Iranian Journal of Blood & Cancer

Iran J Blood Cancer, 2026, 18 (1), 26-39
https://ijbc.ir

Review

Current Challenges and Neoantigen-Based Therapy for Glioblastoma Treatment

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Citation Singh P, Papatrick S, Singh V. Current challenges and Neoantigen-Based therapy for Glioblastoma (GBM) treatment. Iran J Blood Cancer. 2026 March 31;18 (1): 26-39.

doi 0

Article info:
Received: 26 Dec 2025
Accepted: 07 Mar 2026
Published: 31 Mar 2026

Keywords:
Neoantigens
Glioblastoma
Immunotherapy
Treatment

Abstract

Despite common therapies including chemotherapy, surgery, and radiation, glioblastoma (GBM), the most aggressive, challenging, and resistant primary brain metastasis version, has a terrible prognosis when it comes to the survival chances. Although immunotherapy has demonstrated promise in treating a number of malignancies, its effectiveness in GBM is still restricted because of the tumor's extremely immunosuppressive microenvironment. Neoantigen-based treatments target tumor-specific antigens produced by somatic mutations, providing a unique and customized approach. Because tumor cells express these neoantigens exclusively, they are prime candidates for immune identification with the least amount of off-target consequences. Early clinical trials have shown the safety and immunogenicity of strategies like customized cancer vaccines and adoptive cell treatments (ACT). This review explores the potential of neoantigen-based immunotherapy in GBM, highlighting recent advancements, challenges, and future directions for improving treatment efficacy and patient outcomes.

1. INTRODUCTION

One of the most aggressive and resistant to treatment brain tumors, GBM has a dismal prognosis [1,2]. Chemotherapy, radiation, and surgery are common forms of treatment. However, the extremely immunosuppressive and diverse character of GBM presents a significant obstacle to successful immunotherapy [3]. Recent developments in tailored treatments based on nanoantigens, which target mutations unique to tumors, have demonstrated promise in boosting immunity against tumors. It has been noticed in most of the studies that the median survival is still around 14–16 months for GBM patients, even with the incorporation of cutting-edge therapeutic approaches, including complete/partial surgical resection of the tumor and associated areas followed by radiation, chemotherapy, or combined chemotherapy [4]. Another important characteristic of GBM was the production of high amounts of soluble immunosuppressive mediators, including prostaglandin E2, interleukin 10 (IL 10), IL 6, IL 7, and TGF-β (Transforming Growth Factor-β) which inhibit effector T-cell activation to elicit an immune response [5,6]. Thus, in the case of solid tumors, the development of immune checkpoint inhibitors (ICIs) was marked as one of the revolutionized cancer treatment regimes, as seen by their effectiveness against T lymphocytes. Usually acting as brakes for the adaptive immune system, checkpoint-driven inhibitory pathways reduce effector immunological

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responses. ICIs like programmed cell death 1 (PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and programmed cell death ligand 1 (PD L1) are the most commonly used targets for checkpoint inhibitors for therapeutic purposes [7,8]. Both CD4+ and CD8+ T lymphocytes express CTLA-4, which interacts with antigen-presenting cells CD80 and CD86 markers [9]. T-cell response and proliferation are inhibited by this engagement. Although immune checkpoint inhibitors (ICIs) offer the potential to treat a variety of solid tumors, GBM patients have frequently not responded well to them. Other therapeutic advancements include CAR-T (chimeric antigen receptor T-cell) therapy, which has been seen quite successful in most situations in treating hematological malignancies [10].

Neoantigens are tumor-specific mutant antigens that arise from somatic mutations and comprise new peptide sequences within cancer genomic regions. Even though the peptide-based DNA/RNA vaccines which are in under clinical trials are used for vaccinations, inducing high T-cell responses concurrently can also produce powerful and targeted immune responses without endangering healthy tissues, which makes them ideal candidates for immunotherapy as they lack immunological tolerance mechanisms. Since neoantigens are only expressed on tumor cells and are typically the consequence of somatic mutations, they have opened up new possibilities in cancer immunotherapy. Thus, adoptive cell therapy (ACT)-based customized neoantigen vaccines are the main neoantigen-targeting approaches that have become potential immunotherapeutic treatments for a variety of malignancies [11,12]. These techniques provide a highly specialized and customized therapeutic strategy by using the unique genetic alterations present in each tumor to elicit a specific immune response. With early-phase clinical trials proving both safety and the capacity to elicit strong anti-tumor immune responses, tailored neoantigen vaccines have shown particular promise in the context of GBM. These findings shows the potential role of neoantigen-based therapies for addressing the challenges posed by GBM's complex biology. Since patient-derived tumors have a different mutational landscape and neoantigens are highly customized, this serves as the basis for individualized therapy plans. This neoantigen-based treatment can minimize toxicity and off-target effects; at the same time, it increases accuracy and effectiveness of the immune response by focusing on these patient-specific antigens. Immunosuppressive microenvironment and heterogeneity make neoantigen-targeting therapy development is especially appealing in the case of GBM, as personalized neoantigen vaccines can be developed to activate tumor-specific T lymphocytes. Taken together, combining all these strategies marks a revolutionary change in cancer immunotherapy by utilizing the immune responses, specifically T-cells and memory cell activation to target the distinct genetic changes causing each patient's illness.

