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Novel Immunotherapy Strategies for Brain Tumors

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Abstract: Glioblastoma is the most common and aggressive malignant brain tumor, responsible for a poor prognosis and treatment perspective. Despite advancements in investigating novel therapeutic approaches for brain tumors and glioblastoma, there is less progress in improving patients' survival outcomes. Several hurdles hinder effective treatment, including the immunosuppressive tumor microenvironment (TME), the blood-brain barrier, and extensive heterogeneity. Despite these challenges, immunotherapies are promising and effective therapeutic breakthroughs for the therapy of brain tumor types such as gliomas. Multiple new techniques are being explored including chimeric antigen receptor T-cell therapy, oncolytic virus, cytokine-based treatment, immune checkpoint inhibitors, and vaccine-based techniques. Finally, the present review paper aims to summarize the existing developments of microglia, neutrophils, monocyte-derived macrophages, border-associated macrophages, and potential novel therapeutic options and recent advances in immunotherapies for brain tumors.

Keywords: Brain tumor; Glioblastoma; Immunotherapy; CAR T-cell therapy

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1. Introduction

Brain tumors are abnormal growths of cells in or around the brain and can be malignant or benign. Brain tumors can start in the brain as primary or spread from another part of the body as metastatic. Treatment for brain tumors varies depending on the type of tumor, its grade, and the patient's overall health. Treatment options may include surgery, radiation therapy, chemotherapy, or a combination of these therapies. The most common type is gliomas, which arise from supportive cells in the brain. Other notable primary tumors include meningiomas, pituitary tumors, and metastatic brain tumors [1–2].

Glioblastoma (GBM) starts from glial cells and is classified according to its histological characteristics. Together with microvascular proliferation and tumor necrosis, the characteristics that characterize this category also comprise hypercellularity, nuclear atypia, and deregulation of mitotic processes [3]. Therefore, they are categorized as primary when there has been no previous history or as secondary if they have advanced from low-

grade astrocytomas. Primary GBMs account for the bulk of instances, whereas secondary GBMs, which typically affect young people, only make up 5 to 10% of cases [4]. Immunotherapies have produced medicines that have significantly improved overall survival (OS) and changed clinical practice. Relative to those with brain metastases, people with original brain tumors have not benefited as much from OS. The histology of the initial tumor primarily determines the wide range of OS related to secondary brain cancers in adults [5]. Diagnose-specific prognostic instruments, such as the diagnosis-specific Graded Prognostic Assessment, are being developed since OS for individuals with brain metastases differs greatly. Patients with primary brain tumors have not shown a significant improvement in their overall survival during the previous ten years, compared to those with brain metastases [6]. Immunotherapies did have a major therapeutic advantage for patients with brain metastases, but they have not demonstrated a compelling clinical advantage for patients with original brain tumors [7].

In primary brain malignancies and brain metastases, the number of lymphocytes that infiltrate the tumor varies. The infiltration of CD3+ lymphocytes is over 50% higher in brain metastases than in glioblastoma or low-grade glioma [8]. The oncometabolite 2-hydroxyglutarate, which is generated by mutant IDH and prevents T-cell activation, is one theory for the procedure. Microglial cells dominate the inflammatory milieu of gliomas, and a significant portion of monocyte-derived macrophages are present in tumors carrying the IDH mutation. Moreover, it is recognized that several epigenetic subgroups affect lymphocyte infiltration [9].

Secondly, the failure of current immune therapies for glioma may be explained by the lack of checkpoints. A decreased PD-L1 activity is seen in the tumor microenvironment of lower-grade gliomas. A tiny fraction of those with IDH wildtype tumors have alternative checkpoints, such as lymphocyte-activation gene 3 (LAG-3), which are almost nonexistent in glioma patients in general. Soluble PD-L1 (sPD-L1) was found to be positively correlated with survival in peripheral blood, with glioma patients having a greater amount of sPD-L1 than those with brain metastases [10]. Individuals with glioblastoma showed a greater neutrophil-to-lymphocyte ratio (NLR), which is similar to the idea of an immunosuppressive surrounding. Thirdly, glioblastoma individuals often have a smaller tumor mutational burden (TMB) than melanoma or non-small cell lung cancer (NSCLC) individuals. Immune checkpoint inhibitor-treated individuals with melanoma and NSCLC show a link between anti-tumor reactions and TMB. Individuals with glioblastoma do not show this correlation [11].

