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Efficacy and safety of immune checkpoint inhibitors and mTOR inhibitors as targeted therapy for glioblastoma: A systematic review and meta-analysis of randomized clinical trials

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Abstract

Glioblastoma (GB) is the most common and aggressive malignant brain tumor in adults, with poor long-term survival despite standard treatment. Targeted therapies such as immune checkpoint inhibitors (ICIs) and mTOR inhibitors have been explored to improve outcomes, but their clinical benefit in GBM remains unclear. We conducted a systematic review and meta-analysis of randomized clinical trials (RCTs) evaluating the efficacy and safety of ICIs and mTORi in adult patients with newly diagnosed or recurrent GB. Databases searched included PubMed, Cochrane Library, and Semantic Scholar through March 2025. Hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) were extracted or estimated and pooled using a fixed-effect model. Risk of bias was assessed with the Cochrane tool. Twenty-one trials involving 2,130 patients were included (12 on ICIs, 9 on mTOR inhibitors). ICIs showed no significant OS benefit (HR: 1.10; 95% CI: 0.98-1.24; p = 0.10), but a modest improvement in PFS (HR: 1.17; 95% CI: 1.04-1.33; p = 0.01). Pembrolizumab in a neoadjuvant setting demonstrated the most favorable outcomes. In contrast, mTOR inhibitors were associated with significantly worse OS (HR: 1.43; 95% CI: 1.08-1.89; p = 0.01), and no PFS benefit (HR: 1.16; 95% CI: 0.89-1.51). ICIs were commonly associated with immune-related adverse events, while mTOR inhibitors showed hematologic and metabolic toxicities. Neither ICIs nor mTOR inhibitors consistently improved survival in unselected GB populations. However, tailored approaches based on molecular features or delivery methods may offer benefits and should be further investigated.

Keywords: Efficacy; Glioblastoma; High-grade gliomas; MTOR inhibitors and immune checkpoint inhibitors; Safety.