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Immunotherapeutic Approaches Targeting PD-1/PD-L1 Axis in Melanoma Patients with Brain Metastases: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Melanoma brain metastases represent a formidable obstacle in cancer management, severely impacting patient outcomes despite advancements in treating primary melanoma. Immune checkpoint inhibitors, e.g. ipilimumab, nivolumab, and pembrolizumab, that target PD-1/PD-L1 pathways have shown promise in treating advanced melanoma. However, their efficacy for melanoma brain metastases is debated. This systematic review and meta-analysis aimed to comprehensively evaluate the role of anti-PD-1/PD-L1 inhibitors in treating melanoma brain metastases, addressing a critical unmet need and guiding future research efforts.

Search Strategy: A systematic search of major databases (PubMed, Scopus, Embase, and Web of Science) was conducted up to August 2023, following the PRISMA guidelines—eligible studies reported on the use of PD-1/PD-L1 inhibitors in patients with melanoma brain metastases. Data on overall survival, progression-free survival, response rates, and safety outcomes were extracted. Random-effects meta-analyses were performed, and heterogeneity was assessed using appropriate statistical methods. Publication bias was evaluated through funnel plots and statistical tests. The quality assessment used the Newcastle-Ottawa Scale, categorizing studies as low, intermediate, or high quality. Meta-analysis used random effects models with restricted maximum likelihood estimation. Cochran's Q and I2 tests assessed the heterogeneity. Subgroup and sensitivity analyses were conducted. Publication bias was evaluated via funnel plots and Egger and Begg tests.

Results: The meta-analysis included 24 studies involving 1,523 patients with melanoma brain metastases treated with anti-PD-1/PD-L1 inhibitors. The pooled one-year overall survival rate was 0.63 (95% CI: 0.52-0.74), and the one-year progression-free survival rate was 0.45 (95% CI: 0.32-0.58). The objective response rate was 0.31 (95% CI: 0.22-0.40), with a complete response rate of 0.17 (95% CI: 0.09-0.25). Substantial heterogeneity was observed across studies, and publication bias was detected for some outcomes. The combined disease stability rate was 0.11 (95% CI: 0.03-0.18), the progressive disease rate was 0.49 (95% CI: 0.37-0.62), the partial response rate was 0.14 (95% CI: 0.07-0.20), the object response rate was 0.31 (95% CI: 0.22-0.40), and the complete response rate was 0.17 (95% CI: 0.09-0.25).

Conclusion and Discussion: This meta-analysis provides evidence supporting the efficacy of PD-1/PD-L1 inhibitors in melanoma brain metastases, demonstrating promising survival outcomes and response rates. However, the findings also underscore the challenges associated with long-term disease control and the need for further research to optimize treatment strategies, including combination therapies and predictive biomarkers. The observed heterogeneity and potential publication bias highlight the importance of well-designed prospective studies to advance the field and improve patient outcomes. Overall, this study demonstrates that PD-1/PD-L1 inhibitors can provide clinical benefits for MBM patients, particularly when combined with RT. However, significant challenges remain in achieving long-term disease control, and further research is needed to refine treatment strategies.

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