Title

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Journal

The Oncologist, 22(7)

ISSN

1083-7159

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Publication Date

2017-07-01

DOI

10.1634/theoncologist.2016-0456

Peer reviewed

The Oncologist®

Melanoma and Cutaneous Malignancies

Management of Treatment-Related Adverse Events with Agents Targeting the MAPK Pathway in Patients with Metastatic Melanoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Melanoma • BRAF • Mitogen-activated protein kinase signaling system • Protein kinase inhibitors • Drug-related side effects and adverse reactions

Abstract

Tremendous progress has been made in the clinical landscape of advanced-stage *BRAF* V600–mutant melanoma treatment over the past 5 years. Targeted therapies that inhibit specific steps of the mitogen-activated protein kinase pathway have been shown to provide significant overall treatment benefit in patients with this difficult-to-treat disease. Combination therapy with BRAF and MEK inhibitors (dabrafenib plus trametinib or vemurafenib plus cobimetinib, respectively) has become standard of care. These agents are administered until disease progression or unacceptable toxicity occurs; thus, some patients may remain on maintenance therapy for an extended period of time, while toxicities may result in early discontinuation in other patients. Because the goal of treatment is to prolong survival with minimal impairment of quality of life, drug-related adverse events (AEs) require prompt management to ensure that patients derive the best possible benefit from therapy. Proper management depends on an understanding of which AEs are most likely BRAF or MEK inhibitor associated, thus providing a rationale for dose modification of the appropriate drug. Additionally, the unique safety profile of the chosen regimen may influence patient selection and monitoring. This review discusses the toxicity profiles of these agents, with a focus on the most commonly reported and serious AEs. Here, we offer practical guidance derived from our clinical experience for the optimal management of key drug-related AEs. ***The Oncologist*** 2017;22:823–833

Implications for Practice: Targeted therapy with BRAF plus MEK inhibitors has become the standard of care for patients with advanced-stage *BRAF* V600–mutant metastatic melanoma. To provide optimal therapeutic benefit to patients, clinicians need a keen understanding of the toxicity profiles of these drugs. Prompt identification and an understanding of which adverse events are most likely BRAF or MEK inhibitor associated provide a rationale for appropriate therapy adjustments. Practical recommendations derived from clinical experience are provided for management of key drug-related toxicities.

Introduction

Approximately 50% of advanced melanomas harbor *BRAF* V600 mutations that result in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway [1, 2]. The development of targeted agents to block MAPK pathway activation, BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi), has resulted in significant clinical benefit in patients with *BRAF* V600–mutant melanomas [3–7]. Current U.S. Food and Drug Administration (FDA)–approved targeted therapies for the treatment of *BRAF* V600–mutant melanoma include two BRAFi, vemurafenib and dabrafenib, alone or in combination with MEKi cobimetinib and trametinib, respectively [8–11]. Initial approvals for single-agent targeted therapies were based on pivotal phase III trials that demonstrated improved clinical outcomes, including overall survival (OS), progression-free survival (PFS), and overall response rate (ORR) in patients with melanoma receiving BRAFi or MEKi versus chemotherapy (BREAK-3 [dabrafenib vs. dacarbazine] [12], BRIM-3 [vemurafenib vs. dacarbazine] [13], and METRIC [trametinib vs. dacarbazine or paclitaxel] [14]). BRAFi and MEKi combinations dabrafenib plus trametinib and vemurafenib plus cobimetinib were developed to overcome resistance to BRAFi monotherapy. Combination therapy has been approved for the treatment of *BRAF* V600–mutant melanoma

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This article was published online on 18 May 2017. Figure 1 was replaced. This notice is included in the online and print versions to indicate that it has been corrected on 26 June 2017.

based on phase II and III trials that showed improvements in OS, PFS, and/or ORR with the combinations compared with single-agent BRAFi, and pivotal trials to date include BRF113220 [15, 16], COMBI-d (dabrafenib plus trametinib vs. dabrafenib plus placebo) [4, 17, 18], COMBI-v (dabrafenib plus trametinib vs. vemurafenib) [5, 19], and coBRIM (vemurafenib plus cobimetinib vs. vemurafenib) [6, 20]. Results recently reported from COLUMBUS (encorafenib plus binimetinib vs. vemurafenib) [7] again showed ORR and PFS benefits from combination therapy over monotherapy, although the combination of encorafenib plus binimetinib is not yet approved by the FDA.

As these agents are typically administered until disease progression or unacceptable toxicity occurs [8–11], the goal of treatment is to prolong survival with minimal impairment of quality of life. Therefore, drug-related adverse events (AEs) require prompt management to ensure that patients derive optimal benefit from therapy. Some AEs are common with BRAFi and MEKi drug classes, while others appear to be specific to a particular agent. Additionally, with combination therapy, many AEs occur less frequently, while others appear to be exacerbated. Proper management of drug-related AEs depends on an understanding of which AEs are most likely BRAF or MEK inhibitor associated, thus providing a rationale for dose modification of the appropriate drug. Additionally, as the prevalence of some AEs differs depending on the single agent or combination being administered, the safety profiles of the regimen chosen may influence patient selection and monitoring.

This review provides an overview of the AEs associated with BRAFi and MEKi in melanoma, with a focus on the most commonly reported and serious AEs, and offers practical guidance from our clinical experience for the optimal management of key AEs.

Overview of BRAFi- and MEKi-Associated Adverse Events in Clinical Trials

The safety profile of BRAFi and/or MEKi in patients with *BRAF*-mutant melanoma has been well characterized. The most commonly reported AEs and those of special interest with single-agent and combination therapy in phase II and III clinical trials are provided in Table 1 and supplemental online Table 1, respectively. Most AEs reported with either BRAFi or MEKi [12–14] or combination therapy [5, 7, 16, 17, 20] were grade 1–2. The highest rates of AEs have appeared to occur early in treatment and decrease over time [21, 22]. In studies with single-agent BRAFi or MEKi treatment, AEs leading to dose reduction or interruption were reported in about a third (27%–38%) of patients, and 3%–9% of patients discontinued treatment permanently due to AEs [12–14]. With combination treatment, the incidences of dose reduction or interruption due to AEs were 11%–58% and 46%–67%, respectively, and the percentage of patients who discontinued due to AEs was 11%–14% [4, 6, 7, 16, 17, 19, 23].

