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Review article

Active immunization strategies in glioblastoma - clinical outcomes and effect modifiers for dendritic vaccines and adoptive cell therapies: a systematic review

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Abstract

Background

High-grade gliomas are especially known for their high rate of recurrence. Despite the current standard of care treatment protocol—including resection, chemotherapy, and radiation—morbidity and mortality are still commonplace amongst patients diagnosed with glioblastoma (GBM).

Methods

Phase II/III evidence on active immunotherapies for GBM was synthesized, focusing on dendritic cell (DC) vaccines and adoptive cellular approaches, versus contemporary standard therapy, and to identify effect modifiers (MGMT status, extent of resection, and corticosteroids) that should guide surgical and adjuvant decision-making. Following PRISMA methods, a systematic review of MEDLINE (PubMed), Embase, and Cochrane (2020–2025) for adult GBM trials with a comparator arm was conducted. Outcomes included overall survival (OS), progression-free survival (PFS), safety, and prespecified modifiers.

Results

Of 797 records, 13 trials met criteria (9 newly diagnosed, 3 recurrent, 1 mixed).Among active immunotherapies, DC vaccines and adoptive cell therapies showed the most consistent clinical signals. DCVax-L improved median OS versus external controls in newly diagnosed GBM (19.3 vs 16.5 months; 5-year OS 13.0% vs 5.7%). Cytokine-induced killer (CIK) cells prolonged PFS and were an independent predictor of longer OS in pathologically pure GBM (median OS 23.1 vs 14.9 months; PFS 8.1 vs 5.5 months). In contrast, adding PD-1/CTLA-4 inhibition to chemoradiation failed to improve first-line OS/PFS, and at recurrence, bevacizumab outperformed nivolumab for PFS with similar OS; pembrolizumab plus bevacizumab improved 6-month PFS versus pembrolizumab alone. Grade 3 or higher adverse events ranged from approximately 15% to 52% across interventions and were generally manageable. Baseline corticosteroid exposure consistently attenuated the benefit of immunotherapy; maximal safe resection correlated with better outcomes and larger apparent effects of vaccines/adoptive cells. MGMT status displayed modality-specific interactions (i.e., DCVax-L benefit in MGMT-methylated disease; interferon-α signal in unmethylated disease).

Conclusions

Immunotherapy in high-grade glioma remains investigational, with randomized evidence to date demonstrating limited benefit for routine checkpoint inhibition in both newly diagnosed and recurrent disease. Selected vaccine and adoptive cellular strategies have shown encouraging survival signals in defined contexts, particularly when integrated following maximal safe resection. Persistent biological barriers, including tumor heterogeneity, antigen escape, low tumor mutational burden, and an immunosuppressive environment, continue to constrain durable responses. Future progress will depend on biologically informed trial design, optimized delivery strategies, and careful patient selection to ascertain the potential efficacy of immunotherapy in treating GBM.

Introduction

High-grade gliomas (HGGs), particularly glioblastoma (GBM), remain among the most lethal solid tumors despite decades of clinical trials and incremental refinements in surgical and adjuvant care. Contemporary management is anchored by maximal safe resection followed by radiotherapy (RT) with concomitant and adjuvant temozolomide (TMZ), the Stupp protocol, which has improved outcomes compared with RT alone but still yields a median overall survival

(OS) on the order of months, with recurrence in most patients [1].

Attempts to meaningfully improve this backbone through pharmacologic intensification have frequently produced limited or transient gains. For example, adding bevacizumab (BEV) to first-line RT/TMZ improved progression-free outcomes and some functional measures but did not improve OS in a phase III trial of newly diagnosed GBM [2]. Collectively, such patterns illustrate that current regimens often fail to deliver durable, system-level tumor control.

In contrast, immunotherapy has reshaped the natural history of non-central nervous system malignancies by enabling durable tumor control in a subset of patients. Checkpoint inhibition with CTLA-4 blockade (ipilimumab, IPI) provided a landmark survival benefit in metastatic melanoma, establishing proof-of-principle that blocking inhibitory immune signaling can extend survival in advanced cancer [3]. Subsequent clinical development of PD-1 blockade demonstrated objective responses across multiple tumor types with durability in responders, reinforcing the concept that immune reprogramming can produce long-lasting benefit beyond what is typically achievable with cytotoxic therapy alone [4]. Beyond checkpoint inhibitors, adoptive cellular immunotherapy has delivered high remission rates and durable responses in hematologic malignancies, exemplified by CD19-directed chimeric antigen receptor (CAR) T-cell therapy in relapsed acute lymphoblastic leukemia [5].