The investigation has concentrated on finding distinct driver mutations whereby particular inhibitors can be created. Therefore, the creation of such medications may lead to an improvement in OS. Therefore, the identification of novel targets for primary or secondary brain cancers is promised by the identification of molecular mechanisms in gliomagenesis [12]. To investigate the gene expression-based subgroups and their connection to the immune authorization, single-cell investigations have revealed four primary glioblastoma cellular phases that are impacted by distinct genetic processes and microenvironment pieces: (a) Neuron-progenitor-like cells were found to be enriched in cyclin-dependent kinase (CDK) expansions; (b) oligodendrocyte-progenitor-like cells were found to be enhanced in platelet-derived growth factor receptor alpha (PDGFRA) amplification; (c) astrocyte-like cells demonstrated a more regularity of EGFR enhancement; and (d) mesenchymal-like cells were identified as having NF1 mutations. Four pathway-based categories can be identified when all the molecular data is combined: (1) glycolytic/pluriplurimetabolic; (2) neural; (3) mitochondrial; and (4) proliferative/progenitor [13–14].

An additional use for molecular-specified network analysis is the assessment of glioblastoma temporal alterations. This assessment can assist in identifying resistance strategies and ascertain if a target maintains stability over time. This method reveals a great deal of variation over time among the various subgroups, particularly modifications to metabolism. Third, the immunological microenvironment can also be characterized through the

assessment of gene expression. The production of macrophage receptors with collagenous structure (MARCO), which promote mesenchymal transition, is linked to these TAM [15–16].

Intratumoral CD8, stromal PD-L1 expression, and immune cell concentration were linked to reactions in patients with brain metastases, based on initial reactions to immunotherapies in individuals with melanoma and NSCLC [17]. The anatomical place of brain metastases influences the composition of myeloid cells, which varies from other metastatic locations. Previous treatments, including radiation treatment, can alter the microenvironment, resulting in an environment that is either immune-depleted or enriched. The genes linked to metabolic processes such as oxidative phosphorylation are responsible for driving this immunological makeup [18].

In recent times, various novel therapeutic strategies have been investigated, such as vaccinations, chimeric antigen receptor T (CAR-T) cells, immunocytokines, antibody-drug conjugates, and novel immune checkpoint inhibitors. Because glioblastoma expresses EGFR differently, antibody conjugates that target EGFR domain II take advantage of this protein's amplification to provide chemotherapy selectively. The phase 3 trial in patients with freshly confirmed glioblastoma did not demonstrate a survival benefit, whereas the phase 2 research in recurrent glioblastoma seemed to provide the anticipated increased OS [19].

There are many different types of central nervous system (CNS) tumors, however, they are frequently broadly classified as benign or malignant. The most prevalent ones in adults are brain metastases, gliomas, and meningiomas [20]. These investigations demonstrated that tissue-resident and monocyte-derived macrophages (MoMACS), which are thought to be primarily protumorigenic, predominate in aggressive brain malignancies. Studies used immune checkpoint inhibitor therapy because brain tumor cells were shown to contain PDL1 [21]. Therapy rejection is believed to be caused by factors in the tumor immune microenvironment, such as minimal cytotoxic T cell infiltration, minimal mutational stress absence of neoantigens, and local macrophage "corruption" leading to the establishment of an immune suppressive milieu. Chimeric antigen receptor (CAR)-T cells, dendritic cell (DC) immunization, oncolytic viral therapy, and cytokine antibody combinations to boost local infiltration and anti-tumor action are among the additional therapies that are presently being researched [22].

The arachnoid cap cell layer of the meninges, specifically, is where meningiomas originate. Up until the onset of signs, they can grow to considerable sizes and typically expand gradually. While meningiomas are usually classified as benign (WHO Grade 1), 7% of cases appear as atypical (Grade 2) and 2% as malignant (Grade 3). After ten years, the total life rates for Grade 2 and 3 meningiomas are 50–79% and 14–34%, accordingly. 10% to 30% of individuals with systemic tumor burden develop brain metastases; they usually appear at stage IV of the illness [23]. Melanoma, lung cancer, and breast cancer are the three principal tumor types that metastasize to the brain most frequently. Brain metastases are being treated locally with surgery and stereotactic radiotherapy, as well as more recently developed systemic remedies including immune checkpoint inhibitors and targeted medicines. Although brain metastases are amenable to these therapies, they have the potential to advance, return, or multiply [24].

2. Advancements in immunotherapy

The way that various cancer forms are treated has been transformed by immunotherapy. By "turning off" T cells, immunological checkpoints (IC) control the effectiveness of the immune reaction and prevent the death of healthy cells. Inhibitory checkpoint receptors on T cells are normally blocked by immune checkpoint inhibitors (ICI). There are now several clinical trials using CAR-T cells that have been designed to treat high-grade gliomas. Personalized T cells, or CAR-T cells, are derived from the patient's blood and genetically modified in a lab to

possess a particular T-cell receptor that identifies an accurate tumor antigen [25]. The CAR-T cells can attach the antigen following injection and eliminate the cancer cells. There was no cytokine release syndrome or off-tumor damage. In conclusion, larger-scale research has shown that all immunotherapeutic trials for glioblastoma have been unsatisfactory thus far [26]. There is some promise for the future with newer strategies such as CAR-macrophages or immune cytokines fused to IL12. All possible therapeutic options for treating brain tumors are summarized in **Figure 1**.

