Successful dabrafenib transition after vemurafenib-induced toxic epidermal necrolysis in a patient with metastatic melanoma

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INTRODUCTION

Vemurafenib improves survival in advanced metastatic melanoma, but has rarely been associated with severe skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Darabafenib is a BRAF inhibitor that shares a sulfonamide moiety with vemurafenib, and only one prior report documents a switch to dabrafenib after the development of SJS/TEN with vemurafenib. We report a case of vemurafenib-induced TEN followed by successful transition to full-dose therapy with dabrafenib in a patient with metastatic melanoma.

CASE REPORT

A 47-year-old white woman with no known allergies being treated for metastatic melanoma with cobimetinib, 200 mg daily, plus vemurafenib, 960 mg (coBRIM) twice daily for 13 days, was admitted to the hospital with a worsening rash and multiorgan system failure. Erythematosus, tender patches began on the trunk and progressed to the extremities with significant crusting and erosions on the lips and vulva. A dermatology consult confirmed TEN clinically and histologically. After discontinuing all medications, the diagnosis of vemurafenib-induced TEN was established. Despite immediate drug withdrawal, she continued to slowly progress with large bullae and edema in the lower extremities. Her fluid balance remained neutral and creatinine stable. Bullae were drained, and petrolatum gauze was applied to denuded skin. On day 5, her lower extremity wounds started to emit an odor, and cultures confirmed Pseudomonas. The infectious disease department recommended empiric antibiotics and she received dilute bleach water baths daily. Her wounds and odor improved over the next 24 hours, and she remained afebrile with a normal white count. She was discharged after 2 weeks without complications.
Before coBRIM therapy, the patient was diagnosed with brain metastasis with a left, lower eyelid primary tumor. Her initial treatment consisted of surgical resection, radiation, and ipilimumab, which was later switched to nivolumab because of disease progression. Despite 6 months of therapy, her disease progressed, which led to coBRIM therapy and subsequent TEN. After resolution of TEN, positron emission tomography/computed tomography scan found improvement of axillary lymph nodes and mesenteric mass. The improvement was likely caused by drug response, but the dramatic improvement led to speculation about a possible antitumor response generated by the TEN. Because of this improvement, the patient elected for active surveillance over clinical trials.

Two months later, the patient exhibited increased lymph node involvement indicating progressive disease. Because of the patient’s wish to avoid surgery and the lengthy washout period after prior immunotherapy required by available investigational combination therapy studies, she was started on ipilimumab. Considering the patient’s response to previous BRAF inhibitor therapy and continued advancement of disease, it was mutually decided that the greater benefits of therapy outweighed the potential risk of TEN.

Allergists were consulted and recommended against lymphocyte transformation test (LTT) given the low sensitivity. Additionally, a positive LTT may not have precluded treatment, as the patient expressed a desire to attempt gradual dose escalation even with understanding that BRAF inhibitor therapy might result in potentially fatal TEN.

Given the limited options, we proceeded with gradual dose escalation of dabrafenib and close monitoring in combination with trametinib and corticosteroids to prevent recurrent TEN (Table I). Within a week, she had dramatic response of her right axillary lymphadenopathy and greatly decreased discomfort.

The patient’s disease remained stable, and she had minimal side effects on therapy; however, her right axillary disease once again started to progress after 2 months of treatment. Although the development of resistant disease might have been spontaneous, gradual dose escalation may have contributed to the development of a resistant clone.

DISCUSSION

Vemurafenib targets the oncogenic mutation $BRAF^{V600E}$, which drives the MAPK/ERK signaling pathway stimulating cellular proliferation, differentiation, and survival.1 $BRAF$ mutations are found in 40% to 60% of melanomas, although vemurafenib is associated with improved survival in melanoma irrespective of mutation.1

The patient’s medications at the time included omeprazole and Zyrtec daily, which she had been taking for years, in addition to Zofran and acetaminophen or ibuprofen when needed. Given the patient’s previous exposure to all of these medications, no new medications having been administered besides coBRIM therapy, the reaction soon after coBRIM therapy, and the documented history of SJS/TEN with sulfonamide drugs, we suspected vemurafenib-induced TEN. Additionally, SJS/TEN-type toxicity is seen in BRAF inhibitor monotherapy, but this reaction is decreased when MEK inhibitors, such as cobimetinib in coBRIM, are used in combination therapy.5

Grade I-II dermatologic side effects are commonly seen with BRAF inhibitor use, but severe reactions to therapy such as SJS/TEN are more rarely described.6 Overcoming vemurafenib-induced SJS/TEN has been reported twice before; desensitization and treatment with a lower dose of vemurafenib and switching to an alternate BRAF inhibitor have been documented.3,7 Our dose escalation after switching to dabrafenib differs from the previous reported switch, as we administered prednisone concurrently.3

