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

DIGITAL OBJECT IDENTIFIER 10.1188/17.CJON.699-709

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.
Continually assessing for adverse events is a key component of the oncology nursing role. (Dhillon, Hagan, Rath, & Kolch, 2007) (see Figure 1). Acquired (noninherited) mutations in the \( \text{BRAF} \) gene within melanoma cells can lead to expression of mutant \( \text{BRAF} \) protein that is always active and no longer requires extracellular signals. In turn, this can lead to increased MAPK signaling, disruption of cell cycle regulation, and uncontrolled cell growth and migration. The most common of these mutations in melanoma result from a glutamic acid (E) or lysine (K) substitution in place of a valine (V) at position 600 (\( \text{BRAF V600E} \) or \( \text{V600K} \)), leading to increased kinase activity. Vemurafenib and dabrafenib inhibit the activity of mutated \( \text{BRAF} \) protein and are approved for use in patients with \( \text{BRAF V600E} \)-mutant metastatic melanoma. In clinical trials, these therapies increased overall survival (about 40%–60% reduced risk of death versus dacarbazine) and progression-free survival (about 65%–75% reduced risk of progression versus dacarbazine) in patients with \( \text{BRAF} \)-mutated metastatic melanoma (Chapman et al., 2011; Hauschild et al., 2012). Encorafenib, another \( \text{BRAF} \) inhibitor (\( \text{BRAFi} \)), is currently in late-stage clinical development and has demonstrated responses in early trials (Spagnolo et al., 2015). \( \text{MEK} \) inhibitors (\( \text{MEKi} \)) target \( \text{MEK} \) proteins directly downstream of \( \text{BRAF} \) in the MAPK pathway. Therefore, targeting \( \text{MEK} \) can also inhibit hyperactive signaling from mutant \( \text{BRAF} \). Clinically, \( \text{MEKi} \) have resulted in prolonged survival in patients with \( \text{BRAF} \)-mutant unresectable or metastatic melanoma (Flaherty, Robert, et al., 2012).

\( \text{BRAFi} \) promoted significant tumor shrinkage in most patients with \( \text{BRAF} \)-mutant disease (Fedorenko, Gibney, Sondak, & Smalley, 2015). However, despite dramatic and often rapid responses, 50% of patients treated with single-agent \( \text{BRAFi} \) experienced disease progression within six to seven months after starting treatment (Flaherty, Infante, et al., 2012), indicating development of \( \text{BRAFi} \) resistance (Flaherty, Robert, et al., 2012; Hauschild et al., 2012; Sosman et al., 2012). This resistance was influenced by reactivation of the MAPK pathway (Fedorenko et al., 2015; Holderfield, Deuker, McCormick, & McMahon, 2014). Combination \( \text{BRAFi}/\text{MEKi} \) prolonged duration of response and survival when compared to \( \text{BRAFi} \) monotherapy (Flaherty, Infante, et al., 2012; Larkin, Ascierto, et al., 2014; Robert et al., 2015). Dabrafenib plus trametinib and vemurafenib plus cobimetinib were approved by the U.S. Food and Drug Administration in

**FIGURE 1.**
**MECHANISM OF ACTION OF BRAF AND MEK INHIBITORS IN THE MAPK PATHWAY**

- **BRAF**—c- \( \text{Raf} \) murine sarcoma viral oncogene homolog B; **ERK**—extracellular signal–related kinase; **MAPK**—mitogen-activated protein kinase; **MEK**—mitogen-activated protein kinase kinase

BRAF—\( \text{v-Raf} \) murine sarcoma viral oncogene homolog B; ERK—extracellular signal–related kinase; MAPK—mitogen-activated protein kinase; MEK—mitogen-activated protein kinase kinase
2015 for the treatment of patients with BRAF V600E- or V600K-mutant unresectable or metastatic melanoma.

The use of BRAFi and MEKi is contingent upon identification of a BRAF mutation within the tumor, as detected by a test approved by the U.S. Food and Drug Administration. BRAFi are contraindicated in patients without a known BRAF mutation (BRAF wild-type) because of the potential of BRAFi to activate MAPK pathway signaling in BRAF wild-type cells (Sloot, Fedorenko, Smalley, & Gibney, 2014).