Figure 1. Illustrate the all key treatment options for brain tumors and glioblastoma with traditional and novel strategies.

2.1. Microglia

The brain parenchyma contains resident microglia that are embryonic and can regenerate themselves despite the need for replacement by macrophages produced from monocytes (MoMacs). It is unclear exactly what part CNS-resident microglia play in the glioma microenvironment, and it may play several different roles. The homeostatic markers SALL1, TMEM119, and P2RY12 are normally expressed in healthy brains and are occasionally decreased in brain tumors [27]. Apolipoprotein E and the NLRP1 inflammasome facilitated the production of IL-1b in glioma-associated microglia. Primarily found in IHD-WT GBM, microglia producing CX3CR1 and PDGFRA displayed an enhanced sensitivity to TGFb1, indicating the expanding, Ki67+ phenotype. Microglia also exhibited an inflammatory character with an elevation of CD14 and CD64 in human brain tumor tissues. In neocortical slice cultures, they also produce HMOX1 and develop IL10, which leads to CD8 T-cell depletion via the STAT3-BLIMP-1 axis. Reactivated effector T cells, on the other hand, were the outcome of HMOX1 microglia reduction. Inhibitory signals, such as the “do not eat me” signal CD47, which interacts with the receptor SIRPA, are expressed by brain tumor cells. It was recently demonstrated that by increasing macrophage phagocytosis, anti-

CD47 antibodies that interfere with SIRPA anti-phagocytosis reduce tumor development. Subsequent dissection showed that anti-CD47 therapy gave CX3CR1-expressing microglia the ability to inhibit tumor expansion, prolonging longevity in mice lacking CCR2-recruited macrophages [28–29].

2.2. Border associated macrophages

Meningeal macrophages, perivascular macrophages (PVMs), and choroid plexus macrophages are the so-called border-associated macrophages (BAMs) that live at CNS interfaces. It is yet unknown what part they play in the microenvironment of aggressive brain tumors. Better research has been done on BAMs and their ontogeny in the mouse brain. Current studies on mouse brain macrophages using a single-cell atlas revealed six main BAM subgroups [30]. Fate tracing showed that subdural BAMs are of embryonic origin and that a small subset of choroid plexus epithelial macrophages represents an individual type of microglia. PVMs in the tumor microenvironment (TME) of other tumor types have been attributed to various roles. They are the infiltration of malignant cells, the promotion of tumor angiogenesis, and the initiation of metastatic spread [31]. There is a correlation between the density of tumor microvessels and PVM recurrence. PVMs accumulated in the perivascular space of recurrent GBM in human specimens of brain metastases and ICI-treated GBM, while PVMs invaded the tumor tissue in brain metastases [32].

2.3. Monocyte-derived macrophages

There may be variations in the proportion of MoMacs to microglia between distinct kinds of brain tumors. Originating from the bone marrow, MoMacs invade aggressive brain tumors to take over as the predominant population. This is particularly true for IDH wildtype gliomas, while the IDH variant exhibits higher frequencies of microglia. From brain metastases from breast and lung cancer to melanoma, the number of MoMacs developed, while the opposite was true for microglia. Monocytes are the source of MoMacs, which are attracted by chemokine receptors that regulate brain metastasis movement, such as CX3CR1 or C3AR1 [33–34]. These MoMacs take on the characteristics of the tumor type and develop an immune-suppressive nature. An immune checkpoint receptor that may be investigated as a strategy in the future is LILRB2. CSF-1 receptor inhibitors were employed as an immunotherapy strategy and improved survival in GBM mice specimens [35]. Microglia may be impacted by these blockers as well. Using the GL261 glioma cell line, different preclinical research decreased CSF1R restriction exclusively on mature TAMs while increasing the proportion of monocytes, presumably because the monocyte-to-macrophage transformation is changed. This work also demonstrated the competition for space between microglia and MoMacs, as well as the adaptive processes that increase the amount of microglia in the malignancy to preserve TAM concentrations when monocyte inflow is impaired. The compensatory CSF2R-STAT5 pathway drove tumor recurrence and TAM activation after CSF1R suppression in a breast cancer brain metastases model [36].

Tumor-associated microglia generated a proinflammatory phenotype in a preliminary system of lung-brain metastases, while MoMacs established patterns of alternative stimulation, such as antigen presentation and wound recovery, according to large quantities and single-cell RNA sequencing expression accounts. The division of MoMacs into two groups, referred to as M1 and M2, is inaccurate and unsupported by the available data, as there is a complex and flexible framework of overlapping macrophage subtypes [34]. Several indicators expressed on potential anti-inflammatory MoMacs have been investigated as potential therapeutic approaches in animal studies. For instance, in the GL261 model, MerTK inhibition reduced the number of TAMs and vascular development while increasing survival. S100A4 is an additional immunotherapy target on MoMacs, and TAMs depleted of

S100A4 exhibited enhanced phagocytic efficiency. S100A4, a little calcium-binding protein, has been shown in various tumor forms to prevent TAMs from going through apoptosis. MoMacs promote glioma cell phagocytosis and aggressive chemokine release, which in turn promotes T-cell accumulation. Effective T-cell lethality requires the expression of MHC class II antigen on MoMacs, and its absence results in CD8 T-cell malfunction through osteopontin [37].