Deaths due to AEs were rare ($\leq$2% of patients who received approved BRAFi plus MEKi therapy); brain hemorrhage was the most common cause of death due to AEs across combination registration trials [5, 16, 17, 20]. Upon further examination, these deaths were deemed not related to the study drugs [5, 16, 17]. However, we note that based on additional case study reports [24, 25] and our own clinical experience, the temporal relationship between initiation of BRAFi plus MEKi therapy and development of rare bleeding and clotting events (e.g., hemorrhages, venous thromboembolism) suggests that, at least in some cases, these AEs may be related to the targeted therapies.

Single-Agent BRAFi Treatment

Common AEs associated with dabrafenib and vemurafenib include skin toxicities, pyrexia, fatigue, headache, arthralgia, and gastrointestinal (GI) events. The incidences of the most common AEs have been shown to be similar with both BRAFi, with some key exceptions: Pyrexia has been more frequently observed with dabrafenib [12], while photosensitivity and worsening of liver function tests (LFTs) have been more frequently associated with vemurafenib [13, 26].

Dermatologic toxicities have been commonly associated with targeted therapy [27]. The most common skin toxicities associated with BRAFi have included rash, alopecia, dry skin, hyperkeratosis, papillomas, palmar-plantar erythrodysesthesia (PPE; hand-foot syndrome), cutaneous squamous cell carcinoma (cuSCC)/keratoacanthoma (KA), pruritus, and photosensitivity (Table 1 and supplemental online Table 1). Photosensitivity was more frequently associated with vemurafenib (all grades, 41%; grade 3–4, 4%) than dabrafenib (all grades, 3%; no grade 3–4 reported) [12, 26]. Other events associated with vemurafenib have included QT interval prolongation and worsening liver function test results. QT interval prolongation with vemurafenib is considered rare, and although liver function abnormalities are usually asymptomatic, liver injury leading to functional impairment has been reported [26].

Hyperproliferative skin disorders, cuSCC/KA, papillomas, and hyperkeratosis are believed to be due to the paradoxical activation of the MAPK pathway by BRAFi in *BRAF*–wild-type cells [28–32]. In addition to cuSCC, some reports have described patients experiencing other types of secondary premalignant and malignant events during BRAFi treatment, including new primary melanomas, *RAS*-mutant leukemia, and the metastatic recurrence of *RAS*-mutant colorectal cancer, also thought to be driven by paradoxical MAPK activation [33]. Preliminary data suggest that patients treated with BRAFi for long periods of time also have an increased risk of developing hyperplastic gastric polyps and colonic adenomatous polyps [33, 34]. Although the development of colonic polyps may potentially result in gastrointestinal bleeding and/or malignant transformation, additional studies are needed to definitively determine recommendations for or against routine endoscopic surveillance for BRAFi-treated patients.

Single-Agent MEKi Treatment

The MEKi trametinib was evaluated as monotherapy in patients with *BRAF*-mutant unresectable or metastatic melanoma in the METRIC study, an open-label, active-comparator trial [14]. Commonly occurring AEs in patients who received trametinib included rash, diarrhea, fatigue, peripheral edema, and acneiform dermatitis. Unlike with BRAFi, secondary skin neoplasms were not typically observed; however, acneiform dermatitis was much more frequently reported [14]. Cardiac AEs (decreased ejection fraction or left ventricular dysfunction [7%]), ocular AEs (blurred vision [4%], chorioretinopathy [$<$15%]), and pulmonary AEs (interstitial lung disease or pneumonitis [2%]) were also seen with trametinib in the METRIC trial, although they were considered infrequent [9, 14]. Retinal vein occlusion (RVO) was not observed in the

Table 1. Overview of the most common adverse events associated with BRAF and MEK inhibitors as monotherapy or in combination

	Monotherapy			Combination therapy				
Study	**BREAK-3 [12, 61, 62]**	**BRIM-3 [13, 26]**	**METRIC [9, 14]**	**BRF113220 (part C) [16]**	**COMBI-d [4, 17][a]**	**COMBI-v [19, 23]**	**coBRIM [6, 8, 11, 20]**	**COLUMBUS (part 1) [7]**
Agent(s)/study arm	Dabrafenib	Vemurafenib	Trametinib	Dabrafenib + trametinib	Dabrafenib + trametinib	Dabrafenib + trametinib	Vemurafenib + cobimetinib	Encorafenib + binimetinib
Patients (*n*)	187	337	211	55[b]	209	350	254	192
Any AE (%)	—	99	—	100	87	99	96	98
Grade 3–4 AEs (%)	—	71	—	58	32[c]	48[d]	63	58
Most common AEs (≥20% incidence), any grade/grade 3–4) (%)								
Pyrexia	33/4	21/<1	—	71/5	52/7	53/4	26/2	18/4
Chills	12/0	7/0	—	58/2	28/0	31/<1	—	—
Fatigue	26/2	46/3	26/4	53/4	27/2	29/1	32/4	29/2
Nausea	29/<1	38/2	18/1	44/2	20/0	35/<1	39/1	41/2
Vomiting	22/2	21/2	13/1	40/2	14/<1	29/1	21/1	30/2
Diarrhea	17/1	36/1	43/0	36/2	18/<1	32/1	57/6	36/3
Arthralgia	39/2	56/6	—	27/0	16/<1	24/<1	33/2	26/1
Headache	36/0	33/1	—	29/0	19/0	29/<1	—	22/2
Rash	19/0	41/9	57/8	27/0	24/0	22/1	39/6	14/1
Cough	18/0	13/0	—	29/0	—	20/0	—	—
Peripheral edema	—	20/<1	26/1	29/0	11/1	12/<1	—	—
Decreased appetite	13/0	22/<1	—	22/0	—	12/<1	—	—
Pruritus	—	25/1	10/2	—	7/0	9/0	—	—
Acneiform dermatitis	—	5/0	19/<1	16/0	8/0	6/0	—	3/0
Alopecia	29/<1	48/0	17/<1	5/0	5/0	6/0	14/<1	14/0
Constipation	14/2	14/<1	14/0	22/0	—	13/0	—	—
Asthenia	20/<1	14/<1	—	—	—	16/1	—	—
Myalgia	17/0	15/1	—	22/2	—	17/0	—	14/0
Photosensitivity reaction	3/0	41/4	—	—	—	4/0	28/2	5/1
cuSCC/KA	12/9	30/29	0	7/5	3/3	1/1	4/3	—
Dry skin	13/0	23/0	11/0	—	9/0	8/0	—	14/0
Hyperkeratosis	41/2[e]	29/1	—	9/0	6/0	4/0	10/0	14/1
Hand-foot syndrome/PPE[f]	20/2	9/<1	—	—	6/<1	4/0	—	7/0
Skin papilloma	26/0	28/<1	—	4/0	1/0	2/0	—	6/0