Adverse Event Profiles of BRAFi and MEKi
Several AEs associated with BRAFi or MEKi (e.g., fatigue, nausea, diarrhea) are common with cancer treatments and have well-reported management strategies. However, these agents are also associated with less common but noteworthy AEs, of which oncology nurses must be aware. Table 1 lists these AEs along with incidence.

Cutaneous toxicities were the most common AEs observed with BRAFi therapy and included rash, photosensitivity, pruritus, xerosis, papillomas, and hand-foot syndrome. Development of benign or malignant secondary skin neoplasms (e.g., cutaneous squamous cell carcinoma [SCC], keratoacanthoma [KA]) was seen in as many as 25% of patients and is considered a class effect of BRAFi (Lacouture et al., 2013; Mandalá, Massi, & De Giorgi, 2013). Common and notable noncutaneous AEs associated with BRAFi included pyrexia (simple and complex) and arthralgia/joint pain (Chapman et al., 2011; Hauschild et al., 2012; Larkin, Del Vecchio, et al., 2014).

Common AEs reported with MEKi included rash, diarrhea, fatigue, peripheral edema, acniform rash/dermatitis, nausea, and alopecia. Pulmonary (e.g., interstitial lung disease, pneumonia), cardiac (e.g., decreased left ventricular ejection fraction [LVEF], ventricular dysfunction), and ocular (e.g., swelling under the retina [central serous retinopathy]) toxicities were uncommon but clinically significant and warrant careful and timely assessment (Flaherty, Robert, et al., 2012).

No new toxicities were typically observed when BRAFi and MEKi were combined; however, combinations can affect the rate or severity of select BRAFi- and MEKi-associated AEs. For example, the rate of photosensitivity was increased with vemurafenib plus cobimetinib versus vemurafenib alone, and the incidence of pyrexia was increased with dabrafenib plus trametinib versus dabrafenib alone. Conversely, combination BRAFi plus MEKi resulted in a decrease in cutaneous AEs, including a reduced frequency of SCC and KA, compared with BRAFi monotherapy (Larkin, Ascierto, et al., 2014; Robert et al., 2015).

To improve early identification and prompt management of AEs, educating patients regarding expected toxicities is essential. Table 2 provides a summary of toxicities associated with the approved targeted therapy regimens and can be used as a resource for nurses or as tool to educate patients.

Management of BRAFi- and MEKi-Associated Toxicity
This section contains pharmacologic and nonpharmacologic management strategies for notable AEs associated with BRAFi and/or MEKi therapy. Although targeted agents are oral therapies, proper administration is crucial, and patients must be educated on correct dosing, administration, and importance of adherence. Essential information regarding proper dosing and administration of each agent can be found in the corresponding prescribing information provided by the manufacturer. Development of AEs sometimes warrants dose reduction; those recommendations are provided in Table 3. Dose-reduction guidelines for BRAFi plus MEKi combinations are the same as for monotherapy, in which the dose of the drug most likely contributing to an intolerable AE

### Table 1. Incidence of Adverse Events Associated with Selected Targeted Therapies

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>BRAFi</th>
<th>MEKi</th>
<th>BRAFi + MEKi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>25–50</td>
<td>—</td>
<td>25–35</td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF decreased</td>
<td>0–3</td>
<td>5–10</td>
<td>3–8</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>2–5</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>10–25</td>
<td>15</td>
<td>15–25</td>
</tr>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>20–50</td>
<td>57</td>
<td>20–40</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>20–35</td>
<td>—</td>
<td>4 (D + T), 30–45 (V + C)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10–30</td>
<td>10</td>
<td>8 (D + T)</td>
</tr>
<tr>
<td>SCC or KA</td>
<td>10–25</td>
<td>—</td>
<td>1–6</td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1 (D + T), 15 (V + C)</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1–4</td>
<td>4</td>
<td>15 (V + C)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>&lt;1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Retinal vein occlusion</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>—</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20–30</td>
<td>—</td>
<td>25 (V + C), &gt; 50 (D + T)</td>
</tr>
</tbody>
</table>

*Incidence with dabrafenib monotherapy is not listed in the cited references. BRAFi—v-Raf murine sarcoma viral oncogene homolog B inhibitor; C—cobimetinib; D—dabrafenib; KA—keratoacanthoma; LVEF—left ventricular ejection fraction; MEKi—mitogen-activated protein kinase kinase inhibitor; SCC—squamous cell carcinoma; T—trametinib; V—vemurafenib.