2.4. Neutrophils

Neutrophils are the more common form of granulocytes found in circulation in the blood, and they originate from the bone marrow. Increased circulating neutrophil counts were found to be a negative prognostic factor in the context of brain tumors. A higher neutrophil-to-lymphocyte proportion in particular was associated with a more severe general survival rate. It is still unknown what role they play in the tumor microenvironment. According to certain research, active neutrophils in gliomas are myeloid-derived suppressor cells that produce nitric oxide and arginase, which aid in immune regulation [38]. Additionally, it was demonstrated that gliomas can control systemic myeloid differentiation in the bone marrow remotely, producing neutrophils that are predisposed to a morphology that supports malignancies [39]. There are currently few options for treating major brain tumors like GBM. Therapy procedures for patients with GBM take into account multimodal therapeutic techniques that work in concert to eradicate the tumor, although therapy is challenging, costly, and prone to therapeutic failure. However, it is important to consider the drawbacks of present therapies to create new ones or enhance established procedures [40].

2.5. Surgical method

The surgical approach, which depends on the maximum safe resection of the tumor, has become the cornerstone of GBM treatment because it allows for the histological diagnosis and inherited analysis of the tumor along with decreasing the size of the neoplastic mass and the symptoms brought on by parenchymal compression. Achieving a gross total excision as thoroughly and securely as feasible without jeopardizing the patient‘s functioning is the goal of surgery. Compared to partial resection or biopsy, complete resection has been linked to an increased likelihood of survival and no recurrence [41]. In this way, some instruments were created to optimize the surgical process and minimize any potential neurological impairments brought on by the technique. However, surgery alone cannot treat GBMs as nearly the condition will relapse. Additionally, there is a risk that the patient will experience a neurological lack as a consequence of the surgery, which could preclude the need for chemotherapy and radiation therapy, which makes the procedure exceedingly fragile, costly, and complex. It also requires a skilled neurosurgeon and advanced imaging machinery. As a result, it is critical to precisely balance the advantages and disadvantages of the surgical approach [42].

2.6. Radiotherapy

Presently, radiotherapy (RT) is a form of treatment centered on the application of radiation doses targeted at particular areas that have gained popularity in the 1970s and 1980s. Because phase III clinical research established the significance of adjuvant chemotherapy and radiation in the postoperative period of GBM during this year, this approach has been the accepted protocol for GBMs ever since [43]. Although RT is quite effective as a treatment option for tiny recurrent tumors, it has a significant restriction in that there is little evidence to support its use in recurrent gliomas. Radiation usage must also be prudent because the treatment plan necessitates knowledge about the patient’s prior radiation exposure, the tumor‘s location, and the maximum dose that may be administered to a

certain tissue. Lastly, the therapy algorithm evaluates the patient's functional condition and the rate at which the disease is progressing. For this reason, chemoradiotherapy is not recommended for people over 70 who do not have an excellent operational condition as determined by the Intensive Care Unit scale's Functional Status Score [44].

2.7. Chemotherapy

Temozolomide (TMZ) is the highest highly successful treatment for GBM available today. It is an alkylating drug that does not require the cell cycle. The capacity to traverse the blood-brain barrier and transferrable cytosolic transition to the cell nucleus account for this effectiveness. For newly confirmed GBM, the present standard procedure is for daily administration of 75 mg/m^2 of TMZ for the duration of the 6-week radiation treatment. Following that, 5 days are spent at 150–200 mg/m^2 for each 28-day cycle, totaling 6 cycles of the medication [45]. Additionally, non-methylation of the MGMT promoter results in roughly 55% of GBMs having intrinsic or acquired resistance to treatment. This decreases the pharmacological effectiveness of the alkylating drugs by removing the alkyl groups from the guanine's O6 position. By reducing TMZ cytotoxicity through the base excision repair route, chemotherapeutic resistance can also be attributed to another cause [46].