Identification of functional meningeal lymphatic vessels capable of trafficking fluid and immune cells from cerebrospinal fluid compartments to deep cervical lymph nodes supported a mechanistic basis for central nervous system immune communication [6]. Clinically, this evolving concept is supported by the demonstration of meaningful intracranial activity of immunotherapy in central nervous system disease contexts such as untreated melanoma brain metastases, where combined nivolumab (NIV) plus IPI produced substantial intracranial clinical benefit concordant with extracranial responses [7]. Together, these findings establish biological and clinical plausibility for immunotherapeutic strategies within the central nervous system [6].

Nevertheless, translating previous immunotherapy successes in non-central nervous system tumors to GBM has proven difficult. In recurrent GBM, single-agent PD-1 blockade with NIV did not improve OS compared with BEV in a phase III randomized trial [8]. Similarly, in newly diagnosed GBM with methylated or indeterminate MGMT promoter, adding NIV to standard RT/TMZ did not improve survival in a phase III study [9]. These negative trials suggest that conventional checkpoint blockade may be insufficient as a standalone strategy in GBM and that alternative immune approaches, optimized timing, or rational combinations may be required [8].

Active immunization and adoptive cellular strategies offer a distinct approach by priming or supplying tumor-reactive lymphocytes, potentially leveraging minimal residual disease after surgery and chemoradiotherapy (Fig. 1) [10]. Given the persistent limitations of historical therapeutic escalation in HGG and the mixed clinical record of checkpoint blockade in GBM, clarifying where “active” immunotherapies demonstrate reproducible benefit, and which clinical factors may modulate that benefit, remains a high priority. Therefore, this systematic review synthesizes phase II/III evidence on active immunotherapies for adult GBM to inform pragmatic integration with surgery and standard chemoradiotherapy and to highlight key effect modifiers

relevant to neurosurgical and adjuvant decision-making.

Section snippets

Methods

A qualitative systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which included eligible studies that enrolled adults (≥18years) with HGGs who were treated with emerging immunomodulatory therapies. Interventions of interest included cancer vaccines, immune checkpoint inhibitors, adoptive/cellular therapies, oncolytic virotherapy, and tumor-microenvironment or immune-metabolic modulators. Clinical trials …

Results

The search yielded 797 records (PubMed, n=204; Embase, n=123; Cochrane, n=470). After automatic and manual deletion of 214 duplicates, with an additional 71 being marked as ineligible through Covidence, 512 records were screened. 437 manuscripts were excluded at the title and abstract level. 75 studies then underwent full-text screening, whereby 62 were excluded (displayed in Fig. 2). Of the 13 studies included, there were 11 randomized controlled trials (4 phase III, 6 phase II, and 1 …

Discussion

HGG, particularly GBM, remains a disease with substantial unmet need. The success of immunotherapy in non-central nervous system cancers has appropriately motivated extensive investigation in HGG; however, the clinical record to date has been predominantly negative, and immunotherapy is not established as a routine standard-of-care management outside of clinical trials [8], [9], [21]. Accordingly, we interpret our findings conservatively and frame immunotherapy as investigational, with clinical …

Conclusion

Immunotherapy in HGG remains investigational rather than practice-defining. In contrast to melanoma and other systemic malignancies where checkpoint inhibition transformed survival

outcomes, phase III trials in GBM have largely been neutral, including PD-1 blockade in both newly diagnosed and recurrent disease [3], [4], [8], [9]. Accordingly, routine incorporation of checkpoint inhibitors into standard first-line management is not supported by current randomized evidence [8], [9].

While immune …

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Ethics approval/consent

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CRediT authorship contribution statement

Eric M. Kunz: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Devon T. Foster:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Investigation, Data curation, Conceptualization. **Abdullah Durrani:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Ivelina P. Kioutchoukova:** Writing – review & editing, …

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. …

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