Note. Based on information from Flaherty, Robert, et al., 2012; Genentech, 2016, 2017; Larkin, Ascierto, et al., 2014; Long et al., 2015; Novartis, 2017a, 2017b; Robert et al., 2015.
should be reduced. Therefore, understanding AEs associated with each agent is key to appropriate management.

**PYREXIA**

Pyrexia, defined as oral temperature of 38.5°C or greater (101.3°F or greater) in the absence of clinical or microbiologic evidence of infection (Lee et al., 2014), is a toxicity associated with combination dabrafenib plus trametinib. Although it was observed with dabrafenib monotherapy (25%), pyrexia was seen at a much higher rate with dabrafenib plus trametinib (52%) and typically presented within two months of commencing treatment (Long et al., 2015). The etiology of dabrafenib-related pyrexia is not well understood. Lee et al. (2014) hypothesized that it is an off-target effect, possibly driven by one of the known dabrafenib metabolites, and that trametinib may affect dabrafenib metabolism.

Pyrexia is typically managed with dose interruption (guidelines presented in Figure 2), antipyretics (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]), and supportive care (e.g., hydration) (Livingstone, Zimmer, Vaubel, & Schadendorf, 2014; Welsh & Corrie, 2015). Recurrent pyrexia (more than one pyrexic event) is not uncommon. However, use of antipyretics and/or dose reduction has not proven to be effective as secondary prophylaxis for recurrent pyrexia. Instead, data support the use of steroid prophylaxis. For recurrent or complex pyrexia (e.g., associated with rigors, hypotension, dehydrating, or renal failure), some patients may require more intensive treatment and, in rare cases, hospitalization (Lee et al., 2014). Infection was rare in patients treated with dabrafenib with or without trametinib. However, because BRAFi and MEKi can interact with drugs that inhibit cytochrome P450 3A4 (CYP3A4), a key enzyme involved in drug metabolism, concomitant use of CYP3A4-inhibiting antibiotics (e.g., erythromycin, ciprofloxacin) in patients with infection should be avoided or limited (Welsh & Corrie, 2015).

**CUTANEOUS TOXICITIES**

Rashes were common with BRAFi and/or MEKi and comprised a variety of skin disorders that varied in presentation, including

<table>
<thead>
<tr>
<th>ADVERSE EVENT</th>
<th>POTENTIAL SYMPTOMS</th>
<th>DABRAFENIB + TRAMETINIB</th>
<th>DABRAFENIB</th>
<th>VEMURAFENIB</th>
<th>TRAMETINIB</th>
<th>VEMURAFENIB + CORIMETINIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>Feeling unusually tired or weak, severe or persistent joint pain</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Benign or malignant secondary skin neoplasms</td>
<td>Any skin change, including new or changing lesions, sores that bleed or will not heal, any new or evolving bumps, and change in size or appearance of a mole</td>
<td>–</td>
<td>×</td>
<td>×</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Gastrointestinal toxicity</td>
<td>Diarrhea, nausea, vomiting, abdominal pain</td>
<td>×</td>
<td>–</td>
<td>×</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Red or black stools that look like tar, abdominal pain, unusual vaginal bleeding, headache, diziness, feeling weak</td>
<td>×</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Abdominal pain or swelling, yellowing of skin or eyes, dark urine, easy bruising</td>
<td>–</td>
<td>–</td>
<td>×</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Feeling like your heart is racing or “skipping,” irregular heartbeat, high blood pressure</td>
<td>×</td>
<td>–</td>
<td>–</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
<td>Shortness of breath, new or worsening cough, chest pain, increased heart rate</td>
<td>×</td>
<td>–</td>
<td>–</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Chills, night sweats, flu-like illness, low blood pressure</td>
<td>×</td>
<td>×</td>
<td>–</td>
<td>×</td>
<td>–</td>
</tr>
<tr>
<td>Rash</td>
<td>Rash, skin blisters, mouth sores, hair loss</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Decreased urine, blood in urine, swelling of the ankles, loss of or decrease in appetite</td>
<td>×</td>
<td>–</td>
<td>×</td>
<td>–</td>
<td>×</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>Change in vision, including blurriness, red eyes, eye pain, or sensitivity to light</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
</tr>
</tbody>
</table>