(continued)

Table 1. (continued)

Study	Monotherapy			Combination therapy				
	BREAK-3 [12, 61, 62]	BRIM-3 [13, 26]	METRIC [9, 14]	BRF113220 (part C) [16]	COMBI-d [4, 17][a]	COMBI-v [19, 23]	coBRIM [6, 8, 11, 20]	COLUMBUS (part 1) [7]
Hypertension	—	3/1	15/12	9/2	—	26/14	—	11/6
Increased ALT	—	8/2	—	—	10/2	14/3	24/11	—
Increased AST	—	7/<1	—	—	11/3	11/1	22/8	—
Increased creatine kinase	—	7/<1	—	—	—	—	30/10	23/7

[a]Data quoted are for treatment-related AEs rather than all AEs.
[b]Data for dosage arm of dabrafenib 150 mg twice daily plus trametinib 2 mg once daily; this is the approved dosage.
[c]Data are for grade 3 events; one grade 4 event occurred in the dabrafenib and trametinib group (pancytopenia), and three occurred in the dabrafenib and placebo group (thrombocytopenia, febrile neutropenia, hypokalemia).
[d]Data are for grade 3 events; three grade 4 events occurred in three patients in the dabrafenib and trametinib combination arm (headache, asthenia, increased AST), and five occurred in five patients in the vemurafenib arm (hypertension, constipation, increased ALT, cuSCC).
[e]Hyperkeratosis included acanthoma, acrochordon, actinic keratosis, keratosis pilaris, lichenoid keratosis, papilloma, seborrheic keratosis, and skin papilloma.
[f]Hand-foot syndrome includes the terms "palmar-plantar erythrodysesthesia," "plantar-palmar hyperkeratosis," and "palmoplantar keratoderma."
Abbreviations: —, data not reported; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CuSCC, cutaneous squamous cell carcinoma; KA, keratoacanthoma; PPE, palmar-plantar erythrodysesthesia.

METRIC trial but has been reported as a rare event (0.2%) across all trametinib studies [9].

Cobimetinib has not been evaluated as a single agent in patients with advanced melanoma and is approved only in combination with vemurafenib; thus, there are limited AE data available on its use as a single agent [11]. Similarly, binimetinib has been evaluated in patients with *BRAF*-mutant melanoma only in combination with encorafenib [7].

Ocular AEs, particularly retinal changes, are considered a class effect of MEKi [35–39]. Visual disturbances, including blurred vision, serous retinal detachment, RVO, and chorioretinopathy have been regularly reported with MEKi [35–39], although RVO is more commonly reported with cobimetinib. In some cases, RVO, uveitis, and/or iritis have been reported with MEKi as a single agent or in combination with BRAFi [40, 41].

Combination BRAFi and MEKi Treatment

Dabrafenib Plus Trametinib

Combination treatment with dabrafenib and trametinib was evaluated in an open-label, phase I/II dose-escalation study, BRF113220 [14], and in two randomized, controlled, phase III studies, COMBI-d (dabrafenib plus trametinib vs. dabrafenib) [17] and COMBI-v (dabrafenib plus trametinib vs. vemurafenib) [5]. BRF113220 was a four-part study. In part C, patients were randomized 1:1:1 to combination dabrafenib (150 mg twice daily [BID]) plus trametinib (1 mg or 2 mg once daily [QD]) or dabrafenib monotherapy. An overview of AEs in the full combination dose (dabrafenib 150 mg plus trametinib 2 mg) treatment arms in these studies is provided in Table 1 and supplemental online Table 1.

Compared with patients who received single-agent dabrafenib, patients treated with combination dabrafenib plus trametinib experienced similar classes of AEs [5, 12, 16, 17]. The most common AEs were pyrexia, chills, fatigue, headache, nausea, diarrhea, arthralgia, rash, and hypertension. Known MEKi-associated AEs reported at a higher frequency with dabrafenib plus trametinib versus dabrafenib included peripheral edema (11%–29% vs. 2%), decreased cardiac ejection fraction (4%–9% vs. 3%), and acneiform dermatitis (6%–16% vs. 3%). Conversely, known BRAFi-induced hyperproliferative skin lesions were reported less frequently (cuSCC/KA [1%–7% vs. 9%–12%], papilloma [1%–4% vs. 18%–26%], and hyperkeratosis [4%–9% vs. 33%–41%]), as were pruritus (7%–9% vs. 11%), PPE (4%–6% vs. 20%–27%), and dry skin (8%–9% vs. 13%–14%) [5, 12, 16, 17].

The frequency and severity of pyrexia and chills were notably increased with combination dabrafenib plus trametinib versus dabrafenib monotherapy (pyrexia, 52%–71% vs. 25%–33%; chills, 28%–58% vs. 12%–14%). Pyrexia was the most common AE leading to treatment modification, including dose interruption (30%–32%) and dose reduction (13%–14%) as well as permanent discontinuation (2%–3%) [5, 17]. The median time to onset of the first episode was 4.3 weeks, and the median duration was 3 days [17]. Approximately half of patients who experienced pyrexia had at least three episodes [17]. Pyrexia was resolved in 97% of the patients who had a dose reduction or interruption during an acute pyrexia episode [17].

