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Brief Communications

Real-World Toxicity Experience with BRAF/MEK Inhibitors in Patients with Erdheim-Chester Disease

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

Abstract

Background. Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis. The BRAF inhibitor vemurafenib is approved by the U.S. Food and Drug Administration (FDA) for patients with ECD harboring a *BRAF* V600E mutation. Successful treatment has also been reported with MEK-targeted therapies, likely because of the fact that *BRAF* mutant–negative patients harbor MEK pathway alterations. In our Rare Tumor Clinic, we noted that these patients have frequent drug-related toxicity, consistent with previous reports indicating the need to markedly lower doses of interferon-alpha when that agent is used in these patients.

Patients and Methods. We performed a review of ten patients with ECD seen at the Rare Tumor Clinic at University of California San Diego receiving 16 regimens of targeted BRAF, MEK, or combined therapies.

Results. The median age of the ten patients with ECD was 53 years (range, 29–77); seven were men. The median dose percentage (percent of FDA-approved dose) tolerated was 25% (range, 25%–50%). The most common clinically significant adverse effects resulting in dose adjustments of targeted therapies were rash, arthralgias, and uveitis. Renal toxicity and congestive heart failure were seen in one patient each. In spite of these issues, eight of ten patients (80%) achieved a partial remission on therapy.

Discussion. Patients with ECD appear to require substantially reduced doses of BRAF and MEK inhibitors but are responsive to these lower doses. ***The Oncologist*** 2020;25:e386–e390

Introduction

Erdheim-Chester disease (ECD) is a rare non-Langerhans cell histiocytosis. Several treatments have been successfully used in the treatment of ECD, including interferon (IFN)-alpha, imatinib, cladribine, cobimetinib, trametinib, and vemurafenib [1–4]. Vemurafenib, a drug targeting BRAF, is the first treatment approved by the U.S. Food and Drug Administration (FDA) for adult patients with ECD harboring a $BRAF^{V600E}$ mutation [5]. The efficacy of vemurafenib is largely due to the high prevalence of $BRAF^{V600E}$ mutations seen in patients with ECD [5–7].

Prior to the FDA approval of vemurafenib, IFN-alpha was used as first line of therapy for patients with ECD [2, 3]. In our clinic, treatment of ECD has shifted from IFN-alpha to BRAF- and MEK-targeted therapies: vemurafenib, dabrafenib, trametinib, and cobimetinib [5, 8]. Cobimetinib and trametinib inhibit MEK intracellularly, which is downstream from BRAF, resulting in cell growth inhibition and induction of cell death [6]. MEK inhibitors may be especially important in the ~50% of patients who do not have a *BRAF* mutation; these patients often harbor alterations in genes downstream of BRAF [6, 7].

We report ten patients who received BRAF or MEK inhibitors in our clinic, all of whom required significant dose reductions of BRAF and MEK inhibitors because of toxicity at doses approved by the FDA for other indications. Nevertheless, these patients frequently responded to these targeted agents. This experience and the prior reports of high rates of adverse effects after standard doses of IFN-alpha [2] suggest that patients with ECD may be vulnerable to toxicity from a variety of treatments, but

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Table 1. Toxicity and response of BRAF/MEK inhibitors in patients with Erdheim-Chester disease