LTT has been used since the 1970s for identifying particular drugs in drug hypersensitivity reactions and is currently accepted as the best diagnostic assay for severe cutaneous drug reactions.9 The test is performed by isolating a patient’s peripheral mononuclear cells and plating them with buffer and AB-serum or autologous plasma; the pure form of a drug is added to the cell culture, and subsequent cell proliferation is measured on a dose-response curve by methods such as radio-labeled thymidine uptake and flow cytometry.9 Unfortunately, although LTT has a high specificity (98%-99%), it has a considerably low sensitivity of 20% to 48% depending on the drug assayed, with sulfonamide drugs on the lowest end of the spectrum.8 Tang et al10 described markedly decreased sensitivity of LTT after the first week of recovery; however, Kano et al11 found a low sensitivity regardless of when LTT is performed. Thus, LTT was not deemed beneficial in this patient’s case before dabrafenib therapy.

Interestingly, LTT assay exhibits cross-reactivity between vemurafenib, dabrafenib, and sulfamethoxazole, yet no cases of dabrafenib-induced TEN have been reported to date.2,12 Structurally, dabrafenib shares the same sulfonamide functional group as vemurafenib and other sulfonamides predisposing to TEN. Unlike vemurafenib, however, dabrafenib may possess a unique TEN-protective profile due to its strong inhibition of receptor-interacting protein kinase (RIP3). RIP3-dependent
Table I. Dose escalation of dabrafenib

| Day 1       | Day 2       | Day 3       | Day 4       | Day 5       | Day 6       | Day 7       |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 1        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 8       | Day 9       | Day 10      | Day 11      | Day 12      | Day 13      | Day 14      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 2        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 15      | Day 16      | Day 17      | Day 18      | Day 19      | Day 20      | Day 21      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 3        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 22      | Day 23      | Day 24      | Day 25      | Day 26      | Day 27      | Day 28      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 4        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 29      | Day 30      | Day 31      | Day 32      | Day 33      | Day 34      | Day 35      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 5        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 36      | Day 37      | Day 38      | Day 39      | Day 40      | Day 41      | Day 42      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 6        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 43      | Day 44      | Day 45      | Day 46      | Day 47      | Day 48      | Day 49      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 7        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 50      | Day 51      | Day 52      | Day 53      | Day 54      | Day 55      | Day 56      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 8        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 57      | Day 58      | Day 59      | Day 60      | Day 61      | Day 62      | Day 63      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 9        | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (75 mg)|             |             |             |             |             |             |

| Day 64      | Day 65      | Day 66      | Day 67      | Day 68      | Day 69      | Day 70      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 10       | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (150 mg)|            |             |             |             |             |             |

| Day 71      | Day 72      | Day 73      | Day 74      | Day 75      | Day 76      | Day 77      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 11       | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (150 mg)|            |             |             |             |             |             |

| Day 78      | Day 79      | Day 80      | Day 81      | Day 82      | Day 83      | Day 84      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 12       | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (150 mg)|            |             |             |             |             |             |

| Day 85      | Day 86      | Day 87      | Day 88      | Day 89      | Day 90      | Day 91      |
|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Wk 13       | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) | Tram (2 mg) |
| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)| Pred (30 mg)|
| Dabr (150 mg)|            |             |             |             |             |             |

Continued
Table I. Cont’d

| Day 92 | Day 93 | Day 94 | Day 95 | Day 96 | Day 97 | Day 98 |
|--------|--------|--------|--------|--------|--------|--------|
| Wk 14  | Tram (2 mg) | Pred (30 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) |
| Wk 15  | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) |
| Wk 16  | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) |
| Wk 17  | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) | Tram (2 mg) | Pred (30 mg) | Dabr (300 mg) |

Dabr, Dabrafenib; Pred, prednisone; Tram, trametinib.

phosphorylation leads to a potent mechanism of inflammatory disease pathogenesis via activation of pore-forming proteins and disruption of membrane integrity.13 Programmed necrosis mediated by tumor necrosis factor (TNF)-α and nitric oxide (NO) is potentiated by high RIP levels; TNF-alpha, NO, and RIP3 are found in abundance in TEN.14 Importantly, dabrafenib directly inhibits RIP3 kinase activity, in addition to TNF-alpha and NO-induced necroptosis of keratinocytes.14,15

Dabrafenib may be an appropriate first-line agent in patients with an indication for BRAF inhibitor therapy, especially in the setting of sulfonamide hypersensitivity. Working around life-threatening therapy, especially in the setting of sulfonamide-induced toxic epidermal necrolysis.14,15

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