2. Reimagining GBM Therapy: Overcoming the Barriers

GBM has a distinct pathogenesis that offers substantial treatment hurdles. One significant barrier is the blood-brain-barrier (BBB), which limits the effectiveness of systemic treatments by preventing the majority of therapeutic drugs from penetrating through it and release [13,14]. Furthermore, surgical excision is practically difficult because the tumor cells in GBM deeply penetrate the surrounding brain tissue, and the disease has a high recurrence rate in the majority of cases. Additionally, GBM shows significant intratumor and intertumor heterogeneity, which makes it difficult to find universal therapeutic targets and calls for individualized treatment plans. Also, the tumor microenvironment in GBM patients was highly immunosuppressive, marked by the secretion of anti-inflammatory mediator cytokines, infiltration of regulatory T cells, and the presence of myeloid-derived suppressor cells, all of which impede efficient immune responses [15,16]. So, taken together, all these elements, including tumor invasiveness, BBB protection, heterogeneity, and an immunosuppressive microenvironment, represent significant obstacles to the creation of successful GBM treatments.

2.1. Blood-Brain-Barrier (BBB)

In order to preserve optimal neural function, the trafficking of cells, chemicals, and ions is precisely regulated by a highly vascularized organ called the brain. The BBB, one of the human body's most selective barriers, is principally in charge of this regulation. It can maintain neuronal activity at the same time; the BBB shields the central nervous system (CNS) from dangerous blood-borne agents like infections, poisons, and exogenous substances like medications [17,18]. The blood-brain barrier (BBB) is structurally composed of specialized endothelial cells that constitute the walls of capillaries within the brain. These cells include pericytes and astrocytic endfeet and are securely sealed by tight junctions. Delivery of therapeutic drugs to brain tumors, particularly GBM, is severely hampered by this intricate structure, which separates the brain from the flow, causing a barrier. Systemic treatments for GBM have been severely hampered due to BBB's restrictive properties. It has been seen in studies that

only over 1% of systemically administered chemotherapeutic drugs can successfully pass the blood-brain-barrier and achieve therapeutic concentrations applied to reduce the tumor burden in the central nervous system, maintaining a low overall survival (OS). BBB sometimes results in a brain-tumor barrier (BTB), which is partially disrupted in the context of brain cancers. The BBB is largely unaffected at the tumor rim, where invasive glioma cells are found, but there is a noticeable increase in permeability in the tumor core. Vascular endothelial growth factor (VEGF), resulting in promoting immature, leaky blood vessels within the tumor as VEGF expression was on the higher side [19,20]. Also, the hypoxia-driven angiogenesis pathway and releasing inflammatory cytokines, ROS and other chemical mediators together contribute towards the overall complexity and to the development of BTB. As a result, treatment resistance and tumor recurrence continue to obstruct efficient drug distribution, which contributes to, even though this disruption may improve drug delivery to the tumor core. Convection-enhanced delivery (CED) and intrathecal drug administration are two surgical techniques that have demonstrated promise in avoiding the blood-brain barrier and delivering medications straight to the tumor site [21]. Crucially, when provided by intravenous (IV) or oral delivery modalities, BBB presents a barrier to drug distribution inside the central nervous system (CNS); this is avoided by direct infusion via CED. Similarly, CED eliminates dose-related systemic toxicities while allowing therapy with larger doses of chemotherapeutic drugs targeted for the central nervous system by leveraging the BBB's limiting function. Numerous studies have been conducted on CED of traditional chemotherapies that are unable to penetrate the blood-brain barrier. Lidar et al. used CED method for paclitaxel administration in order to get rid of 15 patients with recurrent high-grade gliomas, including 13 GBM patients and 2 anaplastic astrocytoma patients. Out of the 15 patients treated, 11 had an imaging response recorded, and according to reports, 7.5 months of the group's median overall survival (OS) status were identified [22].

Furthermore, to offer localized, sustained medication release, biodegradable wafers or gels have come with new promises. Liposomes or nanoparticles can increase liposolubility, and altering the blood-brain barrier are two pharmacological methods to improve medication for penetration of drug molecules. In various preclinical and clinical research studies, researchers have shown to targeted agonists to leverage receptor-mediated transcytosis, temporarily break tight junctions, or inhibit efflux pumps such as P-glycoprotein. In animal models, early-stage clinical trials of CED and receptor-mediated transport techniques have shown improved tumor targeting and BBB penetration. However, in order to verify the effectiveness and long-term advantages of these advancements in science, they must be thoroughly evaluated in randomized trials before being implemented in clinical practice for GBM therapy. Thus, our goal is to integrate these cutting-edge delivery methods in this review with current treatment regimes, as described in recent research.

