47Δ (DELYTACT). It is a third-generation oncolytic HSV-1, which was modified by deleting the ICP47 gene to enhance antitumor immune response. That virus was used in a group of patients with residual or recurrent glioblastoma. Phase II single-arm trials with 19 subjects resulted in a 1-year survival rate of 84.2%. Additionally, an increase in tumor-infiltrating CD4+/CD8+ lymphocytes was observed. The therapy exhibited a favorable safety profile, with the main side effect being fever. Those effects were subsequently confirmed in a phase I/II study that reported a median overall survival of 7.3 months with a 38.5% one-year survival rate. This breakthrough in the therapy of glioblastoma led to conditional approval in Japan in 2021 [30, 31]. Multimodal use of different strategies is used in combination with parvoviruses. H-1 parvovirus exhibited antitumor effectiveness in the treatment of GBM by inducing apoptosis and overcoming GBM resistance against several chemotherapeutic agents. The latter observation was used in combination therapy with bevacizumab, which increased mean survival to 15.4 months in recurrent GB patients, with remission observed in some cases. Also, the usage of other checkpoint inhibitors like nivolumab resulted in tumor regression and clinical improvement, with 78% of cases achieving complete or partial remission, also in recurrent GBM [32]. A combination of radiotherapy and H-1PV also exhibited favorable results in preclinical trials [33]. PVSRIPO is derived from an attenuated poliovirus type 1 that infects cells via the CD155/PVR receptor, which is commonly over-expressed on malignant cells. This compound was proven to be a breakthrough therapy and was granted that status by the FDA in 2016 due to promising clinical outcomes. Those outcomes exhibited improved survival rates at 24 and 36 months, with a 21% higher survival compared to historical controls. Additionally, proving that convection-enhanced delivery (CED) of PVSRIPO in recurrent GB patients is safe and lacks neurovirulence [34]. Currently, the Phase II trial is taking into consideration the use of PVSRIPO alone or in combination with lomustine in GB patients, which is a chemotherapeutic drug [35].

Drugs counteracting tumor angiogenesis

Glioblastomas are one of the most highly vascularized tumors. Thus, aiming to reduce pro-angiogenic factors like VEGF is one of many possible management strategies. Overvasularisation is a common characteristic of tumors, as it enables them to grow by enhancing the nourishment potential. Anti-VEGF compounds could reduce blood supply or

normalize the vessels to facilitate better adherence of therapeutic compounds delivered by blood. Extensive research on bevacizumab, a monoclonal antibody against VEGF-A, led to approval of this drug for recurrent glioblastomas after MRI exhibited a decrease in enhancement of leaky vessels, but new research questions if this parameter is mirroring a factual tumor response. On the other hand, application of bevacizumab in newly diagnosed patients resulted in prolonged progression-free survival (PFS) with a mean 33% reduction but failed to significantly improve overall survival (OS). Bevacizumab increased PFS by 3-4 months, but OS remained similar, with a median duration of 16 months, which may suggest better symptom control [36]. Nevertheless, bevacizumab exhibited favorable results in a reduction of intracranial pressure by better control of cerebral edema, which subsequently led to lesser steroid requirements. The steroid use in patients with glioblastoma is associated with severe side effects impacting the patient's quality of life, so this possible advantage of bevacizumab can have a significant impact on patients' health, regardless of the unchanged OS [37]. Regorafenib is a small-molecule tyrosine kinase inhibitor (TKI) thats inhibits VEGF receptors but also other angiogenic pathways like PDGFR and FGFR. It showed promising results in recurrent GBN by significantly improving OS in comparison to lomustine chemotherapy. Median overall survival (OS) with regorafenib was 6.6 months versus 5.0 months with lomustine, and one-year survival rates were higher for regorafenib (20%) compared to lomustine (11%), which yielded regorafenib as a first systemic drug in recurrent GBM that demonstrated a survival benefit [38]. On the other hand, the relatively small group in that trial poses a need for larger trials and follow-up analyses to validate these findings. Additionally, more research is needed to establish possible effects that extend beyond angiogenesis. Regorafenib has the potential to inhibit multiple kinase pathways directly associated with tumor cell progression [39]. There is also a growing interest in the combination therapy of bevacizumab and radiation. In Phase II randomized trial combination of those two modalities resulted in prolonged PFS to 7.3 months in comparison to bevacizumab alone. The 6-month progress-free survival increased from 29.1% for bevacizumab alone to 54.3% for combination therapy ($p = 0.001$). Although no significant change in overall survival was observed [40]. Potential downsides of anti-angiogenic therapy may be associated with the promotion of a more invasive tumor phenotype and immunosuppression, which can be induced by tumor hypoxia. There is ongoing research evaluating new pathways by targeting angiopoietin-2, like inhibitors of Ang-Tie2, but none have yet achieved major clinical success [41].