Patient UCSD ID	Age at diagnosis, years Sex	*BRAF*^{V600E} mutation present	Other molecular alteration (tissue or ctDNA NGS) in MAPK pathway	Tx	Line of Tx	Starting dose	Final dose (% of full dose)	Toxicities (CTCAE grade ≥2, at least possibly related to drug)	Duration of Tx, months	Best response	Comment
1	49 F	Yes	*NF1*^{H1494Y}	Vemurafenib	1	960 mg PO BID	240 mg PO BID (25)	Rash, fatigue, dizziness, uveitis	20.5	PR	
				Trametinib	3	0.5 mg PO daily × 1 week, 1 mg PO daily	1 mg PO daily (50)	Rash, dizziness	1.7	Inevaluable	Stopped early because of toxicity
				Cobimetinib	5	20 mg po daily for 21 of 28 days	20 mg PO daily for 21 of 28 days (33)		5[a]	Stable disease	
2	56 M	Yes	No[b]	Vemurafenib ± trametinib	4	480 mg PO BID	240 mg PO BID (25) + 0.5 mg PO daily (25)	Renal toxicity	39.9[a]	PR	Patient started on vemurafenib; trametinib later added and stopped because of renal toxicity
4	51 M	Yes	No	Vemurafenib	1	960 mg PO BID	240 mg PO BID (25)	Hand-foot-skin-reaction, intolerance, rash, arthralgias	25.3[a]	PR	
5	52 M	Yes	*NF1*^{S1407R} *NRAS*^{G60R} *KRAS*^{A59T}	Vemurafenib	1	960 mg PO BID	240 mg PO daily (12.5)	Pyrexia, rash, arthralgias, skin pain	4	Stable disease	
				Trametinib	2	0.5 mg PO daily	0.5 mg PO every other day (12.5)	Uveitis	3.3	Stable disease	Drug stopped because of toxicity
				Dabrafenib	3	75 mg PO QOD	75 mg PO QOD (12.5)	Arthralgias	0.3	N/A	Drug stopped because of toxicity
7	29 F	No	*MAP2K1*^{Q65P}	Trametinib	3	0.5 mg PO daily	0.5 mg PO daily (25)		4[a]	PR	

(continued)

Table 1. (continued)

Patient UCSD ID	Age at diagnosis, years Sex	*BRAF*^{V600E} mutation present	Other molecular alteration (tissue or ctDNA NGS) in MAPK pathway	Tx	Line of Tx	Starting dose	Final dose (% of full dose)	Toxicities (CTCAE grade ≥2, at least possibly related to drug)	Duration of Tx, months	Best response	Comment
8	77 M	Yes	No	Dabrafenib + trametinib	2	100 mg PO BID +2 mg PO daily	100 mg PO BID (67) + 2 mg PO daily (100)	Congestive heart failure	1.4	N/A	Drug stopped because of toxicity
				Dabrafenib	3	100 mg PO BID	50 mg PO daily (33)	Congestive heart failure, adrenal insufficiency, neuropsychiatric symptoms	8.2[a]	PR	
10	53 M	No	*GNAS*^{R201S}	Trametinib	1	1 mg PO daily	0.5 mg PO daily (25)	Mucositis, infection	11.2[a]	PR	
12	52 F	Yes	*TP53*^{R196}	Vemurafenib	1	480 mg PO BID	480 mg PO BID (50)	Arthralgias	5.5[a]	PR	
15	59 M	Yes	*JAK2*^{V617F} *ARID1A*^{R1749fs}	Vemurafenib + cobimetinib	5	240 mg PO daily + 20 mg PO daily for 21 of 28 days	240 mg PO daily (12.5) + 20 mg PO daily for 21 of 28 days (33)	Hypertension, rash	1	Stable disease	Vemurafenib stopped because of toxicity
				Cobimetinib	6	20 mg PO daily for 21 of 28 days	20 mg PO daily for 21 of 28 days (33)		4.2[a]	Stable disease	
16	59 M	No	*KRAS*^{A146P} *GNAS*^{Q227E} *RB1*^{S249}	Trametinib	1	0.5 mg PO daily	0.5 mg PO daily (25)		3.7[a]	PR	

[a]Patient continued on treatment at time of data censoring.
[b]Only BRAF testing completed.
Abbreviations: BID, twice a day; CTCAE, Common Terminology Criteria for Adverse Events version 4.0; ctDNA, circulating tumor DNA; F, female; M, male; N/A, not available; NGS, next-generation sequencing; PO, orally; PR, partial response; QOD, every other day; Tx, treatment; UCSD ID, University of California San Diego identification.

the need for reduced doses does not mitigate potential responsiveness in this disease.

