Immunotherapy in Glioblastoma: Why promising strategies fail to improve survival

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Abstract

Immunotherapy has transformed the management of several extracranial malignancies; however, its efficacy in GBM has been limited. Large clinical trials evaluating immune checkpoint inhibitors have failed to demonstrate meaningful survival benefit in newly diagnosed and recurrent GBM. Other modalities, including dendritic cell vaccines, chimeric antigen receptor (CAR) T-cell therapies, and oncolytic virotherapy, have shown encouraging but modest results in selected patients. This narrative review summarizes the current role of immunotherapy in GBM, focussing on its impact on patient outcomes, underlying barriers to therapeutic success, and future directions.

Keywords: Glioblastoma; Immunotherapy; Oncolytic virotherapy; Dendritic cell vaccine.

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Introduction

Immunotherapy has emerged as a promising approach in oncology by priming and amplifying the host immune response against tumour cells.[1] Multiple immunotherapeutic modalities, including immune checkpoint blockers, therapeutic vaccines, adoptively transferred cellular therapies, targetted monoclonal antibodies, and engineered oncolytic viruses, have been explored in glioblastoma, albeit with variable success.[2] Despite extensive investigation, the failure of immunotherapy in glioblastoma (GBM) contrasts sharply with its success in other malignancies, highlighting a critical need to understand the underlying biological and clinical barriers to its effectiveness. This narrative review aims to summarize and critically evaluate the role of immunotherapy in GBM, with a focus on its impact on patient outcomes and future therapeutic potential.

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Review of Literature

The limited success of immunotherapy in GBM, in contrast to several other extracranial solid tumours, can largely be attributed to its unique and highly immunosuppressive tumour biology.(Fig 1) A major barrier to immunotherapy in GBM is its highly immunoregulatory tumour microenvironment (TME), characterized by a predominance of tumour-associated macrophages/microglia, along with regulatory T cells and myeloid-derived suppressor cells, which interact with tumour cells to suppress cytotoxic T-cell activity and promote immune evasion.[3] In addition, glioblastoma cells actively downregulate major histocompatibility complex (MHC) molecules and tumour-associated antigens, thereby impairing immune recognition. This is further reinforced by the secretion of immunosuppressive cytokines and accumulation of metabolites such as adenosine, which contribute to T-cell exhaustion and sustain a locally tolerogenic microenvironment.[4]

Beyond the cellular milieu, the blood–brain barrier (BBB) poses a significant obstacle to immunotherapy in GBM by restricting both immune cell trafficking and therapeutic delivery. While focal disruption within the tumour core creates a heterogeneous blood-tumour barrier (BTB), this permeability is inconsistent, and infiltrative tumour regions often retain an intact barrier, resulting in limited drug penetration and suboptimal therapeutic efficacy.[5] Furthermore, GBM generally exhibits a relatively low tumour mutational burden (TMB), resulting in limited neoantigen expression and reduced immunogenicity. Notably, the utility of this TMB as a predictive biomarker in GBM remains controversial, with current evidence failing to demonstrate a consistent association with response to immune-based therapies such as immune checkpoint inhibitors (ICIs).[6]

These biological constraints are reflected in the limited clinical efficacy of ICIs in large clinical trials.[4,7] Phase III trials evaluating programmed cell death protein 1 (PD-1) blockade have not demonstrated a survival advantage. The CheckMate-498 and CheckMate-548 trials, which assessed nivolumab in combination with radiotherapy with or without temozolomide in newly diagnosed GBM, did not show improvement in overall survival or

Table 1: Summary of Immunotherapeutic Strategies for GBM Treatment.