Vemurafenib Plus Cobimetinib

Combination treatment with vemurafenib plus cobimetinib was evaluated in an open-label, phase Ib dose-escalation study,

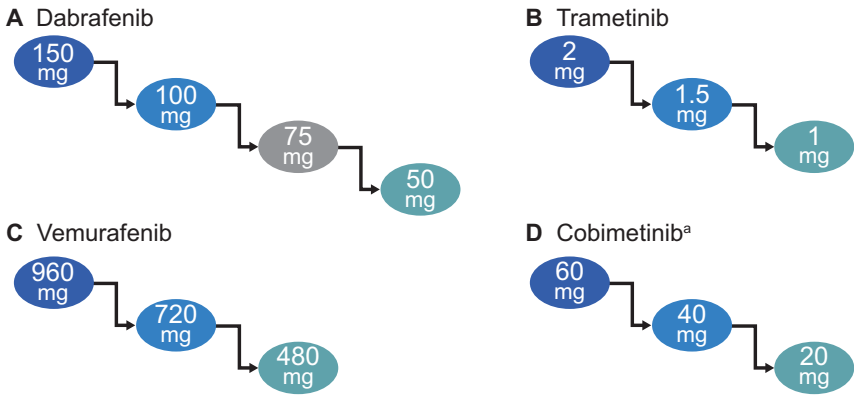

Figure 1. Recommended dose adjustments and modifications for dabrafenib **(A)**, trametinib **(B)**, vemurafenib **(C)**, and cobimetinib **(D)**. Treatment initiation doses for the combinations (dabrafenib plus trametinib and vemurafenib plus cobimetinib) are the same as the recommended monotherapy doses; if dose reductions for the combination are needed, then the dose of the drug that is most likely causing the adverse event should be reduced. Each drug should be discontinued if a reduction below the lowest dose level shown is needed.

[a]Cobimetinib is approved for use in combination with vemurafenib, not as a single agent, and administered the first 21 days of each 28-day cycle.

BRIM7 [42], and in a randomized, controlled, phase III study, coBRIM [20]. Due to differences in study groups, dosing, and trial designs, an overview of AEs only in the coBRIM study is provided (Table 1 and supplemental online Table 1).

The coBRIM study randomized previously untreated patients to combination vemurafenib plus cobimetinib or vemurafenib monotherapy [20]. Compared with single-agent vemurafenib, patients treated with vemurafenib plus cobimetinib experienced similar classes of AEs. The most common AEs were GI events (diarrhea, nausea, and vomiting), rash, fatigue, pyrexia, arthralgia, photosensitivity, and worsening LFTs (Table 1 and supplemental online Table 1). Of these, higher frequencies of GI events, photosensitivity, and LFTs were observed with combination therapy than with monotherapy. In addition, AEs believed to be MEKi-specific, elevated creatine kinase and ocular conditions (chorioretinopathy and retinal detachment), were observed at higher frequencies with combination therapy. Consistent with preliminary findings for the combination in the BRIM7 study [42], BRAFi-induced hyperproliferative skin lesions occurred less frequently with combination vemurafenib plus cobimetinib compared with vemurafenib alone (hyperkeratosis, 10% vs. 28%; cuSCC, 3% vs. 11%; keratoacanthoma, 1% vs. 8%).

Encorafenib Plus Binimetinib

In the ongoing phase III, two-part, open-label COLUMBUS study, the combination of encorafenib plus binimetinib versus vemurafenib monotherapy is being evaluated in treatment-naive patients with unresectable or metastatic *BRAF* V600–mutant melanoma [7]. This combination is promising, although it is not currently approved by the FDA for the treatment of advanced *BRAF*-mutant melanoma. Similar to what has been reported for other BRAFi and MEKi combinations, in preliminary results from part 1 of the study, the most common AEs with encorafenib plus binimetinib included GI events (nausea, diarrhea, and vomiting), fatigue, increased blood creatine phosphokinase, and headache (Table 1 and supplemental online Table 1). Again, the tolerability profile of the combination in terms of BRAFi-induced hyperproliferative skin events was more favorable for the combination than for encorafenib or vemurafenib alone (hyperkeratosis, 14% vs. 38% vs. 29%; palmoplantar keratoderma, 9% vs. 26% vs. 16%; PPE, 7% vs. 51% vs. 14%; secondary nonmelanoma skin neoplasms, 4% vs. 9% vs. 18%) [7].

Current Management Strategies for BRAFi- and MEKi-Associated Adverse Events

The recommended dosage regimens for currently approved BRAFi and MEKi are dabrafenib 150 mg orally BID plus trametinib 2 mg orally QD, and vemurafenib 960 mg orally BID plus cobimetinib 60 mg orally QD for the first 21 days of each 28-day cycle [8–11]. In the phase III clinical trials, the majority of intolerable AEs were managed with dose reductions and/or interruptions [5, 17, 20]. General dose-modification guidelines are shown in Figure 1. If a dose modification is needed, the dose of the drug that is most likely causing the AE should be reduced.

Pyrexia and Related Adverse Events

The underlying mechanism of pyrexia observed with targeted therapies for melanoma is unknown. These events are not associated with sepsis, nor do they appear to correlate with any predictive baseline characteristics or be predictive of clinical outcome or response to treatment [43]. Routine infectious workup is not recommended for patients with uncomplicated pyrexia without localizing symptoms [43, 44].

A trend has been observed for a correlation of pyrexia with exposure to dabrafenib. However, because dabrafenib is administered daily, the pyrexia is not likely to be directly related to exposure. Pyrexia often occurs during the first month of treatment, with the first episode lasting a median of 9 days and subsequent episodes lasting 4–5 days.