*Adverse events listed are more likely to occur with the drugs in the associated columns but may occur with any of the drugs. Drugs may not have all adverse events listed.

Note. Based on information from Genentech, 2016, 2017; Novartis, 2017a, 2017b.
macular, maculopapular, verrucous, hyperkeratotic, keratosis pilaris–like (Lacouture et al., 2013; Livingstone et al., 2014), and, in some patients, acneiform similar to that observed with epidermal growth factor receptor inhibitors (Segaert, 2008; Segaert & Van Cutsem, 2005) (see Figure 3). These rashes can be pruritic and uncomfortable and, for some patients, can cause physical and emotional stress that may profoundly affect quality of life (Chan et al., 2015; Livingstone et al., 2014). Anticipatory guidance regarding cutaneous toxicity is an essential component of nursing care. Because the onset of rash can be rapid (usually occurring within the first two weeks of treatment), patients should have access to the clinical team during the initial weeks of treatment to consult on potential treatment interruption or dose modification (Lacouture et al., 2013; Novartis, 2017a). Figure 4 provides management guidelines for common cutaneous toxicities associated with MEKi or BRAFi therapy. The main goal of management is to improve comfort and quality of life, thereby keeping patients on treatment. Antihistamines, steroids, and NSAIDs are commonly used to help alleviate pruritus and pain; doses of BRAFi and/or MEKi are optimized if necessary (Eaby-Sandy & Lynch, 2014; Livingstone et al., 2014; Sinha et al., 2012; Welsh & Corrie, 2015).

Pruritus and xerosis may occur in the absence of rash or following rash resolution. Similar to rash symptoms, these events can be extremely distressing for patients (Bryce & Boers-Doets, 2014; Ensslin, Rosen, Wu, & Lacouture, 2013; Sinha et al., 2012; Valentine et al., 2015). Figure 5 includes essential patient education with strategies to alleviate or minimize symptoms. Harsh soaps (alcohol-based soaps and those containing fragrance) should be avoided to minimize skin irritation, and strategies to break the itch-scratch cycle should be discussed with patients (Ensslin et al., 2013).

Photosensitivity is a unique toxicity most often observed with vemurafenib-based regimens and is preventable and treatable (Bryce & Boers-Doets, 2014; Livingstone et al., 2014; Sinha et al., 2012). Typical cutaneous findings include a burning sensation, with marked erythema on sun-exposed skin often accompanied by edema and blisters (Mavropoulos & Wang, 2014). Strict sun avoidance and photoprotection must be advised. Patients must be informed that severe burns can occur even with brief exposure to ultraviolet (UV) light and can occur through glass, such as when driving a car (Dummer, Rinderknecht, & Goldinger, 2012; Macdonald, Macdonald, Golitz, LoRusso, & Sekulic, 2015). Vemurafenib-related phototoxicity has been attributed to UVA rays because UVB rays cannot pass through glass; therefore, clothing and sunscreen recommendations should be directed specifically at UVA or products offering broad-spectrum protection (UVA/UVB). Physical sunscreens (e.g., zinc oxide, titanium dioxide) reflect and scatter UV rays from the skin, whereas chemical sunscreens (e.g., avobenzene, oxybenzone, octocrylene) work by absorbing UV and then filtering it to reduce penetration into the skin. Because physical sunscreens are less irritating and work as soon as they are applied (unlike chemical sunscreens, which take about 20 minutes to work), they are preferred over chemical sunscreens.