2.8. Tumor microenvironment involvement

It is becoming increasingly evident how the tumor microenvironment affects how the defense system responds to cancer. It is common to refer to the central nervous system (CNS) as an immune-privileged region that responds to alloantigen assaults with diminished vigor. Two theories have historically been proposed to explain the characteristics of CNS immune access: (1) the blood-brain barrier (BBB); and (2) the lack of traditional lymphatic outflow of CNS antigens. The blood-brain barrier (BBB) is a partially permeable biological barrier made up of pericytes, astrocyte end-feet, and particular endothelial cells (which are not fenestrated but are securely linked by tight junctions). Its primary job is to closely control the flow of ions, chemicals, and cells such as immune cells between the brain and the blood [47]. One of the greatest obstacles to immunotherapy is the capacity to restrict the movement of potentially neurotoxic chemicals, mainly through ATP-binding cassette transporter-mediated efflux. The CNS offers an immune-privileged setting that promotes tumor development and growth, as evidenced by the requirement for both the generation of cancer-specific T cells and their direct interaction with malignant cells for effective anti-tumor reactions [48].

2.9. Immunosuppressive mechanisms in GBM

Immunotherapy is a novel cancer medication, but it depends heavily on the presence of preexisting anti-tumor antibodies. It is well known that GBM causes systemic and local immunosuppression, which makes immune-modulating treatments more difficult to apply. By releasing a range of soluble substances that have diverse immunosuppressive impacts, GBM cells can elude immune surveillance. Prostaglandin E2, interleukin 10, and transforming growth factor β (TGF-β) are the most well-characterized GBM-derived immunomodulatory proteins [49]. In addition to not producing Th-1 or Th-2 cytokines in response to TCR stimulation, these transformed suppressor cells additionally exhibit TGF-β and impede the growth of regular T cells in vitro. Furthermore, natural killer (NK) cells and CD8+ T lymphocytes have the activating receptor NKG2D downregulated by TGF-β1, which prevents them from being cytotoxic to GBM cells. However, TGF-β2 can downregulate HLA-DR antigen expression on tumor cells, which can help immunological evasion from T lymphocytes and avoid neoantigen delivery. When combined, these stimulations of T or NK cell activity impair the immune system's ability to

effectively eliminate tumor cells [50]. In GBM, IL-10 is also essential for regulating the proliferation of resident, invading, and tumor cells, mostly causing an immunosuppressive phenotype. Elevated levels of TGF-β, CCL2, IL-4, and several anti-inflammatory cytokines were linked to higher production of IL-10. TAMs inhibit antigen-presenting protein development when IL-10 is present, which reduces CD4+ T cell activation. In addition to TGF-β, IL-10 can also induce the transformation of naive T cells expressing FOXP3 into Treg cells, which in turn results in immunosuppression mediated by Tregs. On the other hand, new research has demonstrated that a subgroup of HMOX1+ myeloid cells that release IL-10 and are spatially localized in tumor areas that resemble mesenchymal tissue also causes T-cell exhaustion and hence serves the tumor microenvironment [51].

Consequently, it has been demonstrated that PGE-2 plays a crucial role in mediating immunosuppressive action by promoting the growth of myeloid-derived suppressor cells (MDSCs). VEGF is one of the primary goals in the therapy of glioblastoma since it is the greatest significant modulator of angiogenesis in this disease. Lastly, hypoxia inhibits efficient anti-tumor immune reactions by regulating the expression patterns of immunomodulatory surface ligands such as programmed death-ligand 1 (PDL-1), cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and others via the stimulation of hypoxia-inducible factor 1-α [52]. Through the production of several cell surface immunosuppressive factors, including the so-called immunological checkpoint molecules (ICs), GBM cells might weaken anti-tumor reactions. Membrane-bound PDL-1, which is coupled to programmed cell death-1 (PD-1) on the surface of activated T-cells, can cause T-cell exhaustion in GBM and immunosuppressive cells. To prevent T cell-mediated death, PDL-1 overexpression in the tumor microenvironment promotes obstruction, a mechanism known as a “molecular shield.” On the other hand, GBM cells that express the CD95 (Fas) ligand can also reduce the intensity of an immune response by causing invading lymphocytes to undergo CD95-dependent apoptosis. Last but not least, it has been demonstrated that lectin-like transcript-1 (LLT-1) and indoleamine 2,3-dioxygenase 1 (IDO) respectively restrict NK cell function and boost intratumoral Treg and myeloid-derived suppressor cells [53].

2.10. Cytokine Therapy

The foundation of cytokine therapy for GBM is the application of pro-inflammatory cytokines to encourage the immune system’s stimulation and the restoration of the tumor’s immunosuppressive milieu. IL-12, TNF-α, and IFN-α have primarily been evaluated as potential glioblastoma treatments. IFN-α inhibits tumor angiogenesis and immune suppression-related gene expression, but it also increases T cell and macrophage performance and reduces their fatigue in this way. Conversely, TNF-α stimulates T cell activation by promoting dendritic cell maturation, while IL-12 is linked to higher CAR-T cell efficiency, improved CD4+ T cell infiltration, and reduced T-regulatory cell abundance in the tumor microenvironment [54].