2.2. Tumor Heterogeneity and Plasticity

It is thought that the intrinsic intra-tumor heterogeneity, which causes notable changes in several signature cellular behaviors that are major causes of aggressive metastatic nature in the majority of cancer patients. Compared to lung cancer, which has more than eight somatic mutations per megabase 74 (Mb), and 75 melanoma, which has more than twelve somatic mutations per Mb [23–25]. However, in case of GBM per Mb it has a median value of 2.2 with somatic mutations. Glioma stem cells (GSCs), which are clonal and subclonal varieties of tumor cell types, and other non-tumor cells, mainly inflammatory and endothelial cells with the other elements of the tumor microenvironment (TME), account for the differences in GBMs. This tremendous heterogeneity of GBM, both inside individual tumors (intra-tumoral) and between patients (inter-tumoral), is a defining feature that greatly contributes to treatment failure. The molecular profiles of tumors can differ significantly, even when they have identical histological appearances. This can result in varied reactions to treatments. This intricacy stems from the dysregulation of several signaling transduction pathways, including p53 axis, retinoblastoma (RB-MDM2), and phosphatidylinositol 3 kinase (PI3K-Akt) pathways, which are key factors for tumor growth, survival, and treatment resistance [26–32]. Nevertheless, histology has influenced GBM research, and association with histological features is necessary for a number of molecular evaluation patterns, including fluorescence in situ hybridization (FISH) technique and immunohistochemistry (IHC) technique. According to these investigations, there are three main molecular subtypes of GBM, including classical, mesenchymal, and perineural. The original purpose of these subgroups was to help with diagnosis and patient stratification for individualized treatment plans. However, as they haven't yet resulted in appreciable enhancements in therapeutic outcomes, their clinical utility is still restricted. The expression of GBM markers, including MGMT (O6-methylguanine-DNA methyltransferase), IDH1 (isocitrate dehydrogenase 1), ATRX (alpha-thalassemia, mental retardation, X-linked) and EGFR (epidermal growth factor

receptor) in tumor cells has been thoroughly demonstrated by a number of publications utilizing IHC, which is far more useful for routine neuropathology [33,34]. Single-cell investigations of intra-tumor heterogeneity may have prognostic consequences. The scientists found that the percentage of tumor-bearing cells of different clonal subtypes affects the clinical expectations when evaluating bulk proneural GBMs, with higher heterogeneity being linked to worse OS. However, in recent years, research has shifted towards a more comprehensive understanding of GBM heterogeneity by incorporating the TME, which includes immune cells, extracellular matrices, and stromal components. Within a single tumor, there exists a diverse and evolving population of tumor cells that differ at the transcriptomic, epigenetic, proteomic, and metabolic levels. Adding to the challenge of intertumoral heterogeneity is the dynamic and plastic nature of intratumoral heterogeneity. The next phase of functional imaging advancements will be driven by the implementation of innovative techniques aimed at analyzing tumor heterogeneity in GBM at the protein and metabolite levels. These developments are expected to enhance early diagnosis, improve the precision of surgical resection, refine histomolecular classification, and accelerate drug discovery. Collectively, these breakthroughs will play a pivotal role in advancing personalized treatment strategies for GBM patients [35,36]. The scope and level of complexity of research on intra-tumor heterogeneity in GBM are expected to grow over the course of the next ten years. There are chances to gain a deeper understanding of GBM in the fields of proteomics and metabolomics. Thus, emerging research on the TME and intra-tumoral heterogeneity offers new avenues for precision medicine, but overcoming the adaptive plasticity and resistance mechanisms of GBM will require a multifaceted and dynamic approach to therapy.

2.3. Anatomical Location

Fundamentally controlling the processes that make up human existence, the brain is a key organ that controls vital abilities like movement, sensation, emotion, cognition, memory, and survival instincts. Because of its vital function, GBM can only be surgically treated if the tumor is found in non-eloquent brain regions—those that do not regulate speech, vision, motor abilities, or memory. The European Association of Neuro-Oncology (EANO) guidelines suggest that surgeons should put patients' quality of life before maximizing surgical excision of tumors [37]. Since permanent neurological impairments cause many faulty damages, which are in important brain areas, highlighting the necessity of a well-rounded strategy that treats the tumor with the least amount of damage to good tissue. In order to attain this equilibrium, advanced preoperative and intraoperative procedures have to be developed to improve surgical precision and lower the risk of harming functional brain areas. Various pre-operative technologies, including guided diffusion tensor imaging (DTI), transcranial magnetic stimulation (nTMS), magnetoencephalography (MEG), and also functional MRI (fMRI), offer precise maps of brain function and connection [38]. Techniques such as cerebral perfusion measures with intraoperative ultrasonography or direct electrostimulation, followed by 5-aminolevulinic acid (5-ALA) targeted tumor labeling by fluorescence method, can be used during surgery to further improve the overall survival of patients. This strategy is in line with the changing paradigm in the neuro-oncology field, where patient-centered care and accuracy will be more in critical areas.

3. Identification and Selection of Neoantigen in GBM

Several computational methods are being employed to better characterize neoantigens. Together, all these developments enable us to obtain more predictable neoantigen molecules. Immunological-based strategies, including the molecule and presenting it to MHC, are required to generate an immune response. Computationally, we can predict the crucial binding sites of the neoantigens to their MHC molecules, which have a varied expression pattern across all species [11]. In addition to these, the algorithm is using additional biological features, such as those that influence how well a proposed neoepitope candidate activates T cells [39]. Correlating these traits with context-dependent classes of neoantigens, evaluating each of these classes of neoantigens, and ranking them according to their functional aspects shows a prioritizing vaccine design need to better understand their role in immunomodulation and research.

