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The current status of immune checkpoint inhibitors in pediatric CNS tumors: a systematic review with a representative case of CMMRD-associated glioma

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Abstract

Purpose: Immune checkpoint inhibitors (ICIs) have shown promise in adult oncology, but their role in pediatric central nervous system (CNS) tumors remains unclear. This systematic review evaluates the efficacy, safety, and clinical outcomes associated with ICI use in children and adolescents with primary CNS tumors, with the addition of a representative illustrative case to contextualize findings.

Methods: A systematic literature search was conducted across databases through September 2025 to identify studies reporting ICI use in pediatric CNS tumors. Eligible studies included clinical trials, retrospective cohorts, and case reports. Extracted data included patient demographics, tumor characteristics, treatment regimens, clinical outcomes, and adverse events. Disease progression was analyzed quantitatively; other endpoints were synthesized descriptively.

Results: Twelve studies with 309 pediatric CNS tumor patients (mean age 10.35 years, range 1-21; F/M ratio 0.8) using ICIs were analyzed. Eight studies (n = 198, 64%) predominantly included high-grade gliomas (HGGs); others (n = 111, 36%) included medulloblastoma, ependymoma, ATRT, and rare tumors. Pooled ORR was 4.1% (95% CI: 1.8-6.4), with 3 complete and 9 partial responses. Stable disease occurred in 30.7% (n = 67), often transient; progressive disease was common. HGG ORR was 4.5% (95% CI: 2.0-7.0), with PFS 1.5-6.2 months and OS 3.2-25.5 months. Non-HGG ORR was 3.6% (95% CI: 1.0-6.5), with PFS 2.1-4.5 months and OS 9.7-22.9 months. CMMRD/hypermutated HGGs had higher ORR (10%). Grade ≥3 irAEs occurred in up to 50% with dual ICI/combination therapy, mainly rash, colitis, and fatigue; no treatment-related deaths reported.

Conclusions: In pediatric CNS tumors, ICIs provide limited benefit outside select molecularly defined subgroups. Although toxicities are generally manageable, evidence remains insufficient to support routine clinical use. Future efforts should emphasize biomarker-driven selection and combination regimens.

Keywords: Brain tumors; Immune checkpoint inhibitors; Immunotherapy; Neuro-oncology; Pediatric.