However, at maximal tolerable doses, IFN-α treatment has limited efficacy and a considerable possibility for systemic toxicity. A user’s injury is implied by the risk of collateral consequences. Research studies include headaches, chills, gastrointestinal complaints, hypotension, and a drop in both systolic and diastolic blood pressure. This indicates that, at least for the time being, the therapy is a restricted supply. Furthermore, administering TNF-α presents a challenge due to its documented ability to create toxicities in patients when administered intravenously. Interleukin-7 agonists were recently discovered to have the potential to reverse the lymphopenia brought on by the conventional treatment for GBM and to strengthen the immune system by increasing CD8 serial lymphocytes in murine models. However, further research is required to apply these findings to patients with primary glioma [55].

2.11. Inhibitors used for immune checkpoint

Molecular receptors known as immune checkpoints serve as inhibitory mechanisms to limit exaggerated immune responses and stop the system from becoming uncontrollably active. T cells (CD4 and CD8), dendritic cells (DC), natural killer (NK) cells, and B cells all have these receptors. Certain processes seen in cancer cells enable them to lessen the immune system's efficacy while attacking mutant cells. One of these ways involves the production of chemicals that communicate directly with immune checkpoint receptors, reducing immunological activity by blocking vital defense system cells [56]. As a result, immune checkpoint inhibitors have become a viable treatment option to stop immune cells from being inhibited due to interactions between their receptors and chemicals made by glioblastoma cancer cells. In this context, research has determined the primary immune checkpoint receptors and their physiological significance in glioblastoma. The immune system cells that express PD-1, T-cell immunoglobulin and mucin domain 3 (TIM3), CTLA4, lymphocyte activation gene 3 (LAG3), T-cell immunoglobulin and ITIM domain (TIGIT), and CD96 are inhibitory receptors. Cancer cells produce the ligands that bind to these receptors [57].

2.12. CAR T-cell therapy

Chimeric antigen receptors are artificial receptors that can reroute T lymphocyte immune reactions to a particular target antigen. As a result, T cells can produce both immediate and long-term impacts by inducing intricate antitumor reactions. The extracellular domain of CAR-Ts includes an internal T cell signaling domain, a flexible hinge, a transmembrane region, and a tumor binding site in the form of the single-chain variable fragment (scFv). Furthermore, CARs can be classified as first, second, or third generation based on the quantity of CD3ζ stimulatory domains they contain. The majority of contemporary CARs feature two costimulatory domains connected to CD3ζ to enhance their signaling activation capacity [58]. Since CAR-Ts have proven to be a successful therapy for hematological malignancies, the goal is to modify the approach for solid tumors like GBM so that, independent of the delivery of the peptide by histocompatibility complexes, the stimulation of T cells in the tumor microenvironment supports targeted immunological mechanisms of cell death to specific targets in the tumor, yielding the same level of success as the treatment in non-solid tumors [59].

EGFRvIII is an oncogenic mutation type found in human malignancies that enables the immune system to recognize particular tumor antigens. EGFRvIII is comparatively prevalent, particularly in GBM, where the alteration is seen in about 30% of cases. Because EGFRvIII promotes tumor oncogenic signaling, its levels in GBM patients are thought to be a poor prognostic indicator. In this regard, 10 patients with recurrent EGFRvIII + GBM were assessed in the first clinical trial that looked into CAR-T therapy targeted at EGFRvIII [60]. The outcomes showed that infusion-based delivery of CAR-T cells is an appropriate technique to employ, as there was no indication of cytokine release syndrome or harm irrespective of the tumor microenvironment. No patient experienced GBM regression, and one patient maintained stable disease for longer than 18 months, even though the study's goal was not to assess the therapy's efficacy [61]. In addition, current research that examined EGFRvIII as a potential therapeutic target for GBM analyzed the apheresis and infusion products from the earlier investigation and found that PD1 is a predictor of peripheral graft and progression-free survival in transduction products of patients with EGFRvIII-targeted CAR-Ts. However, before the development of CAR-Ts, the aforementioned relationships did not exist. Consequently, it has been suggested that the PD1 marker may indicate a greater outcome to treatment for recurrent GBM and that the variations in therapeutic outcomes observed in the research are due to the infusion product's manufacture [62–63].

About 80% of GBMs express HER2, another tumor-associated antigen. Nevertheless, the receptor is also present in healthy host cells, which means that when HER2 is employed as a specific target antigen, it may cause autoimmunity. The initial study using HER2 CAR T cells in cancer patients did not yield encouraging results. One patient's acute toxicity resulted in death as a result of the trial. Although it exists in normal tissues, IL-13Rα2 is not significantly expressed in normal brain tissue, and it is another tumor-associated antigen that is present in up to 50% of GBM. It's significant to note that three patients with recurrent GBM were enrolled in the first trial that assessed the safety and viability of using CAR-Ts that targetIL-13Rα2 for therapy [64]. As a result, by inhibiting antigen release and lowering excess tumor toxic effects, it turned out to be a viable solution for problems with the present therapy. Furthermore, an additional preliminary study generated an IL-13Rα2 directed towards a humanized third-generation CAR, assessed its effectiveness against GBM in vitro, and documented that the receptor produced good findings that validate its application in clinical research [65].