MHC presentation on the cell surface, stability, and binding, which is a crucial prerequisite for T-cell recognition, is the mutant peptide's capacity to attach to MHC alleles of the patients. At the cellular level, protein levels and transcript expression are connected with the density of the peptide-MHC complex, but downregulating the neoantigens is employed as an immune bypass tactic, whereas ICB therapy effectively eliminates most of the selective neoantigens produced by tumoral cells with a high transcript ratio. To have effective antitumor immunity, antigen-specific T-cells including CD4+ and CD8+ must work together. In tumor mice models, significant antitumor immunity activity requires the expression of one MHC-I/MHC-II-bound neoantigenic peptide, however, single

MHC-I neoantigen bound peptide expression was not sufficient to elevate response [40,41]. Therefore, neoepitopes are expected to bind MHC I and II forms and should be combined in the customized vaccination procedure. To summarize, the high MHC-II bound with neoantigen expression results in higher T-cell activation, leading to a stronger immune response.

It has been suggested that, because of the increased likelihood of T cell recognition, stability factor of the MHC-peptide binding complex is more significant in predicting immunogenicity than the binding affinity. The probability of cross-reactivity of the T lymphocyte population against a common molecular pattern increases with the degree to which the neoepitope resembles pathogenic sequences more frequently. Recognition of T-cell receptor (TCR) and predictions of TCR amino acid side chains taking part in MHC-to-peptide binding complexes serves as the building foundation for TCR-peptide-MHC complex interactions [42–44]. This increases chances of TCR binding more frequently. Various research has shown some deep learning methods predicting immunogenicity of neoantigens. Truncated clonal mutations are more effective in addressing tumor heterogeneity as they specifically target tumorigenic mutations that drive tumor survival and enable evasion of T-cell-mediated damage. These mutations, characterized by greater fitness and tumor-promoting capabilities, are considered more advantageous compared to subclonal mutations. Data representing T cell responses, as well as the challenge of differentiating data sets that reflect immunogenicity from those that show antigenicity and reducing apoptosis tendency in the cell [45]. Additionally, the putative neoantigens found in a primary tumor or second metastasis are different from those found in a metastatic lesion in one patient. A well-preserved data set is crucial for determining actual parameters for neoantigen prediction via different algorithms developed so far. However, there is a real gap in standardized procedures for sequencing, mutation identification, and neoantigen candidate ranking, based on which the immunogenicity testing will be done, followed by data integration and comparability with other currently developed neoantigens, which is the major challenge in neoantigen-mediated therapy.

4. Cancer Immunogenomics and Neoantigen

HLA-A2 can restrict the neoantigens, which were proposed by Segal et al. for the first time. Subsequently, in various preclinical studies, mouse cancer models showed neoantigens identified by T cells resulting in an immunogenic response [46–49]. A pioneering study by Schreiber et al. demonstrated that predicted neoantigens, derived from a comprehensive list of variants in preclinical melanoma and fibrosarcoma models, exhibited higher immunogenicity compared to others. Today, the integration of sequencing technologies and computational biology has streamlined the process of linking functional genomics to cancer immunology at a molecular level. This approach involves mining genomic data to identify structural variants with immunogenic potential, shifting the focus from traditional druggable targets such as enzymes or dependencies. However, these two approaches—targeting immunogenic properties and conventional druggable targets—are not mutually exclusive and can coexist in advancing cancer therapeutics.

The field needed the equivalent immunologic data on T cells to identify the mutant sequences of peptides suggested by in silico approaches in order to translate therapeutics designed to target cancer neoantigens. These papers were therefore important additions to the field of neoantigen identification at the intersection of immunology and genetics. More proof for the value of neoantigen target finding was provided by the discovery of immunogenic neoantigens in glioblastoma and other preclinical models of colorectal cancer. Crucially, human malignancies such as ovarian, lung, cholangiocarcinomas, and melanoma have also been shown to have immune reactivity to expected neoantigens. Genomic variations that develop in somatically altered cells are the driving force behind the creation of neoantigens. In general, MHC molecules are capable of processing and potentially presenting structural variants (peptide-bound) can be transcribed and followed by translated into a long peptide chain [50–52]. Missense mutations or single nucleotide variations (SNVs), caused by an amino acid substitution in a specific site, have attracted considerable interest in the field. To identify genetic variants, confirm their expression, and uncover fusion events or splicing alterations that may not be detectable at the DNA level, most methodologies combine whole exome DNA sequencing with RNA sequencing. Additional support for RNA expression is therefore essential to identify particular variations where frame shifts are incorporated and then may be translated into protein, as this procedure is solely intended to infer protein biochemistry. As a result, the MHC can present neoantigens produced by several genetic changes that are inherent to altered cells. The possibility of producing novel immunogenic peptide sequences in the latter frameshift scenario might outweigh the impact of single amino acid modifications. In malignancies like renal cell carcinoma, Indels have been found to be important immunogenic targets. Modifications