Modality	Mechanism of Action	Subtypes		Examples	Clinical Status in Glioblastoma	Key Limitations
Immune Checkpoint Inhibitors	Block classical or novel immune checkpoints to enhance T-cell activity	Classical	Anti-PD-1	Nivolumab, Pembrolizumab	No significant survival benefit in phase III trials (e.g., Check Mate-143, 498, 548)[7,8,9]	Immuno suppressive tumour micro environment, low mutational burden
			Anti-PD-L1	Durvalumab, Atezolizumab, Avelumab		
			Anti-CTLA-4	Ipilimumab		
		Novel	Anti-LAG-3	Relatlimab	For novel ICIs: Early-phase/ preclinical investigation; limited GBM-specific data[4]	
			Anti-TIM-3	Sabatolimab		
			Anti-TIGIT	Domvanalimab		
			Anti-IDO1	Indoximod		
Therapeutic Vaccines	Stimulate adaptive immune response by using tumour antigens	Peptide vaccines		Rindopepimut	Mixed results; some promise in selected patients[4,10]	Tumour heterogeneity, antigen escape
		DC vaccines		DCVax-L		
		Nucleic acid vaccines (DNA/ RNA)		VXM01		
		Viral vector vaccines		VBI-1901		
Adoptive Cellular Therapies	Infusion of activated or engineered immune cells targeting tumour antigens	Activated	TILs		Early-phase clinical trials with limited efficacy[11]	Limited persistence, tumour infiltration issues, antigen variability
		Engineered	CMV-specific T cells			
			CAR-T cells	EGFRvIIIIL13Rα2		
Oncolytic Virotherapy	Use engineered viruses to selectively infect and lyse tumour cells while stimulating immunity	Herpes Simplex virus		HSV-1716	Promising early-phase results except Toca511, failed to improve survival in phase III trial[4,12]	Delivery challenges, immune clearance
		Poliovirus		PVSRIPO		
		Adenovirus		DNX-2401		
		Retrovirus		Toca511		
Targeted/ Adjunctive Therapy (non-immuno therapeutic)[a]	Bind specific tumour antigens to inhibit growth or mediate immune destruction	Anti-VEGF		Bevacizumab	Provides symptomatic and progression-free survival benefit; no overall survival advantage[17]	Resistance development, non-curative

Abbreviations: Anti-PD-1 Anti-programmed cell death protein 1, Anti-PD-L1 Anti-programmed cell death protein ligand 1, Anti-CTLA-4 Anti-cytotoxic T lymphocyte associated protein 4, Anti-LAG-3 Anti- lymphocyte activation gene-3, Anti-TIM-3 Anti-T cell immunoglobulin and mucin domain 3, Anti-TIGIT Anti-T-cell immunoreceptor with immunoglobulin, Anti-IDO1 Anti-indoleamine 2,3-dioxygenase 1, DCs dendritic cell vaccines, TILs Tumour infiltrating lymphocytes, CMV-specific T cells Cytomegalovirus-specific T cells, CAR-T cells Chimeric antigen receptor T cells, Anti-VEGF Anti-vascular endothelial growth factor [a]Although not a direct immunotherapeutic agent, bevacizumab is included due to its clinical relevance and potential indirect effects on the tumour microenvironment.

progression-free survival compared to standard therapy.[7,8] Similarly, the CheckMate-143 trial in recurrent GBM showed no survival benefit of nivolumab over bevacizumab.[9] These findings suggest that checkpoint blockade alone is insufficient in GBM. Unlike tumours with pre-existing T-cell infiltration ("hot" tumours), GBM largely represents an immunologically "cold" tumour, thereby limiting the effectiveness of therapies that rely on reinvigorating existing anti-tumour immune responses.[4]

Other immunotherapeutic modalities, including therapeutic vaccines, adoptive cellular therapies, and oncolytic viruses, have shown variable but modest success (Table 1). Vaccine-based strategies, such as peptide-based and dendritic cell-based vaccines, aim to enhance tumour-specific immune priming. The phase III DCVax-L trial reported a survival signal in patients with newly diagnosed GBM; however, interpretation of these findings is limited by methodological considerations, including the use of external control populations and crossover design, which complicate direct comparison with standard-of-care therapy.[10]

Adoptive cellular therapies, particularly chimeric antigen receptor (CAR) T-cell therapies targetting antigens such as EGFRvIII and IL13Rα2, have demonstrated feasibility and