Materials and Methods

We performed a review of patients with ECD seen at the Rare Tumor Clinic at University of California San Diego. All patients were treated with BRAF- or MEK-targeted therapy: vemurafenib, dabrafenib, trametinib, or cobimetinib. Molecular alterations were determined by next-generation sequencing via FoundationOne (Cambridge, MA; https://www.foundationmedicine.com/) or Guardant (Redwood City, CA; https://guardanthealth.com/) for tissue and circulating tumor DNA, respectively; Sanger sequencing; or polymerase chain reaction (PCR). Pharmacogenomic (PGx) alterations were determined by PCR from buccal swabs via OneOme (Minneapolis, MN; www.oneome.com). This study was performed in accordance with University of California San Diego Institutional Review Board guidelines for data analysis (NCT02478931) and for any investigational treatments for which patients provided consent. Data censoring was completed as of December 31, 2018.

Results

Patient Characteristics

The median age at diagnosis was 53 years (range, 29–77 years) and the majority of patients were white (70%) and men (70%). Seven patients (70%) were tissue positive for the *BRAF*^{V600E} alteration. The median number of dose adjustments throughout therapy was two (range, one to five), and the median follow-up on treatment was 5 months (range, 0.3–39.9 months). PGx analyses were performed in two patients and showed decreased and severely decreased activity of methylenetetrahydrofolate reductase (MTHFR).

Treatment Regimens and Dosing

Our ten patients received 16 regimens that included BRAF and/or MEK inhibitors: trametinib (n = 5), vemurafenib (n = 4), dabrafenib (n = 2), cobimetinib (n = 2), and dual BRAF and MEK inhibitor therapy (vemurafenib plus trametinib, dabrafenib plus trametinib, and vemurafenib plus cobimetinib; n = 1 each). The median dose (as a percentage of the usual FDA-approved dose) for these 16 regimens was 25% (range, 12.5%–83.5%). The median dose percentage tolerated was 25% (range, 25%–50%). One patient did not tolerate 12.5% of the dose, and another did not tolerate 22.5% (Table 1, cases 5 and 15).

The most common adverse effects resulting in dose adjustments were rash and arthralgias (n = 5 of 16 regimens [31%] for rash and n = 4 of 16 [25%] for arthralgias). Two patients developed uveitis resulting in drug discontinuation; drugs given were vemurafenib (n = 1) and trametinib (n = 1), and the doses were reduced to 25% and 12.5%, respectively, without alleviation of the adverse effect. Three patients received dual therapies (BRAF plus MEK inhibitor; cases 2, 8 and 15) and developed more serious adverse effects including renal toxicity, congestive heart failure, and hypertension, resulting in drug discontinuation. In case 2, the resulting renal toxicity had an unclear relationship to the utilization of vemurafenib combined with trametinib. In case 8, the patient experienced a decreased left ventricular ejection fraction possibly related to trametinib and dabrafenib that remained decreased after trametinib was stopped and dabrafenib was continued at lower doses. Both patients required referral to nephrology and cardiology specialists, respectively. In spite of these issues, eight of ten patients (80%) achieved a partial remission on therapy. Our observations are consistent with those in the pivotal VE-BASKET trial [5] for ECD, which also demonstrated that these patients all required dose interruptions and/or modifications because of adverse effects.

Discussion

The primary objective of this review was to describe the toxicity associated with targeted therapies in patients with ECD. Although the etiology of the toxicity in this patient population is largely unknown, it is possible that the elevated levels of serum interleukin-6 (IL-6) in these patients contributed to the downregulation of major cytochrome P450 (CYP) isozymes, which are responsible for the metabolism of vemurafenib and cobimetinib [9]. Furthermore, serum IL-6 levels are inversely correlated with CYP-metabolized drug clearance in patients with malignancy [10]. As deacetylation is largely responsible for the metabolism of trametinib, the etiology of toxicity in patients with ECD receiving trametinib is unclear, and further research is needed. Of note, two patients who were examined at the pharmacogenomic level showed deficient MTHFR activity. However, because alterations in MTHFR are frequent in the general population, it is unlikely that this deficiency affected drug metabolism.

Patients with ECD experience significant toxicity at standard FDA-approved doses of BRAF and MEK inhibitors. Interestingly, the dose of other drugs such as interferon-alpha also need to be substantially reduced in patients with ECD because of adverse effects [2]. Our data indicate that patients with ECD should start treatment with BRAF and MEK inhibitors at doses substantially lower than those approved by the FDA for other indications. Even so, the vast majority of patients with ECD can achieve an objective response despite the need for lower dosing.

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