like gene fusions into reading frames, splicing of different variants, endogenous retrovirus entry, post-translational (phosphorylation, acetylation, methylation) protein modifications, and other types of genetic alterations can also contribute to the formation of neoantigens. The MHC alleles, which exhibit significant diversity across species, include approximately 13,000 class I molecules comprises of HLA-A, HLA-B, and HLA-C and 8,000 class II molecules of HLA-DP, HLA-DQ, and HLA-DR [53,54]. These are encoded by the highly polymorphic HLA locus, present in both patients and the general population. Consequently, prediction algorithms must account for both the patient's unique HLA haplotype and the catalog of expressed genetic variations across populations for identifying patient HLA type which binds with a greater affinity. Notably, there is no universally accepted computational method for predicting neoantigens. The Immune Epitope Database (IEDB) provides a comprehensive overview of tools designed for HLA class I prediction . These tools employ various approaches, such as linear regression models (e.g., PickPocket), artificial neural networks (e.g., NetMHC4 and NetMHCPan4), and hybrid methods combining multiple techniques. More recently, neoantigen prediction and variant calling have been integrated into software packages like PVAC-Seq [55,56]. Numerous research teams have developed methodologies to assess neoantigen "fitness," a metric that evaluates both the binding affinity of a neoantigen relative to its wild-type counterpart and the level of sequence similarity between the neoantigen and known antigens. In comparison, HLA class II prediction algorithms are less developed, primarily due to the greater complexity of peptide binding within the more open binding groove of class II molecules, as opposed to the more restricted structure of class I molecules. These methodologies are continually advancing, and no single pipeline has emerged as a definitive leader among the currently available options. To that end, recent work from the Tumor Neoantigen Selection Alliance (TESLA) supported the combination of two strong methods in order to integrate distinct predictions into an aggregate neoantigen candidate list [57]. Genetically driven antigen identification based on is therefore a stand-in for the proteomic ground. Mass spectrometry (MS) can be used To identify which peptides bind to MHC/HLA protein complexes, specific prediction can be done by computation algorithms, and this method has been extensively explored for its application in detecting cancer neoantigens [58,59]. The broader approach in cancer immunogenomics will be understood to precisely characterize and identify the role of biochemistry in terms of peptide identification, which is actively represented by antigen-presenting cells (APCs). To increase the number of candidates to examine and describe, neoantigen discovery may eventually combine immunogenomics and MS-based techniques as MS methodologies continue to evolve.

5. Neoantigen-Based Immunotherapeutic Strategies

Several strategies have been implemented regarding neoantigens and glioma therapy. Here in this section, we are discussing them as follows:

5.1. Tissue Expression-based Personalized Neoantigen Vaccines

Tumor antigens capable of triggering immune responses come in three major types including tumor-associated antigens (TAAs), cancer-testis antigens (CTAs) and tumor-specific antigens (TSAs) [60,61]. In normal host genome TSAs antigens are not found and these abnormal proteins also known as neoantigens arise from somatic mutations. As tumors develop, cells undergo mutations that result in the production of abnormal proteins. Some of these proteins are recognized as an external threat by the immune system because they differ from normal proteins. TAAs, on the other hand, are encoded by the genome but it may involve either normal differentiation antigens or proteins that are expressed inappropriately. Normal regular proteins overexpressed and supporting growth and survival of cells can lead to the appearance of TAAs. For T cells to recognize these proteins, a certain threshold of antigen must be presented. If tumor cells express more peptide-HLA complexes than normal cells, it could trigger an immune response. However, TAAs generally have a lower affinity for T cell receptors (TCR) compared to foreign antigens or TSAs. For example, ERBB2 or HER2 growth factor receptor which is highly overexpressed in several epithelial cancer forms, including breast (TNBC) and ovarian cancers [49,62]. TAAs can also formed due to different types of posttranslational modifications of proteins, like phosphorylation, acetylation, methylation etc. TAAs are much more superior compared to TSAs, as they are more abundant in tumors. Secondly, while TSAs are typically specific to each patient, TAAs are very common across tumors [63]. On the other hand, the third category includes CTAs. These types of genes are typically expressed in the germline area but are also found in different types of tumors, such as melanoma liver, lung, and bladder carcinoma [64]. These kinds of immunogenic proteins are being actively researched because they can be crucial therapeutic targets for cancer vaccines. The activation of CTA genes in tumors is found to be linked with promoter

