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EDITORIAL

Immunotherapy as a Promising Strategy for High-Grade Meningiomas: Current Insights and Future Directions

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Dear Editor,

High-grade meningiomas (HGM) remain a formidable clinical challenge due to their aggressive biological behavior, high recurrence rates, and limited responsiveness to conventional therapies. Standard approaches such as surgical resection, radiation, and chemotherapy often fail to achieve durable disease control or significantly improve progression-free survival (PFS) in hemodialysis and non-dialysis patients alike [1-4]. These limitations underscore the urgent need for novel therapeutic strategies, particularly immunotherapy, which aims to harness and modulate the host immune system to recognize and eliminate tumor cells.

Immunological Barriers in CNS Tumors

The CNS has long been considered an immune-privileged site due to the presence of the blood-brain barrier (BBB), limited lymphatic drainage, and immunosuppressive microenvironment [5]. GBM, in particular, is categorized as an immunologically "cold" tumor, characterized by poor T cell infiltration, low mutational burden, and upregulation of immune-inhibitory signals [6, 7]. In the CheckMate-143 trial, nivolumab, an anti-PD-1 agent, yielded an objective response in only 8% of recurrent GBM patients, highlighting the formidable barriers to immunotherapy in this setting [8].

Interestingly, meningiomas especially HGM do not reside entirely within the BBB, allowing for greater immune cell access. Nonetheless, these tumors have evolved mechanisms to evade immune surveillance, including the expression of immune checkpoint ligands (PD-L1, PD-L2, CTLA-4, B7-H3), the recruitment of immunosuppressive regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and myeloid-derived suppressor cells (MDSCs), and the promotion of a tolerogenic microenvironment [9-13].

Immunological Landscape of High-Grade Meningiomas

Recent immunogenomic and transcriptomic profiling studies have revealed significant heterogeneity in immune infiltration patterns among meningiomas of different WHO grades [14-16]. Grade III meningiomas exhibit a higher density of immune infiltrates, particularly CD8+ T cells, but also an increased presence of immunosuppressive elements, including PD-1+ exhausted T cells, FOXP3+ Tregs, and M2-polarized TAMs [17, 18].

Fang et al. conducted an in-depth analysis of meningioma-infiltrating immune cells, revealing that both CD4+ and CD8+ T cells exhibited antigen experience and checkpoint receptor expression (PD-1, TIM-3), indicative of functional exhaustion [19]. B cell infiltration was rare but notable for somatic hypermutation and clonal expansion, implying active antigen presentation and participation in intratumoral immunity [20].

Interestingly, WHO grade III tumors exhibit elevated levels of MDSCs and PD-L1-expressing macrophages, which correlate with poor prognosis [21-23]. The presence of chromosomal 22q deletions, frequently observed in high-grade tumors, has also been associated with enhanced M1/M2 macrophage polarization and increased immune infiltration [24, 25].

Opportunities for Immunotherapeutic Intervention

The expression of immune checkpoints in HGM makes them attractive candidates for ICIs. PD-L1 is particularly overexpressed in WHO grade II and III meningiomas, correlating with tumor progression and recurrence [26]. Preclinical studies suggest that blocking PD-1/PD-L1 interactions can restore T cell function and enhance anti-tumor immunity [27-29]. Moreover, CAR-T cells targeting antigens such as IL13Rα2, HER2, and EphA2 though more commonly studied in gliomas are being investigated for their applicability in meningioma [30-32].

Vaccination strategies utilizing tumor-specific peptides or dendritic cells (DCs) loaded with meningioma antigens have shown early promise in generating robust cytotoxic T lymphocyte (CTL) responses [33-35]. Similarly, oncolytic viral therapies are being explored to lyse tumor cells

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directly while inducing systemic anti-tumor immunity [36].

Novel Perspectives and Future Directions

Recent efforts have focused on improving patient stratification using immunohistochemical, genomic, and proteomic biomarkers to predict responsiveness to immunotherapy [37-40]. For example, immune gene expression profiling has identified "immune hot" and "cold" meningiomas, analogous to the classification used in melanoma and lung cancer [41, 42].

The integration of immunotherapy with radiation therapy is another promising avenue. Radiation may enhance antigen presentation and upregulate checkpoint molecule expression, potentially synergizing with ICIs or CAR-T therapy [43, 44]. Additionally, modulation of the gut microbiome has emerged as a novel means of enhancing systemic immunity in CNS tumors [45-47].

In conclusion, this article underscores the growing promise of immunotherapy as a transformative approach in the management of high-grade meningiomas (HGMs), which have long demonstrated resistance to conventional treatment modalities. In contrast to glioblastomas, HGMs exhibit partial immune accessibility and harbor distinct immunogenomic characteristics, including elevated PD-L1 expression and activation of immune checkpoints. These features render HGMs viable candidates for immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T-cell (CAR-T) therapies. Furthermore, emerging insights into the tumor immune microenvironment particularly the regulatory roles of T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages highlight critical mechanisms of immune evasion and potential targets for therapeutic intervention. Integrative treatment strategies, encompassing the combination of immunotherapy with radiotherapy, the use of personalized immune biomarkers, and modulation of the microbiome, represent the forefront of precision oncology for patients with high-grade meningiomas.

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