Although pyrexia is commonly associated with both BRAFi, the extent and severity of pyrexia appears to be unique to combination dabrafenib plus trametinib [17, 20]. Pyrexia is usually

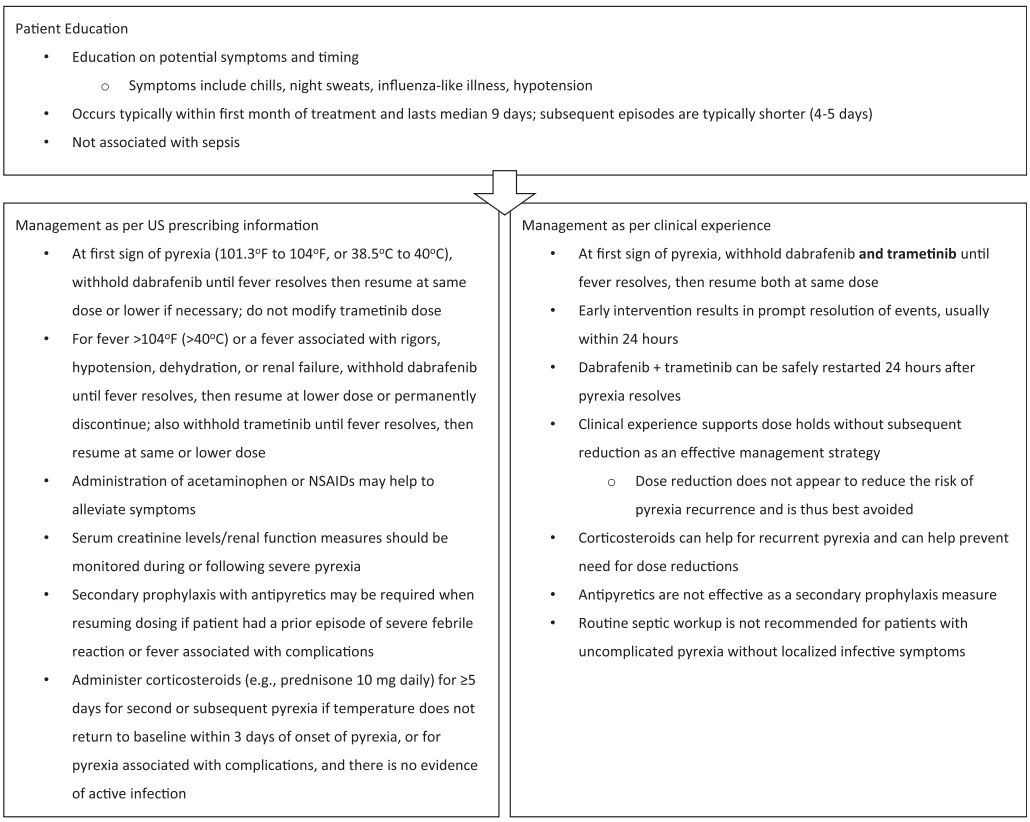

Figure 2. Management of pyrexia [8, 9, 43, 44].
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

episodic. A trend has been observed for a correlation of pyrexia with exposure to dabrafenib. However, because dabrafenib is administered daily, the pyrexia is not likely to be directly related to exposure [44]. Pyrexia often occurs during the first month of treatment, with the first episode lasting a median of 9 days and subsequent episodes lasting 4–5 days [44]. Symptoms often associated with pyrexia include chills, night sweats, rash, dehydration, electrolyte abnormalities, and hypotension [45]. Approximately 25% of patients experience associated symptoms without an elevated core body temperature [44].

Clinical experience shows that pyrexia prophylaxis and management strategies require prompt interruption of both dabrafenib and trametinib at the first episode or associated symptom(s) (Fig. 2). Usually this results in rapid resolution of events within 24 hours, at which time both drugs can be safely restarted [8, 9, 43, 44].

Treatment guidelines and prescribing information recommend dose reduction/intermittent dosing and use of corticosteroids for recurrent or severe pyrexia, and acetaminophen or nonsteroidal anti-inflammatory drugs to alleviate symptoms (Fig. 2) [45]; however, some of these recommended strategies are not always appropriate for what is observed in the clinic [43, 44]. Our clinical experience suggests that dose reduction, particularly recommended in complicated cases, may not lower the risk of pyrexia recurrence; therefore, dose interruption may be the most effective management strategy. Additionally, according to our clinical experience, use of antipyretics under certain conditions (e.g., in patients with prior pyrexia with complications) may not be an effective prophylactic measure.

Considering current treatment guidelines and prescribing information for targeted melanoma therapies, as well as our clinical experience with these drugs, we recommend that, for the initial management of pyrexia, therapy be withheld and then restarted at the same dose. If pyrexia is a recurrent event, we have found that scheduled antipyretics (e.g., ibuprofen, acetaminophen) are helpful, and we recommend continuing their administration upon reinitiating the targeted therapy. If a patient's body temperature does not return to baseline within 3 days after implementing these strategies, we consider starting the patient on a limited burst of corticosteroids (e.g., prednisone 10 mg daily for 5 days). Although restarting the targeted therapy at full dose is always preferable, for these refractory cases, we have found that restarting at a lower dose and then attempting reescalation to the full dose upon resolution of symptoms is helpful for pyrexia control. Additionally, in our clinical experience, of the limited number of patients we have treated who discontinued dabrafenib plus trametinib due to intractable pyrexia and then initiated vemurafenib plus cobimetinib, we have observed improved tolerability of vemurafenib plus cobimetinib in terms of this AE. Finally, we typically consider permanent discontinuation of the drug when a patient experiences fever events associated with refractory rigors, renal failure, or other serious AEs that occur despite the management strategies described above.