demethylation, which are normally identified as methylated in all cells except germline cells. This demethylation is more common during tumor progression which aligns with increased abnormal DNA-methylation patterns in GBM patients [65,66]. In the past decade, exploration of TSAs has been increased in cancer immunotherapy as therapeutic targets, with most research focusing on identifying CTAs and TAAs. Using large-scale sequencing techniques early efforts are mainly concentrated on mutated gene encoded TSAs discovery via comparing DNA from normal and tumor tissue. Given the vast size of the genome (3 billion base pairs) and its complexity, researchers have focused on the 1% coding exons genome via exome analysis. Notably, recent technological advancements have significantly shortened the time required for this process, now allowing researchers to produce exome capture data and generate a somatic mutations list within just three days. By aligning sequence reads with the reference genome mutation identification from exome sequencing is achieved with tumor variants being compared to data collected from matched normal tissue derived DNA. TAAs generated from non-protein coding sequences through splicing and epigenetic abnormalities result in a higher number of proteins that are absent in normal cells [66–68]. However, these variants are extremely challenging to decode, particularly using exome data cDNA capture sequencing (cDNA Cap-Seq) can confirm these types of antigens via analyzing bulk RNA-seq data obtained from patients [69–72]. During overexpression, by checking through qRT-PCR or immunohistochemical analysis abundant amounts of epitopes are measured for both tumor and normal tissues. Finally, to assess their potential to trigger immune responses, tumor DNA portion vs normal DNA comparisons were majorly recognized by bioinformatic evaluation. Currently, the most effective epitope prediction tools focus on predicting how peptides bind to class I MHC (MHC-I). The MHC-I-mediated antigen presentation pathway presents peptides from endogenous proteins to CD8+ CTLs in both humans and mice [73]. Several tools are available to predict the binding capacity of peptide to MHC-I/II molecules, with some algorithms using artificial neural networks to give the prediction of binding to various MHC-I/II variants, generating predicted IC50 values as outputs. Among these tools, NetMHC is widely recognized highly verified programs for such predictions. With the integration of immunological methods, NGS sequencing followed by computational epitope calculation researchers have successfully identified and validated different kinds of TSAs in various tumor types, such as sarcoma and murine B16-F10 melanoma [51,74,75]. There is considerable excitement about applying cancer immunotherapies to treat malignant brain tumors, inspired by successes in other types of cancers. This has created a pressing need to identify and target TSAs that can effectively trigger T cells responses in GBM. As part of this effort, in various preclinical models several groups have explored antigen in GBM, recognizing that presence of neoantigens can modulate the checkpoint blockade immunotherapy response. Across the exomes, Glioblastomas reported typically having fewer than 100 mutations where a small fraction of these mutations being potential neoantigens. However, in case of a subset of glioblastomas that are hypermutated has been identified, which have mutational loads 10 to 50 times higher than average. This hypermutation is seen in roughly 25% of recurrent glioblastomas which are followed by chemotherapeutic drug temozolomide treatment. Additionally, limited number of immune cells infiltration have been observed in GBMs which is challenging for treatment. Therefore, tumor-derived antigens (unmutated) neoepitopes could provide more precise immunotherapy options, particularly for low-mutational-load tumors like gliomas. CT2A, GL261 and SMA-560 are the three major murine models generated via RNA sequencing approach for tumor-specific mutations commonly arises in glioblastoma (GBM) [40,76,77]. These studies revealed 2401, 4932, and 2171 non-synonymous mutations in the exomes of these models, respectively, with less than half of these mutations being expressed. Additionally, potential immunogenic antigens were identified in silico by predicting their ability to induce tumor-infiltrating T cells. Several of the leading candidates underwent testing through neoantigen vaccination, such as CT2A. Among the 29 CT2A neoantigens that are tested, CD8+ T cells specific for endogenous neoantigen were identified within the murine GBM model that is resistant to αPD-L1 [76]. These findings demonstrate that neoantigen vaccination, when combined with αPD-L1 treatment, significantly enhances survival, highlighting the potential for further research on multi-modal immunotherapeutic strategies to improve anti-glioma immunity.

5.2. Neoantigens Based on Clinical Application

Guarding neoantigens refer to a group of T cells that are typically specific for neoantigen and can be stimulated even before the tumor clinically manifests. Notably, the existence of these types of neoantigens are sufficient to trigger a significant clinical response without the need for immunotherapy; they can help to accelerate tumor rejection or prevent its growth. There are two recognized types of guarding neoantigens: an immunodominant type, driven by

exceptionally rare mutations, which can improve clinical outcomes and mutational burden, as those with MSA instability. Another type is a cross-reactive memory T cell, which has a lower rate of activation threshold for immature T cell response. Neo-epitopes that can engage broader range of TCR responses, particularly those with more pronounced differences to self-antigens, are more likely to belong to this cross-reactive subclass [39,78]. Conversely, neoantigens with low affinity for MHC molecules having a unstable binding to the MHC-peptide complex, or sometimes insufficient enough for expression to activate immature T-cells into mature T-cells may be less potent but can still be amplified through cross-reactive memory T cells. In therapeutic contexts, immune checkpoint blockade (ICB) or neoantigen vaccines can enhance the pre-existing T cell-mediated response, either qualitatively or quantitatively, targeting protective neoantigens. On the other hand, restrained neoantigens are those that trigger T cells that are not inherently functional and require additional stimulation, such as ICB, to become effective. In contrast to guarding neoantigens, which are recognized based on their effect on prognosis, restrained neoantigens are defined by their ability to predict clinical benefit from immunotherapy. As for ignored neoantigens, it was found that only a small fraction of them were noticed by spontaneous T cells. In fact, many of the immune responses generated are undetectable before treatment and are instead triggered after the vaccination process. Frankziska Lang et al. introduced the term "ignored neoantigens" to describe these cases. While neoantigens that are present by MHC molecules may require an additive vaccine to generate a meaningful response [39]. A particular vaccine can trigger DC in lymph nodes and start the stimulation of other immune cells. Notably, vaccine-induced T-cell population showed increased PD1 expression. The key advantage of vaccines is that they can expand the pool of pre-existing T cell populations while simultaneously aggregating the availability of previously ignored neoantigens that are primed during ICB therapy [79,80]. Moreover, by counteracting the T regulatory cells-mediated immunosuppressive effects, ICB technology can lower the threshold required for immature to mature T cell priming effectively, thus T cell-mediated response through antigen spreading.