Summary

Each approach comes with its own set of challenges, and no single modality has yet been heralded as a definitive cure for glioblastomas. However, what emerges from this review is a picture of multidimensional progress. Expressed in constantly progressing, significant advances in the overall survival of patients diagnosed with GBM and improved understanding of the reasons for past failures. Next research will hopefully bring to light solutions to delivery problems and effective multimodal therapies [2].

Gene therapy holds a promise in many emerging strategies for managing brain tumors, especially glioblastomas (GBM), which are one of the most aggressive types with less favorable treatment outcomes. Many clinical trials have been conducted, but none have been identified as a definitive treatment. Oftentimes, primary phases exhibited favorable results, which failed to be confirmed in phase III trials. That tendency was also observed with a very promising trial on suicide gene Toca 511 with 5-FC prodrug other gene therapies that hold a promise for future clinical results are the PNP/fludarabine system and CRISPR/Cas9, which was used to effectively knock out oncogenes and sensitize tumor cells to treatment, but remains an experimental treatment [5]. Tumor suppressing strategy proved to be the most effective with PTEN gene therapy, which is associated with inhibition of angiogenesis and proliferation of tumor cells, resulting in an increase of sensitivity to standard treatment. With the use of gene therapy, a "bystander effect" can be observed, which causes the apoptosis of cells that weren't infused with modified genes by the diffusion of toxic metabolites or immune activation [13].

The most effective strategies for immunotherapy are dendritic cells and CAR-T therapy. Promising outcomes have been recently exhibited by DCVax-L, which comprises of lysate of GBM. Those results were indicated by prolonged mean overall survival time and reduced risk of death, both in newly diagnosed patients and in recurring GBM. Also, similar results were observed for the HSP-peptide complex vaccine (HSPPC-96) in phase II trials. Additionally, safety profile for both types of vaccines appeared to be favorable [18, 20].

CAR-T therapies targeted against IL13Rα2 and EGFRvIII manage to result in durable response, progression of recurrent GBM, and prolonged survival, but their safety profile can pose a significant threat to patients' well-being, causing potential neurotoxicity, cytokine release syndrome (CRS), and on-target, off-tumor toxicity [3, 23]. Even though immune checkpoint inhibitors manage to achieve positive results in other CNS tumors, for glioblastoma, only results observed were in combination with other modalities like the use of nivolumab and IL-12 gene therapy (veledimex). Combination immunotherapy, using vaccines with checkpoint inhibitors, or oncolytic virus with immune checkpoint inhibitors, appears to be a prospective strategy in early trials, but there is still a need for more research and finding more possible combinations with appropriate dosage [4]. Oncolytic viruses are another promising strategy, and also a rapidly growing research field. Encouraging results were achieved with trials of G47Δ (DELYTACT) and PVSRIPO, resulting in significantly improved survival rates. New research is also focusing on new delivery systems like CED to bypass the BBB and safety profile, reducing the neurovirulence [28-35]. Drug targeting angiogenesis has been around for quite some time and has been successfully used in many diseases. However, their importance in the treatment of GBM is limited. Bevacizumab is mostly used as a palliative treatment to decrease the need for steroids to control brain edema. It has good results in prolongation of PFS, especially in combination with radiation, but no significant improvement of overall survival has been noted [36, 37]. Regorafenib is a novel drug that interacts with more pathways than just VEGF. There is a possible impact of other compounds playing a role in tumor regression. Its effectiveness is exhibited in a higher

survival rate and slightly improved overall survival in comparison to chemotherapy. Some researchers suggest a potential downside of anti-angiogenic therapy, arguing that it may induce more invasive phenotypes of GBM. Surely, more assessment of the safety profile is needed [38, 39]. Recently, new anti-angiogenic strategies are under consideration, like angiopoietin-2, but those trials are still in early phases. Despite some reservations, anti-angiogenic therapy remains an important strategy for clinical stabilization of GBM [41]. Ongoing research should be centered around looking for effective combinational use of different approaches and solutions to challenges posed by the microenvironment of the tumor and difficulties in the transportation of compounds. Broader-spectrum research is also needed to establish effective dosage and confirm efficacy in strategies, which now appear to be promising [2].

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