Cutaneous Skin Reactions

Dermatologic AEs are considered a class effect of BRAFi and MEKi, although the type, extent, and etiology of the particular AE may differ for the particular agents [27, 28]. General types of cutaneous toxicities commonly reported include rashes and

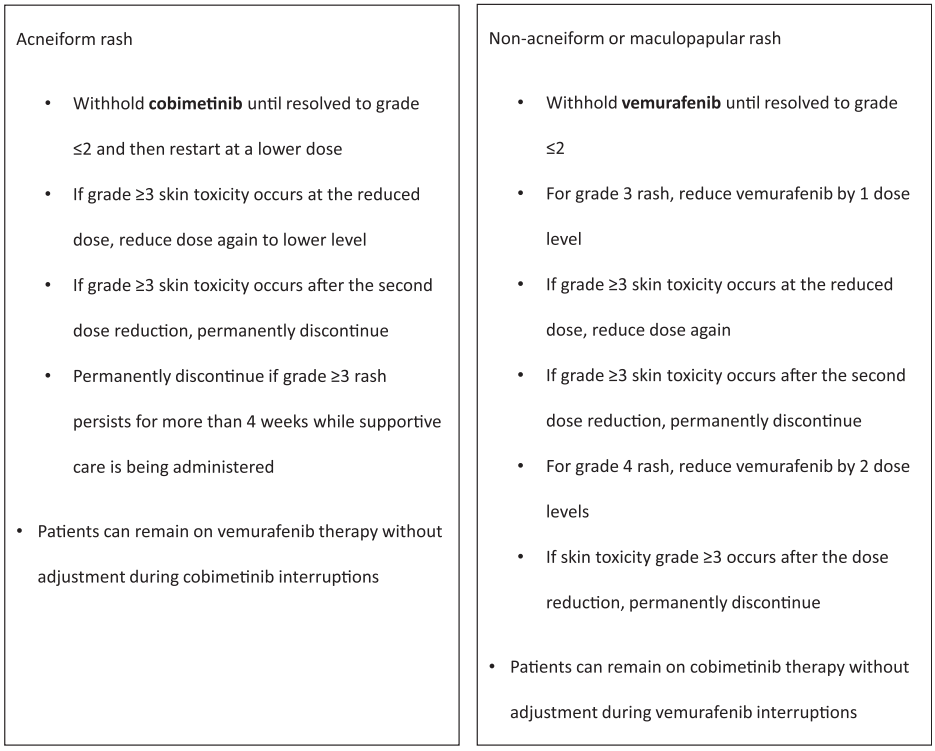

Figure 3. Rash management strategies for cobimetinib plus vemurafenib from coBRIM [10, 11, 20].

other skin irritations, acneiform dermatitis, hyperproliferative skin disorders, and photosensitivity (Table 1).

These AEs can be particularly distressing for patients. For example, patients with noticeable skin toxicities, particularly on exposed areas such as the face, may feel stigmatized. Additionally, severe dermatologic AEs may lead to impairments in patients' daily lives, particularly for those with hand and/or foot lesions. Therefore, proper proactive management of these cutaneous AEs is critical to avoid drug delays, interruptions, or discontinuations, and to limit their impact on quality of life [27, 28, 46].

Guidelines for prophylaxis and management of cutaneous AEs have been published previously [31, 47]. Treatment is aimed mostly at alleviating the symptoms, including the use of emollients, antihistamines, and analgesics; a short course of steroids may also be appropriate. The prescribing information for each agent provides management strategies for rash events (acneiform or non-acneiform/maculopapular; Fig. 3) [8–11].

For intolerable grade 2 or grade 3–4 cutaneous AEs, dabrafenib and trametinib alone or in combination should be withheld for $\leq$3 weeks. If the AE improves, the drug(s) can be resumed at a lower dose; if the AE does not improve, the drug(s) should be permanently discontinued [8, 9]. The management strategy for cobimetinib in the event of intolerable grade 2 or grade 3–4 cutaneous AEs is to withhold or reduce the dose (Fig. 3) [10, 11].

Hyperproliferative Events and Cutaneous Malignancies

As previously stated, the etiology of hyperproliferative skin disorders and cutaneous malignancies is due to the paradoxical activation of the MAPK pathway by BRAFi in *BRAF*–wild-type cells [28–32]. The incidence of these events is decreased with combination BRAFi plus MEKi therapy [4–7].

Dermatologic evaluations should be performed by a dermatologist or provider experienced in the diagnosis and management of cutaneous toxicities of targeted therapy [45]. It is recommended for both targeted therapy combinations that patients be evaluated prior to treatment initiation, every 2 months during therapy, and for $\leq$6 months following discontinuation of therapy [8–11]. However, we note that for patients who do not demonstrate active cutaneous toxicities upon initiation of targeted therapy, a provider may consider performing dermatologic surveillance evaluations at more prolonged intervals (e.g., every 3 months) or as needed based on the provider's discretion. Any suspicious skin lesions should be surgically excised and dermatopathologically evaluated. No dose modifications are required for any new primary cutaneous malignancies [8–11].

Photosensitivity

Photosensitivity reactions are primarily associated with vemurafenib treatment. This UV-A–dependent toxicity is likely due to the chemical structure of vemurafenib [48, 49]. Serious photosensitivity reactions have been observed in approximately 30% of patients treated with vemurafenib. Patients may experience severe sunburns with blistering. Even with patient education on preventing phototoxicity, a high incidence of such reactions has been reported (NCT02052193, clinicaltrials.gov) [50].

Patient education on protecting skin from UV-A exposure can be effective in preventing these events [10, 49], and communication with patients prior to treatment initiation is especially important. The use of broad-spectrum sunscreens, lip balm, and UV-dense clothing are effective in the prevention of UV-A–induced photosensitivity. Patients should also be informed that UV-A intensity is relatively constant regardless of