5.3. Neoantigen-Specific Immuno-cell Therapy

Recent reports suggest that there are various challenges to overcome in application of Neoantigen -based cell therapeutic administration. However, these obstacles include crucial phases like quickly identifying and generating immunogenic NeoAgs, expanding NeoAg-reactive cells ex vivo, and guaranteeing the in vivo persistence of adoptively transferred cells [81–83]. Compared to CAR-T gene therapy, neoantigen-based ACT often exhibits a very promising and safe expression across treated patients. Sometimes patients with high grade ovarian cancer saw tumor regression as a result of tailored Neoantigen -based T cell treatment. Following cell therapy, both patients showed partial responses, and their life span was expanded in terms of times. In circulation, more polyclonal Neoantigen -specific CTLs have been found, which were characterized by increased cytotoxicity in cells and the active development of immunological synapse mechanisms [84–86]. Furthermore, the immunogenic effect of neoantigen and the variety of TCR expression profiles were substantially correlated with the targeting efficacy. Neoantigen peptide-loaded DC administered intra-nodally produced a partial immune response in a patient with high malignant ascites and chemoresistant ovarian cancer, according to recent research. In a study with 10 patients who underwent curative resection or radiofrequency ablation, combination of and adoptive T-cell transfer and neoantigen-based DC administration technology showed promising anticancer responses, effectively targeting the recurrence of hepatocellular carcinoma on patients with reduced tumor burden at the sites. Furthermore, Phase-I and Phase-II clinical trials have confirmed the safety and efficacy properties. One of the clinical trial vaccine candidates is DC based vaccines, when loaded with tumor-regional sites with multi-epitopes, show great potential treatment regimes, which will be explored in detail in the next section.

6. Neoantigens Vaccines on Clinical Trials

From immunotherapy to broad developments in cancer immune-therapeutics, a recognizable pattern of development is being seen. Tumor immunotherapy has long employed and investigated vaccines that target tumor-associated antigens (TAA), which are overexpressed on tumor cells. These vaccinations typically cause systemic toxicity. The majority of the clinical trials have not demonstrated a successful antitumor response. A phase I study, GAPVAC-101 (NCT02149225), directed by Hilf et al., included 15 patients with newly diagnosed GBM who tested positive for human leukocyte antigen (HLA) type-A [87,88]. In APVAC1, patients received a vaccination that targeted unmutated antigens; in APVAC2, patients received a vaccine that targeted neoantigens. Numerous studies examining a range of immunization regimens targeting the three primary antigen categories in GBM—tumor lysate, TAAs, and TSAs—showed superior effectiveness and comparable safety. These vaccination regimens included

SurVaxM targeting survivin (survival protein), Rindopepimut, which targets specifically EGFR-vIII (a mutated version of the receptor present in 20–30% patients of GBM), the WT-1 vaccine (targeting a modified 9-mer peptide from Wilms' tumor gene 1), and prophage-based vaccines (such as Oncophage, G100, G200, and Vitespen) targeting the HSPPC-96 have shown promise in clinical study perspectives [89–92]. In a recurrent GBM scenario, SurVaxM has demonstrated immunogenicity without significant safety concerns. Additionally, the HSPPC-96 vaccine has been associated with improved PFS, status, with a median survival increases to 11-17.8 months, and overall survival (OS), with a median survival rising from 23.8 to 31.4 months, highlighting its immunogenic potential . However, a Phase-III clinical trial with a peptide vaccination based on a personalized approach, similar to GAPVAC-101 trial for APVAC1 (antigen unmutated), showed safe and significant efficacy in comparison with control groups, which was really reduced [93,94]. These vaccines have largely demonstrated safety when used alone or in combination, and in smaller trials, they have demonstrated somewhat greater efficacy than SOC alone. Post-vaccination of these patients often exhibits T cell exhaustion which was marked increase in inhibitory checkpoints viz. PD-1, CTLA-4, TIGIT (T-cell immunoreceptor with Ig and ITIM domains) and TIM 3 (T-cell immunoglobulin domain and mucin domain-3) [95]. In both trials, after vaccination, increased PD-1 expression was observed for CD8+ T cell populations, including circulating plus infiltrating T cells on the tumor site. Additionally, IMA950, a highly personalized vaccine targeting patient-specific antigens presented on HLA surface receptors, was evaluated and demonstrated both safety and efficacy in individuals with high metastatic load [96–98].