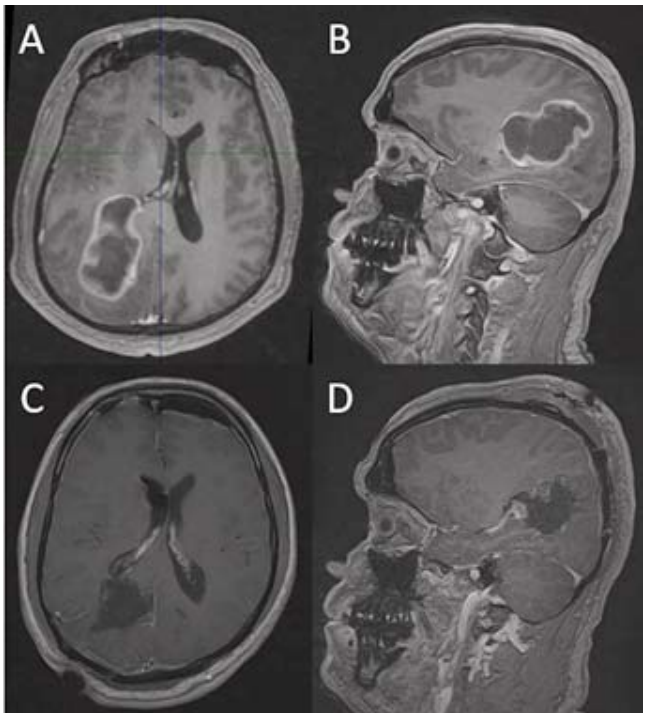

Figure: Preoperative axial and sagittal post-contrast T1-weighted MRI demonstrating a heterogeneously enhancing right posterior parietal glioblastoma (A & B). Postoperative axial and sagittal post-contrast T1-weighted MRI demonstrating gross total resection of the enhancing lesion (C & D).

early signs of activity in early-phase clinical studies. Nevertheless, their clinical efficacy remains constrained by antigen heterogeneity, limited T-cell persistence, poor trafficking across the BBB, and the emergence of antigen-negative tumour clones.[11]

Oncolytic virotherapy represents another promising strategy that employs genetically modified viruses to induce direct tumour lysis while simultaneously stimulating systemic anti-tumour immune responses. DNX-2401 (Delta-24-RGD), an oncolytic adenovirus evaluated in a phase I trial in recurrent glioblastomas, has demonstrated durable responses in a subset of patients.[12] However, its clinical utility remains limited by challenges related to intratumoral delivery, immune-mediated viral clearance, and inconsistent treatment response.

Given these limitations, there is growing interest in multimodal strategies aimed at enhancing the efficacy of immunotherapy. Radiotherapy has been shown to enhance antigen presentation and promote immune cell infiltration, providing a strong biological rationale for combination with ICIs[13] Early-phase studies suggest that such combinations are feasible and may augment immune activation; however, this has not yet translated into meaningful survival benefit in randomized phase III trials.[7,8]

The timing of immunotherapy administration has also emerged as a critical factor. Neoadjuvant administration of ICIs, prior to surgical resection, has been associated with enhance intratumoral immune activation and a potential survival benefit compared to adjuvant administration.[14] Mechanistic analyses have shown increased T-cell infiltration, interferon-γ-related gene expression, and T-cell receptor clonal expansion with neoadjuvant therapy, suggesting a more robust and anti-tumour response.[14]

Intratumoral and intertumoral heterogeneity in GBM contributes to variable antigen expression, driving differential treatment responses and immune escape.[4] This underscores the need for reliable predictive biomarkers to guide patient selection. To date, no biomarker has been consistently validated in GBM. While programmed death-ligand 1 (PD-L1) expression, tumour mutational burden, and immune gene signatures have been explored, their predictive value remains inconsistent.[4] Exploratory analyses from trials such as CheckMate-548 suggest that responses to ICIs may be restricted to specific subgroups, potentially defined by intermediate levels of PD-L1 expression, highlighting the need for more refined and integrative biomarker strategies.[15]

In addition to tumour-intrinsic factors, other clinical factors also influence the efficacy of immunotherapy. Corticosteroids, commonly used for the management of peritumoral oedema in GBM, exert potent immunosuppressive effects and have been associated with reduced survival in patients receiving ICIs.[16]

Conclusion

Immunotherapy has not yet translated into meaningful survival benefit in glioblastoma, primarily due to its profoundly immunosuppressive microenvironment, limited immunogenicity, and therapeutic delivery challenges. Future progress will depend on rational combination strategies, improved patient selection through biomarkers, and optimization of treatment timing. A deeper understanding of tumour-immune interactions will be essential to unlock the potential of immunotherapy in this disease.

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