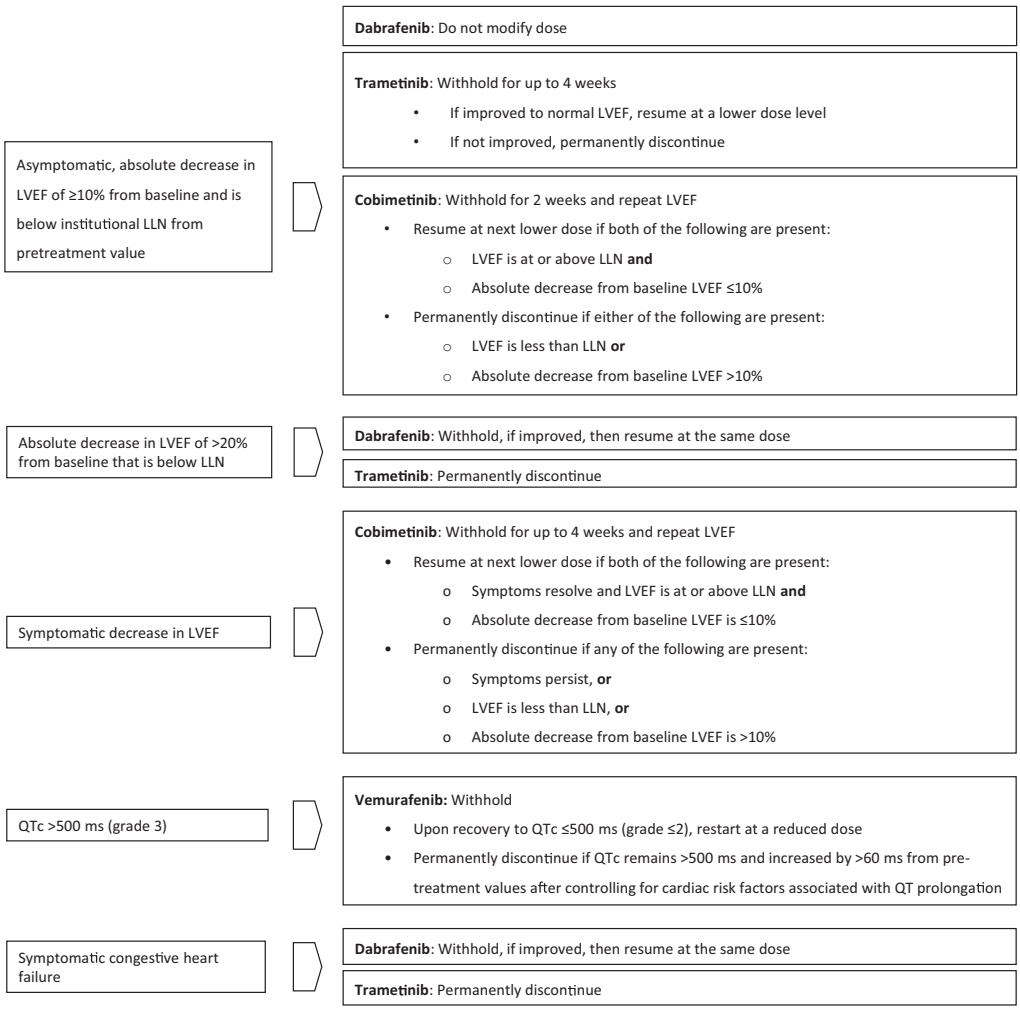

Figure 4. Recommendations for managing cardiac adverse events in the US prescribing information [8–11].
Abbreviations: LLN, lower limit of normal; LVEF, left ventricular ejection fraction; QTc, corrected QT interval.

daylight hours and season and that UV-A can also penetrate glass [45, 49].

For intolerable grade 2 or grade 3–4 phototoxicity, treatment with vemurafenib plus cobimetinib should be withheld; if the AE improves to grade 0 or 1, treatment can be resumed at the next lower dose. If no improvement occurs, treatment should be permanently discontinued [10, 11].

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Vemurafenib can also cause severe dermatologic reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) [10]. Symptoms include generalized erythema with peeling or blister formation and mucosal involvement [47]. If SJS or TEN is suspected, treatment should be permanently discontinued [10].

Ocular Toxicities

Preclinical studies suggest that MAPK pathway inhibition can lead to an inflammatory response and breakdown of the blood-retinal barrier, potentially enhancing susceptibility to ocular toxicities. While ocular events are frequently described as class effect of MEKi with or without BRAFi, the etiology of these events has yet to be fully understood [35–41, 51, 52].

Guidance on the frequency of surveillance for ocular events during treatment with BRAFi and MEKi differs slightly between targeted therapy regimens per current prescribing information, from evaluation at regular intervals (vemurafenib plus cobimetinib) [10, 11] to evaluation only in response to patient reports of visual disturbances (dabrafenib plus trametinib) [8, 9]. Based on our clinical experience, we generally recommend that patients be proactively monitored for signs and symptoms of ocular toxicities, with ophthalmologic evaluations conducted periodically, where possible. Regular ophthalmologic exams are useful in asymptomatic patients being treated with MEKi regimens to ensure that any potential ocular toxicities (e.g., retinal detachments) are managed at the earliest stage of development. If a patient reports visual disturbances, an ophthalmologic evaluation must be performed, as RVO can lead to macular edema, decreased visual function, neovascularization, and glaucoma [8–11]. Fortunately, serious ocular AEs associated with MEKi, alone or in combination with BRAFi, appear to be mostly transient and self-limiting or reversible with dose reduction, interruption, or discontinuation [35, 37–41, 52].

It is generally recommended that the MEKi be permanently discontinued in patients experiencing RVO. If grade 2–3 retinal pigment epithelial detachment is observed in patients being treated with trametinib, it is advised that treatment be

withheld for ≤3 weeks and then resumed at the same or lower dose on improvement [9]. When either RVO or grade 2–3 retinal pigment epithelial detachment events occur with dabrafenib plus trametinib combination therapy, dabrafenib dose modification is not needed. For patients who experience serous retinopathy during treatment with vemurafenib plus cobimetinib, cobimetinib can be withheld for ≤4 weeks and resumed at a lower dose on improvement. For trametinib- or cobimetinib-related retinal events that show no improvement, and/or if symptoms recur at a lower dose, the MEKi should be permanently discontinued [9, 11].

It is generally recommended that the MEKi be permanently discontinued in patients experiencing RVO. If grade 2–3 retinal pigment epithelial detachment is observed in patients being treated with trametinib, it is advised that treatment be withheld for ≤3 weeks and then resumed at the same or lower dose on improvement.

Patients should also be monitored for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, and eye pain) [8–11]. Uveitis can be managed with steroid and mydriatic ophthalmic drops [8, 10]. For patients on dabrafenib-based regimens who experience severe uveitis or mild to moderate uveitis that does not respond to therapy, dabrafenib should be withheld for ≤6 weeks. If the uveitis improves to grade 0–1, dabrafenib can be resumed at the same dose; otherwise, it should be permanently discontinued [8].

