Abstract

Prevalence of Treatment-Related Adverse Events in Patients with Cutaneous Melanoma Treated with BRAF/MEK Inhibitors: A Systematic Review and Meta-Analysis

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Introduction. Cutaneous melanoma (CM) is an aggressive malignancy whose management has been significantly improved by the introduction of targeted therapies, particularly BRAF and MEK inhibitors. However, these treatments are associated with a wide spectrum of treatment-related adverse events (TRAEs) that may affect treatment adherence, clinical outcomes, and quality of life. The aim of this study was to systematically review the safety profile of currently approved BRAF and MEK inhibitors in adults with CM and to estimate the pooled prevalence of TRAEs.

Methods. A systematic search of six databases was conducted for studies published from 2009 onward, including clinical trials and case reports evaluating BRAF and MEK inhibitors in adults with CM. TRAE frequencies reported in primary studies were aggregated using the Metaprop command in Stata 17, which calculates pooled prevalence with 95% confidence intervals (CIs) using the Freeman-Tukey double arcsine transformation within random-effects models. Methodological quality was assessed using the RoB 2 tool for randomized controlled trials (RCTs) and the ROBINS-I tool for non-

randomized studies.

Results. A total of 12 RCTs, 13 prospective cohort studies, and 10 case reports were included. Meta-analysis was feasible for two treatment regimens: vemurafenib 960 mg monotherapy and dabrafenib 150 mg twice daily plus trametinib 1–2 mg daily. During vemurafenib therapy, the most frequent TRAEs were musculoskeletal and connective tissue disorders (24%, 95% CI: 6–41%, $p = 0.01$), with arthralgia being the most prevalent symptom (44%, 95% CI: 29–59%, $p < 0.001$), followed by rash (39%, 95% CI: 22–56%, $p < 0.001$). For the dabrafenib plus trametinib regimen, the most common TRAEs were constitutional toxicities classified as general disorders and administration-site conditions (25%, 95% CI: 14–37%, $p < 0.001$), with fatigue (47%, 95% CI: 38–56%, $p < 0.001$) and pyrexia (40%, 95% CI: 26–54%, $p < 0.001$) being the most frequently reported symptoms. Squamous cell carcinoma and keratoacanthoma were among the most frequent grade ≥3 cutaneous adverse events associated with vemurafenib.

Discussion. BRAF and MEK inhibitor therapies show distinct toxicity profiles that should be carefully considered when developing personalized treatment strategies for patients with CM. Understanding the prevalence and patterns of TRAEs may support risk-stratified clinical decision-making and improve healthcare resource allocation in melanoma care. Further large-scale studies are needed to confirm these findings.

Keywords: Cutaneous Melanoma, BRAF/MEK Inhibitors, Treatment-Related Adverse Events

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