Educating patients about the risk of phototoxicity cannot be underestimated, particularly for patients who live in sun-intensive areas. Sunburns can be painful and disfiguring, and these events can have a profound effect on patients’ quality of life and have been associated with increased levels of anxiety and depression (Jong et al., 2008; Richards et al., 2008). As such, an emphasis on anticipatory guidance is of utmost importance. In addition, a sunburn-like dermatitis in areas of the skin that received prior

### Table 3: Recommended Dose Reductions for Adverse Events

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSE REDUCTION FOR FIRST OCCURRENCE OF TOXICITY</th>
<th>DOSE REDUCTION FOR SECOND OCCURRENCE OF TOXICITY</th>
<th>DOSE REDUCTION FOR THIRD OCCURRENCE OF TOXICITY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vemurafenib</strong></td>
<td>Recommend dose: 960 mg BID</td>
<td>720 mg BID</td>
<td>480 mg BID</td>
</tr>
<tr>
<td><strong>Cobimetinib</strong></td>
<td>Recommended dose: 60 mg QD for the first 21 days of each 28-day cycle</td>
<td>40 mg QD</td>
<td>20 mg QD</td>
</tr>
<tr>
<td><strong>Dabrafenib</strong></td>
<td>Recommend dose: 150 mg BID</td>
<td>100 mg BID</td>
<td>75 mg BID</td>
</tr>
<tr>
<td><strong>Trametinib</strong></td>
<td>Recommend dose: 2 mg QD</td>
<td>15 mg QD</td>
<td>1 mg QD</td>
</tr>
</tbody>
</table>

* Cobimetinib is approved for use in combination with vemurafenib.

Doses less than 480 mg BID are not recommended.

Note. Based on information from Genentech, 2016, 2017; Novartis, 2017a, 2017b.

BID—twice daily; QD—once daily.

Note. Medications are typically held for grade 3 toxicity and restarted with dose modifications upon improvement to grade 1 or patient’s baseline.

* Based on information from Genentech, 2016, 2017; Novartis, 2017a, 2017b.
radiation therapy, known as radiation recall dermatitis, has been reported in patients receiving vemurafenib therapy. These events were managed successfully using topical steroids (Boussemart et al., 2013).

Another cutaneous toxicity related to BRAFi treatment was the development of benign or malignant secondary skin neoplasms, including SCC and KA (Flaherty, Infante, et al., 2012; Larkin, Ascierto, et al., 2014; Long et al., 2015) and verrucous keratoses (hyperkeratotic wart-like lesions). This is a novel toxicity thought to be caused by activation of MAPK pathway signaling in BRAF wild-type cells. Patients should be instructed to promptly report any skin changes, and a dermatologic examination should be performed prior to initiating treatment, every two months during treatment, and for as many as six months following treatment discontinuation (Genentech, 2017; Novartis, 2017a, 2017b). Any suspicious or atypical lesion should be examined by a dermatology specialist, and a biopsy is recommended because of the associated risk of secondary skin malignancy. SCC or KA is generally managed with surgical excision without need for dose interruption or modification; in some cases, small SCCs will resolve without intervention. Benign growths (e.g., squamous papillomas, warts) may be a cosmetic concern for some patients and can be treated with topical medications or destroyed using cryotherapy or curettage (Mandalá et al., 2013; Welsh & Corrie, 2015).

Other notable cutaneous toxicities include palmoplantar hyperkeratosis, panniculitis-like lesions, and alopecia. Hyperkeratosis may occur rapidly following the initiation of BRAFi therapy (Anforth et al., 2012; Livingstone et al., 2014). Typically, it presents as thickened, yellow plaques, occasionally with desquamation over sites of friction, particularly on the soles of the feet. For some patients, hyperkeratosis can be debilitating and even dose limiting (Macdonald et al., 2015). Unlike the hand-foot syndrome associated with multikinase inhibitors, BRAFi-induced hyperkeratosis is not usually accompanied by significant inflammation, blistering, or peeling (Anforth et al., 2012; Livingstone et al., 2014). Avoidance of pressure and friction is the main preventive and therapeutic measure; this includes avoiding tight-fitting footwear and wearing padded gloves. Other measures include frequent, gentle paring of hyperkeratosis by a podiatrist, use of keratolytic medications (e.g., urea), and or use of class III–IV topical steroids (Livingstone et al., 2014; Macdonald et al., 2015). For severe symptoms, a dose reduction or treatment holiday may be necessary. Panniculitis-like lesions generally present as asymptomatic pink or red hair follicle openings with spicules. Often, lesions will resolve spontaneously; however, strategies for management should be employed based on severity and may require treatment interruption, systemic steroids, and or use of COX-2 inhibitors (Livingstone et al., 2014; Zimmer et al., 2012). Patients receiving BRAFi or MEKi may also experience mild to frank alopecia during the course of treatment (often several months after treatment initiation), most often associated with a slowing of hair growth (Livingstone et al., 2014; Sinha et al., 2012). In addition, curling of previously straight hair and graying of hair can be seen as a result of modifications to the hair shaft.
(Mavropoulos & Wang, 2014). No specific management is medically necessary; however, if patients are bothered by these effects, as many are, topical minoxidil may be used for alopecia, and cosmetic techniques, such as hair color or dye, may also be used.