7. Conclusion and Future Prospects

We can now comprehend the intricacy of the immune milieu thanks to high-precision genomic approaches, which have led to a meta-analysis of tumor-bearing gene expression that has grouped all human tumor types into six immunological types. However, because of the immunosuppressive TME, GBM therapy results have been unsatisfactory. Since only a limited subset of cancer patients responds to checkpoint inhibitors, understand the underlying mechanisms and develop strategies to overcome this resistance. On the other hand, anti-PD1-efficient T cell-mediated immunotherapy has shown remarkable success in treating certain subtypes of brain metastases. These subtypes were linked to immunomodulatory, genetic, and prognostic changes that influence the particular forms of TME treatment. This subtype of tumor is characterized by a significant M2 response, Th1 suppression, a pronounced macrophage hallmark, and lymphocyte depletion. Cytotoxic CD8+ T lymphocytes in gliomas play an effective role in mediating the main cause of immunotherapy. So, the actual cause of immunotherapy failure was the lack of CD8+ T-cells in the glioma environment.

Cellular vaccines are now acknowledged as another promising strategy for therapeutic developments that can be made in case of glioma individuals. These vaccine therapies have evolved to have high reproducibility and are generally well-tolerated treatment options for patients. However, their impact on GBM has been relatively modest compared to other therapies (radiation, chemotherapy, etc.) that have shown significant clinical benefits including temozolomide (TMZ and PCV) and targeted delivery of bevacizumab as a potent anti-cancer molecule. Although there is much disagreement regarding the best combination of immunotherapeutic modalities. For long-term protection against tumor recurrence, immune modifiers combining with cellular vaccines in gliomas hold significant promise for unlocking the full potential of cellular vaccines. The TME immunoprofile revealed a notable reduction in effector T cell populations, alongside the dominant presence of macrophages exhibiting both immune-stimulatory and suppressive properties upon receiving the signals. Putting aside the inherent response, evidence also suggests that it may hold the secret to enhancing immunotherapy for malignancies that do not respond to treatment. This related to the undervalued role of the innate immune responses for preventing tumor progression. The PD1+ macrophage population is more strong in GBM which is targeted by ICI since the absence of T cells indicates the oncologic setting. ICI aiming PD1 dramatically improves immunocompetent mice's survival, even in the absence of CD8+ T cell populations. When treated with an antiPD1 antibody, the remaining macrophages polarize to the anticancer M1 phenotype. In previous GBM clinical studies, treated with antiPD1 before surgery. Some studies conducted by others in recent years have proven high CD8 T cells significantly impact on tumor microenvironment and immunogenicity through immunoediting; nevertheless, these T-cells may not be the only cause of the ICI response. T cells are not the only critical players in immunotherapy responses, which is reinforced by insights into immune system dynamics and activation in preclinical murine/human models, which outline a cancer-immunity cycle. In tumors such as GBM, where T cells may be scarce, anti-PD1 therapies could release therapeutic effects by interfering with other immune populations, including macrophages and microglial cells. Depending on their relative abundance, therapeutic effects

of anti-PD1 may vary across different immune cell populations. In GBM tumors with a significant T-cell infiltration rate, anti-PD1 likely exerts its primary effects by directly interacting with T cell populations. The most commonly used immunomodulatory agents in brain tumor vaccines is poly-ICLC, which is frequently combined with various neoantigen vaccines, particularly peptide and mRNA-based vaccines (examples from clinical trials: NCT03068832, NCT02287428). This substance promotes TLR3 and MDA5, two pattern recognition receptors (PRRs), which in turn boost innate immunity. By stimulating the activation of cytokines, these receptors improve T-cell activation responses. Proinflammatory GM-CSF is frequently utilized in conjunction with DNA and peptide vaccinations to improve T-cell activation and DC maturation. In conclusion, most people will agree that science has entered into a new era of immunotherapy, even if there are still a lot of unsolved concerns, difficulties, and uncertainties with vaccine-based immunotherapy.

Neoantigen-based customized therapy, is a new and promising therapeutic strategy for GBM. Even though there are still obstacles to overcome, developments in immunotherapy, genetics, and bioinformatics are propelling progress and opening the door to more long-lasting and efficient treatment plans for GBM patients. Ultimately, to enhance efficacy and promote clonal expansion of T-cells, it will be essential to explore which immunotherapies are most compatible to use in combination with conventional therapeutic vaccination strategies. The area of cancer vaccines is still developing quickly. It is obvious that further research is required to determine how the most effective cancer vaccine fits into the precision immunooncology framework. The choice of vaccine platform plays a critical role in maximizing the ability to immunize against specific targets. The pandemic of COVID-19 in 2021 showed the potential risk factors and challenges of vaccine development on a global scale. Though peptide vaccines have a long history of use, their application is limited by manufacturing constraints and the variable solubility problem of certain peptides, which may alter the production of patient-specific, microscale peptide formulations on a mass scale. However, peptide vaccines continue to be a reliable platform in this field. So, neoantigen-based treatment regimens might revolutionize GBM therapy overall and get us one step closer to efficient, customized immunotherapies for this debilitating illness with more investigation and clinical confirmation with validations for a better future.

Acknowledgment

The authors sincerely acknowledge all the co-authors.

Conflict of interest

No competing interests to declare.

Funding

No funding was received.

Ethical statement

No ethical study required

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