As a result, CAR-T therapy that targets particular antigens is extremely promising and may one day be used as a treatment option for solid tumors like GBM that have a bad prognosis. The scant data, however, nevertheless presents several obstacles for the therapeutic approach to overcome. The intricacy of the tumor microenvironment and immune cells' ability to enter the central nervous system are the primary barriers to a safe and successful CAR-T treatment. The primary cause of the first is the presence of both the endothelium and epithelial blood-brain barriers. The second happens as a result of GBM's complicated and dynamic tumor microenvironment, which can thwart CAR-T cells' ability to recognize a single, distinct target antigen [66].

2.13. Oncolytic viruses

Oncolytic viruses (OVs) have been more widely used in the therapy of tumors, particularly GBM, in recent years. Because of its advantages, including its tumor restrictions and absence of distant metastases, OVs are especially well-suited for GBM therapy. This makes the employment of viruses at this location a viable method of immunotherapy. For its mitigating impacts, they are delivered intratumorally or intravenously. Viruses known as OVs are classified as mildly pathogenic viruses since they can only infect, multiply, and kill cancer cells while sparing healthy cells and causing tumor cells to undergo apoptosis [67]. Tumor-specific cell death and the stimulation of the host's systemic antitumor and/or antiviral immunity are the mechanisms by which this happens. By using pattern recognition receptors and pathogen-associated molecular trends, OVs thus trigger the innate immune system and trigger the attraction of immune cells such as Th1 cells, neutrophils, macrophages, natural killer cells, and their cytokines, which in turn stimulate cell lysis. Additionally, this process triggers an adaptive immune response to novel cancer antigens and may result in a long-term immunotherapy side effect. Moreover, OVs can be employed as non-replicating viral vectors to transfer therapeutic genes, acting as an effective means of delivering genes to cancer cells [68–69].

2.14. Vaccine-based therapy

The idea of vaccination treatments is a noteworthy development in the recent discussion of immunotherapy's enormous potential for treating and stabilizing oncological disorders. In this regard, the idea of a different treatment for GBM that uses vaccination to provide patients with a better prognosis is a topic of considerable discussion and investigation. Numerous vaccines with diverse immunological foundations have been created and evaluated for the management of GBM. There are four standard methods on which to develop GBM vaccines: Using genetic data from the tumor itself, peptide and DNA vaccines are more targeted in their application. mRNA-based

vaccines using viral vectors and cellular vaccines based on dendritic cells manufactured additionally with tumor antigens [70–71]. Generally speaking, the idea underlying this wager is the immune response, taking into account the tumor's capacity to elude the specific immune reaction. Thus, the immune system itself more particularly, a reaction orchestrated by T cells competent of identifying tumor antigens and retaliating against them, is one of the strategies discovered to "fight" this illness. Thus, the first suggestion seeks to elicit an immune reaction using targeted tumor antigens (TSAs), utilizing as a starting point peptides derived from tumor features that elicit an anti-tumor immune response by imitating neoantigens in glioblastoma cells. A second strategy for developing anti-tumor vaccines is the use of personalized neoantigen vaccines, which have shown promise in improving mortality in patients recently diagnosed with GBM by changing the immunological milieu of the disease [72].

There are, however, some areas of disagreement with this vaccine treatment due to tumor heterogeneity, which results in factors conveyed distinctly in each individual and would require high specificity when manufacturing the vaccine. Additionally, the vaccine is not very effective when used on a large scale, which makes it difficult to include patients. Antigenic escape in the face of cancers lacking this antigen is another drawback of this treatment. Furthermore, the collection of peptides for the vaccine base encounters an obstacle because the connection between a variable tumor profile and the potential formation of nonspecific epitopes, a tumor formed not from mutations but rather from heightened manifestations of variables found in normal tissues, raises the risk of reactions that extend outside the tumor affection, including inflammatory events and autoimmune reactions in other areas [73].

DC vaccines are one of the most exciting fields of research right now, and they have been receiving attention as well. This is because of their function in immune modulation in the context of GBM. As a result, they play a crucial role in the development of developed immunity as well as the differentiation, antigen presentation, and lymphocytic reaction. In light of this, it can be observed in GBM images that DCs appear to exist in an impeded or immature state, resulting in decreased work. This could be linked to the severe tumor microenvironment. The immune microenvironment's inhibitory effect also contributes to DCs' low function, which is detrimental to bodily functions but can be corrected by DC vaccinations. This is because DC vaccines work by activating previously inhibited T cells in vitro, typically from the influenced individual themselves. This boosts the patient's adaptable reaction, increases the production of MHCs, cytokines, and chemokines, and encourages a rapid movement of immune cells to the immunosuppressive microenvironment present in GBM [74]. According to some research, DC vaccinations can currently enhance the prognosis for GBM, with younger patients showing better outcomes in some age-related parameters. Another study, a phase II clinical trial, revealed that some patients who received the vaccination following tumor removal had a median overall survival of 23.4 months. However, as a meta-analysis of randomized controlled studies on DC vaccine efficacy showed, there was no appreciable difference in overall patient survival when the vaccination was given to recently identified glioblastoma individuals. Therefore, more research and trials with more advanced phases are still needed in this field, and future research should better examine its capacity to inhibit glioma [75].