Cardiovascular Toxicities

Cardiomyopathy

The mechanism of MAPKi-mediated cardiotoxicities (heart failure, left ventricular dysfunction) is not well characterized, but preclinical data suggest that the MAPK pathway has a role in cardiac hypertrophy and cell survival [53]. It has been understood since the early development of this drug class that cardiomyopathy is associated with MEKi, either alone or in combination with BRAFi [31, 54, 55].

Decreased left ventricular ejection fraction (LVEF) has been observed at rates of 4%–9% in randomized clinical trials evaluating MEKi or combined MEKi and BRAFi in melanoma [5, 14, 16, 17, 20]. Peripheral edema, a symptom suggestive of heart failure, has also been frequently observed with both trametinib and vemurafenib monotherapy [14, 26]. In addition, hypertension was frequently reported with trametinib monotherapy in the METRIC study and with both dabrafenib plus trametinib and vemurafenib monotherapy in the COMBI-v study, with grade 3–4 hypertension occurring in 9%–14% of patients [5, 14]. Cardiac function did not recover fully in 17%–38% of patients treated with MEKi with or without BRAFi following treatment discontinuation [8, 9, 11].

Patients should have their LVEF assessed by echocardiogram or multigated acquisition scan prior to initiation of targeted therapy, after 1 month, and at 2- to 3-month intervals while on treatment [8–11]. Decrease in LVEF is managed by treatment interruption, reduction, or discontinuation. Additional monitoring is required in patients who restart therapy following dose reduction or interruption for decreased LVEF [11]. Additional guidelines for management of BRAFi- and/or MEKi-related cardiac AEs are provided in Figure 4.

QT Prolongation

In rare cases, exposure-dependent corrected QT interval (QTc) prolongation is observed with vemurafenib therapy; MEKi monotherapy, however, does not appear to be associated with increased risk of this cardiac toxicity [31]. In patients with uncorrectable electrolyte abnormalities, QTc >500 ms, or long QT syndrome, or in patients being treated with other medications known to prolong the QT interval, treatment with vemurafenib or dabrafenib is not recommended. Echocardiogram should be performed and electrolytes should be evaluated at treatment initiation and if dose modifications are needed for QTc prolongation after 15 days and then at regular monthly intervals for 3 months, followed by every 3 months thereafter or more as needed. Vemurafenib should be permanently discontinued in patients with QTc prolongation >500 ms and an increase of >60 ms from pretreatment values [10].

GI-Related Events

GI-related AEs reported in trials for BRAFi and MEKi include diarrhea, nausea, vomiting, constipation, abdominal pain, and stomatitis [5, 7, 9, 17, 20]. The majority of these events have been considered mild to moderate in severity and are common to many other cancer treatments. Management is well characterized based on clinician experience with other cytotoxic therapies. Incidences of diarrhea are treated symptomatically; strategies include loperamide treatment as well as dose interruption and resumption at a lower level [31].

Other Clinically Relevant Adverse Events

Other clinically relevant AEs associated with BRAFi and/or MEKi, such as hemorrhage, venous thromboembolism, pulmonary-related AEs (interstitial lung disease or pneumonitis), hepatotoxicity, rhabdomyolysis/creatine phosphokinase elevation, hyperglycemia, and glucose-6-phosphate dehydrogenase deficiency, are generally managed with specific dose-modification strategies provided in the prescribing information for each drug [8–11].

Conclusion

Since the approval of dabrafenib plus trametinib and vemurafenib plus cobimetinib, these agents have entered routine clinical use for patients with advanced *BRAF* V600-mutant melanoma. Consequently, medical oncologists should not only understand the AEs associated with these molecularly targeted agents but also become skilled in their detection, diagnosis, and management. Optimizing dosing regimens to achieve the best clinical response while preserving quality of life continues to be a subject of active clinical investigation. Small clinical studies have shown that approximately half of patients with *BRAF*-mutant melanoma who cease BRAFi alone or in combination with MEKi after achieving a complete response on therapy ultimately relapse [56, 57], suggesting that permanent discontinuation of targeted therapy due to AEs in patients responding to treatment should be avoided where possible. However, preclinical data have shown that intermittent rather than continuous BRAFi therapy may delay the development of acquired resistance [58] and that melanoma clones already resistant to BRAFi

and MEKi seem to display increased drug addiction compared with those resistant only to BRAFi [59]. Studies investigating sequential and intermittent dosing of BRAFi and MEKi are thus ongoing (NCT02224781, NCT02196181).

Molecularly targeted therapies remain relevant despite the development of immune checkpoint inhibitors. Given the high ORRs seen with combined BRAF and MEK inhibition (but at the risk of development of acquired resistance) and the relatively lower response rate but longer-term treatment-free survival seen in some patients treated with immune checkpoint inhibition, there has been increasing interest in combining molecularly targeted therapy with immunotherapy. Prospective clinical trials are ongoing to determine whether these combinatorial strategies will synergistically optimize response rate and long-term disease control in patients with *BRAF* V600–mutant melanoma (NCT01656642, NCT02130466, NCT02027961) [60].

Updated clinical trial data regarding novel combinations and dosing/sequencing regimens involving molecularly targeted therapy are awaited. Novel BRAFi and MEKi agents, regimens, and combinations with other targeted agents or with immunotherapy could lead to more effective approaches in the treatment of advanced *BRAF* V600–mutant melanoma, as well as new challenges in the management of the resulting AEs.

Acknowledgments

The authors acknowledge ArticulateScience LLC, Atlanta, Georgia, for editorial support, funded by Novartis Pharmaceuticals Corporation, and would like to thank Heather Edens, Ph.D., Amanda L. Kauffman, Ph.D., and Michael Demars, Ph.D., for medical writing assistance. Neither Novartis Pharmaceuticals Corporation nor ArticulateScience LLC influenced the content of this manuscript, nor did the authors receive financial compensation for authorship.

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Disclosures

Adil Daud: Merck, Bristol-Myers Squibb, Genentech/Roche, Pfizer, OncoSec (C/A). The other author indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

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