**ARTHRALGIA**
The development of joint pain was common with BRAFi monotherapy but occurred less frequently with combination BRAF and MEK inhibition. Pain typically developed shortly after starting treatment and often increased or decreased in severity (Edmonds et al., 2012; Welsh & Corrie, 2015). For mild arthralgia (grade 1), management is conservative, with a focus on minimizing pain using analgesics (acetaminophen with or without NSAIDs). For more severe arthralgia (grade 2 or greater), interruption of BRAFi therapy until improvement of symptoms to less than grade 1 is recommended, and the BRAFi should be reduced one dose level when reinitiated. If patients experience moderate or severe grade 3 or greater recurrent joint pain, treatment with low-dose steroids or further dose reduction of the BRAFi should be considered. Switching of the BRAFi (vemurafenib to dabrafenib or dabrafenib to vemurafenib) may also be helpful in patients with persistent arthralgia (Welsh & Corrie, 2015).

**OCULAR TOXICITIES**
Eye-related AEs were rare with BRAFi and MEKi but may be serious if left untreated. The mechanism mediating BRAFi- and MEKi-related ocular toxicities is not fully understood, but evidence suggests that inhibition of the MAPK pathway can lead to an inflammatory response and breakdown of the blood–retina barrier, leaving the eye more vulnerable (Huang et al., 2009; Joshi, Karydis, Gemenetzi, Shao, & Taylor, 2013; Yang & Huang, 2012). Although potentially serious, these AEs were mostly transient and commonly resolved without intervention. Persistent symptoms necessitate dose interruption with dose reduction upon improvement or, in severe cases, permanent drug discontinuation (Urner-Bloch et al., 2014; van der Noll, Leijen, Neuteboom, Beijnen, & Schellens, 2013; Yang & Huang, 2012). Early recognition and intervention are critical to the management of ocular AEs, and patients should be advised to immediately report any visual disturbances, including blurred or double vision, redness of the eyes, or any type of eye pain. Ophthalmologic screening is recommended at regular intervals (for patients treated with MEKi with or without BRAFi) and/or whenever a patient reports visual symptoms.

**CARDIAC TOXICITIES**
BRAFi and MEKi have been associated with rare but potentially serious cardiac toxicities. Treatment with BRAFi has resulted in electrocardiogram (ECG) irregularities, including prolongation of the corrected QT (QTc) interval. BRAFi therapy is not recommended in patients with uncorrectable electrolyte abnormalities (e.g., low magnesium), long QT syndrome, concomitant medications known to prolong the QT interval (e.g., 5-hydroxytryptamine inhibitors, antiemetics, antihistamines, antidepressants), or QTc greater than 500 ms (Welsh & Corrie, 2015). An ECG to determine baseline QTc and baseline electrolytes should be obtained prior to starting BRAFi therapy, one month after initiation, and
following any dose modification. In the event that QTc is greater than 500 ms, the BRAFi should be withheld until QTc decreases to less than 500 ms, and then treatment can be reinitiated at a lower dose level. If QTc is greater than 500 ms and the change from baseline QTc is greater than 60 ms, permanent discontinuation is recommended (Livingstone et al., 2014).