Other vaccination concepts have been tried out, such as basing the vaccine on isocitrate dehydrogenase, an enzyme whose mutation only happens in tumor cells, providing an intriguing tumor-specific antigen. Furthermore, given their effectiveness in treating and preventing other diseases, vaccines that inactivate tumors are also attracting research attention. However, the efficacy of these treatments for treating neoplasms is still low, necessitating further study for their growth and utilization in GBM. The application of these alternative vaccination strategies requires more sophisticated study. Therefore, selecting the right immunological activation

while lowering vaccination toxicity is crucial for vaccine therapy. The immunological changes brought on by the tumor microenvironment, the patient's immune condition, and potential negative events that must be minimized must all be considered in the hunt for TSA and potential substitutes. Furthermore, a crucial factor is that, despite the fleeting pattern toward customized vaccinations, figuring out how to render this fresh reality possible prompts the requirement to look for a combination of antigens with a wider range. This requires considering the long-term immunological reaction, how the vaccine handle will affect the creature, and future projections, all of which make the development of studies with more reliable results imperative. Furthermore, when compared to the use of particular vaccinations alone, the potential for combining vaccines with other immunotherapies has demonstrated significant benefit and this strategy should be further researched and taken into account in patient care [76–77].

3. Immunotherapy limitations and challenges

There are numerous treatments for immunotherapy accessible now to treat GBM. These comprise genetically engineered T cells, immune checkpoint inhibitors, oncolytic viruses, and vaccinations. Given the ability to alter or strengthen the immune system equipment to target and eliminate tumor cells, immunotherapy has shed light and produced a great deal of excitement for the cure of glioblastoma multiforme (GBM). In this regard, the numerous ongoing research and clinical trials may yield positive outcomes in growing the application of these treatments in the coming years. However, there are still several barriers that prevent immunotherapy from being effectively used to treat glioblastoma. These barriers can be connected to specific immunological and anatomical aspects, as well as administration routes and side effects [78].

Immunotherapy for GBM is severely limited by the blood-brain barrier. The ineffective treatment activity of these specialized endothelial cells linked to astrocytes and pericytes is caused by their obstruction of medication transport. Furthermore, GBM can change the BBB, creating the brain tumor barrier, a structurally distinct barrier that further impairs the absorption of therapeutic drugs [79]. Furthermore, considering the quick development of resistant clones following the deliberate eradication of vulnerable ones, intratumoral heterogeneity is crucial to immunotherapy tolerance. The tumor's immunosuppressive milieu presents another difficulty for the immunotherapeutic strategy. The use of CAR-T cells is hampered by Treg cell overexpression because it inhibits effector T cells. The practical application of cytokine therapy is severely limited by its systemic usage, which displays serious side effects and inadequate absorption, despite its ability to modify the microenvironment of GBM and result in greater maturation of DC cells, T cell infiltration, and decreased exhaustion. In this sense, more research on the subject may offer more choices for overcoming these obstacles in the near future [80–81].

4. Conclusion

A shortened survival time and a decreased standard of life are linked to malignant brain tumors. Myeloid cells have just been identified as the dominant component of the immune microenvironment of malignant cancers. It is getting more obvious that comprehending therapy failures and tumor progression depends on understanding the myeloid landscape in the TME. For GBM patients, the immunotherapy's promise as demonstrated by earlier and ongoing clinical trials offers hope. It is anticipated that a variety of therapies will be applied to minimize side effects and enhance healing. The hazards and expenditures associated with surgery, radiotherapy, and chemotherapy point to several problems that other methods do not have. Additionally, these methods are better suited for palliative care than for healing. Nevertheless, before they can be used, some issues related to their use

must be resolved. Immune checkpoint inhibitors have the potential to impede GBM's immunosuppressive tactics, although the human reaction to these drugs has never yet equaled the effectiveness seen in studies on animals. Since chimeric antigen receptor T cell therapy can reroute the immune reaction to particular objectives, it is also an exciting therapy option. Additionally, vaccine-based therapy is being explored for the immunotherapy of brain tumors. To sum up, there are benefits and drawbacks to the immunotherapy choices. Therefore, it is essential to make more progress in preventing adverse effects and the ineffectiveness of the promising new immunotherapies that have just been found to extend patient life and lessen suffering in the near future.

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Disclosure statement

The authors declare that they have no conflict of interest.

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