MAPK Pathway–Targeted Therapies

Care and management of unique toxicities in patients with advanced melanoma

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BACKGROUND: Agents targeting the MAPK pathway, including inhibitors of BRAF and MEK, have dramatically transformed the treatment landscape for patients with *BRAF*-mutant metastatic melanoma. Although generally well tolerated, targeted agents were associated with unique toxicities.

OBJECTIVES: This article aims to provide nurses with an overview of the key toxicities and associated management strategies of the characteristic adverse event (AE) profile associated with agents targeting the MAPK pathway.

METHODS: Data from clinical trials evaluating vemurafenib, dabrafenib, trametinib, and cobimetinib were reviewed and summarized along with research on management of AEs identified in clinical trials.

FINDINGS: The key AEs associated with these agents included pyrexia and cutaneous toxicities. Other notable AEs included arthralgias, ocular toxicities, and cardiac events. Because these agents are administered until progressive disease or unacceptable toxicity, nurses should be aware of management strategies to optimize treatment outcomes.

KEYWORDS
melanoma; BRAF; MEK; mitogen-activated protein kinase

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SINCE 2011, TREATMENT FOR UNRESECTABLE OR METASTATIC MELANOMA has rapidly evolved, with several new agents approved in the United States, including vemurafenib (Zelboraf®), dabrafenib (Tafinlar®), trametinib (Mekinist®), cobimetinib (Cotellic®), ipilimumab (Yervoy®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), and talimogene laherparepvec (T-VEC) (Imlygic®). Generally, these agents fall into two groups: (a) targeted therapies (orally administered agents that directly inhibit v-Raf murine sarcoma viral oncogene homolog B [BRAF] [vemurafenib and dabrafenib] and mitogen-activated protein kinase [MAPK] kinase [MEK] [trametinib and cobimetinib]) and (b) immunotherapies (immune checkpoint inhibitors targeting cytotoxic T lymphocyte–associated protein 4 [CTLA4] [ipilimumab] and programmed death 1 [PD-1] [nivolumab and pembrolizumab] administered via IV to indirectly activate the immune system). T-VEC is a unique modified viral therapy injected directly into melanoma lesions in patients with unresectable melanoma that has recurred following surgery.

These novel therapies have transformed treatment for metastatic melanoma, but they pose a challenge to the oncology nursing community because of their unique adverse event (AE) profiles. Early recognition of treatment-related toxicity and prompt intervention are critical to improving patient outcomes; therefore, anticipatory guidance and education about treatment-related AEs are a crucial part of patient care. Oncology nurses play a vital role by ensuring that patients understand their diagnosis, treatment recommendations, and management plan.

Guidelines for the care of patients receiving immune checkpoint inhibitors for the treatment of metastatic melanoma have previously been outlined (Rubin, 2012, 2015). This article aims to provide nurses with an overview of the care of patients with *BRAF*-mutant metastatic melanoma receiving targeted therapies, with a focus on management strategies for common and serious AEs.

MAPK Pathway: BRAF and MEK Inhibitors

About 50% of cutaneous melanomas have mutations in the *BRAF* gene (Davies et al., 2002; Jakob et al., 2012). BRAF is a key signaling protein at the top of the MAPK pathway that links extracellular signals to intracellular machinery controlling cellular growth, proliferation, differentiation, migration, and apoptosis