**FIGURE 4. MANAGEMENT OF CUTANEOUS TOXICITIES**

<table>
<thead>
<tr>
<th>GRADE 0</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3 OR GREATER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MACULAR RASH</strong></td>
<td>Dose adjustment: Continue at current dose. Concomitant treatment: Topical steroid or oral anti-histamine. Follow-up: Reassess after two weeks. If no improvement, proceed to next step.</td>
<td>Dose adjustment: Continue at current dose. Concomitant treatment: Topical steroid cream, oral antihistamine, or oral steroid (e.g., prednisone 0.5 mg/kg). Follow-up: Reassess after two weeks. If no improvement, proceed to next step.</td>
<td>Dose adjustment: Modify dose per protocol. Perform bacterial/viral culture if infection is suspected. Concomitant treatment: Topical steroid cream, antihistamine, or oral steroid (e.g., prednisone 0.5 mg/kg). Follow-up: Reassess after two weeks. If no improvement, dose interruption or discontinuation may be necessary.</td>
</tr>
<tr>
<td><strong>KERATOSIS PILARIS RASH</strong></td>
<td>Concomitant treatment: Ammonium lactate 12% cream twice daily or heavy moisturizer twice daily.</td>
<td>Dose adjustment: Continue at current dose. Concomitant treatment: Topical steroid cream or exfoliants. Follow-up: Reassess after two weeks. If no improvement, proceed to next step.</td>
<td>Dose adjustment: Modify dose per protocol. Perform bacterial/viral culture if infection is suspected. Concomitant treatment: Topical steroid cream or exfoliants. Follow-up: Reassess after two weeks. If no improvement, dose interruption or discontinuation may be necessary.</td>
</tr>
<tr>
<td><strong>HAND-FOOT SYNDROME</strong></td>
<td>Dose adjustment: Continue at current dose. Concomitant treatment: Topical moisturizer or keratolytic. Follow-up: Reassess after two weeks. If no improvement, proceed to next step.</td>
<td>Dose adjustment: Continue at current dose. Concomitant treatment: Topical high-potency steroid cream and pain control (NSAIDs, GABA agonists, narcotics). Follow-up: Reassess after two weeks. If no improvement, proceed to next step.</td>
<td>Dose adjustment: Interrupt treatment until severity reduces to grade 1 or less. Concomitant treatment: Topical high-potency steroid cream and pain control (NSAIDs, GABA agonists, narcotics). Follow-up: Reassess after two weeks. If no improvement, dose interruption or discontinuation may be necessary.</td>
</tr>
</tbody>
</table>

GABA—gamma-aminobutyric acid; NSAID—nonsteroidal anti-inflammatory drug

Note. Grade 3 or greater recommendations can also be used with intolerable grade 2.

Patients treated with MEKi have experienced decreased LVEF and/or hypertension (Welsh & Corrie, 2015). A baseline echocardiogram or multigated acquisition scan should be considered prior to starting treatment, repeated one month into therapy and again every two to three months, and after any dose modification to assess LVEF. In patients with an asymptomatic decrease in LVEF of 10% or greater from baseline, the MEKi should be withheld for as many as four weeks and can be reinitiated at a lower dose if improvement is observed. Patients with symptomatic congestive heart failure or an absolute decrease in LVEF of 20% or greater are advised to permanently discontinue MEKi therapy (Livingstone et al., 2014).

HEPATIC AND RENAL TOXICITY
Hepatotoxicity that potentially leads to functional liver injury has been reported with vemurafenib alone and in combination with cobimetinib. Monitoring of aminotransferase, alkaline phosphatase, and bilirubin levels at monthly intervals during treatment is recommended (Genentech, 2017). Typically, abnormalities can be managed with dose reduction, interruption, or discontinuation if clinically necessary. Renal dysfunction, including kidney failure, can occur with BRAFi or BRAFi plus MEKi therapy. Renal dysfunction is usually accompanied by severe febrile reaction in patients receiving dabrafenib or dabrafenib plus trametinib. Serum creatinine levels should be determined prior to starting therapy and monitored periodically during treatment (Genentech, 2017; Novartis, 2017b).

HEMORRHAGE
Abnormal bleeding events can occur with MEKi or combination BRAFi plus MEKi therapy. In rare cases, hemorrhages may be severe and life threatening, particularly with cerebral and gastrointestinal events. MEKi therapy should be permanently discontinued for all grade 4 events. Grade 3 events warrant interruption of MEKi therapy. If grade 3 events improve within four weeks, MEKi therapy can be resumed at a lower dose level (Genentech, 2016; Novartis, 2017a).

Implications for Nursing
Although targeted agents are generally well tolerated, the associated AEs may differ from those seen with traditional cancer therapy. Cutaneous AEs, such as rash, xerosis, and SCC, are a common class effect of BRAFi and/or MEKi. Combination BRAFi plus MEKi has been associated with a reduced incidence of several cutaneous AEs and has become the preferred targeted therapy regimen. Some AEs were observed differentially between agents in the same class. For example, dabrafenib was associated with a higher incidence of pyrexia, and vemurafenib was associated with an increased incidence of photosensitivity. Educating patients about what to expect during treatment and continually assessing for AEs are key components of the oncology nursing role. Educational tools detailed in the current article provide a framework for this communication. Proactive and timely referrals to specialists regarding specific AE management (e.g., dermatology referrals for suspicious cutaneous lesions) or referral to social work or other mental health providers for psychological support are essential to improving the quality of care. With the use of these communication tools, nurses are at the forefront of early recognition and proactive management of AEs, as well

FIGURE 5.
PATIENT EDUCATION FOR STRATEGIES TO REDUCE SKIN-RELATED COMPLICATIONS

XEROSIS MANAGEMENT
- Be gentle to your skin: Avoid hot baths; use nonperfumed, nonalcohol soaps and emollient cream (urea or oatmeal based) to keep skin moisturized.
- Scaly areas can be treated with exfoliants (lactate or lactic acid) if skin is not irritated.
- In severe cases, topical steroids may be prescribed.
- Medicated shampoos (e.g., those containing zinc pyrithione) can be used to treat dry or itchy scalp.

PRURITUS MANAGEMENT
- Avoid tight clothing and exposure to heat and sun.
- Keep fingernails short to avoid scratching.
- Cool compress can be used to relieve symptoms.
- Topical steroid cream or topical anti-itch medications may be used to manage symptoms.
- For persistent itch, topical or oral antihistamines may be used.
- In severe cases, oral steroids (e.g. prednisone) may be prescribed.

PREVENTION OF PHOTOTOXICITY
- Advise strict photoprotection, including use of UV-protective clothing (long-sleeved garments, long pants or skirts, and wide-brimmed hats; consider UV-protective parasols).
- Encourage SPF 30+ UVA-specific or broad-spectrum (UVA/UVB) physical sunscreen (zinc oxide or titanium dioxide); reapply every 1.5–2 hours or sooner if skin becomes wet.
- Avoid staying near sunny windows; UVA rays can pass through glass.

SUNBURN MANAGEMENT
- Water-based emollients, analgesics (such as NSAIDs), and topical steroids can be used.
- Advise patients to increase intake of oral fluids; in cases of severe sunburn, IV hydration may be necessary.
- Advise patients to seek medical help if the sunburn is painful or results in skin sloughing, or if they experience dizziness, light-headedness, syncope, or near-syncope, or if they develop fever, chills, extreme thirst, or nausea.
- Dose interruptions may be necessary.

NSAID—nonsteroidal anti-inflammatory drug; UV—ultraviolet.
Note. Based on information from Bryce & Boers-Doets, 2014; Genentech, 2016, 2017; Turner et al., 2015.
as identification of unmet supportive care needs, providing for optimized patient outcomes and experiences.

Conclusion

Understanding the mechanism of action and toxicity profile of BRAFi and MEKi has clear implications for oncology nurses regarding communication of treatment options and prevention and management of AEs. Screening for BRAF mutations prior to treatment is critical when considering targeted therapy. The presence of a BRAF mutation within a patient tumor is predictive of response to targeted agents. However, in the absence of a BRAF mutation, the use of BRAFi is contraindicated because of the potential of these agents to enhance MAPK signaling in BRAF wild-type cells.

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