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Low-dose Vemurafenib Monotherapy in *BRAF*^{V600E}-mutated Erdheim-Chester Disease

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Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm derived from the macrophage/dendritic cell lineage and harbors the *BRAF*^{V600E} mutation in 50–60% of patients (1). The U.S. Food and Drug Administration (FDA) approved vemurafenib 960 mg twice daily for the treatment of adult patients with *BRAF*^{V600E}-mutated ECD based on a phase II trial that showed high efficacy with an overall response rate of 61.5% (2).

Despite vemurafenib being highly effective in treating ECD, it has many adverse effects (AEs) that are not well tolerated. The most common AEs include arthralgia, maculopapular rash, fatigue, alopecia, prolonged QT interval, cutaneous papilloma, hyperkeratosis, and cutaneous squamous cell cancer (2). In the phase II trial that led to vemurafenib's FDA approval, all patients required dose reductions below the 960 mg twice daily dose due to intolerable AEs (2). Additionally, two smaller case series studying vemurafenib observed that all patients [n=3 (3) and n=4 (4)] who were on the FDA-approved dose of vemurafenib required dose reductions.

Given the AE profile of BRAF-inhibitors, it would be of interest to assess whether lowering the starting dose of vemurafenib in ECD patients may provide a better balance of tolerability and efficacy. Consensus guidelines currently recommend starting at 25–50% of the FDA-approved dose (1), but there is a lack of published literature on vemurafenib dosing that is lower than that approved by the FDA. Two case series describe their limited experience of starting vemurafenib at 50% of the FDA-approved dose [n= 2 (3) and n=4 (4)] and to our knowledge, there is no published data on vemurafenib monotherapy less than 50% of the FDA-approved dose. In this study, we report vemurafenib experience for ECD with a focus on non-FDA approved doses of vemurafenib.

A waiver of informed consent and approval of the study was obtained from the Institutional Review Board at the Mayo Clinic. The records of ECD patients who were seen at the Mayo Clinic from January 2005 to November 2019 were retrospectively reviewed. The diagnosis of ECD was determined by clinical criteria in conjunction with histopathologic findings (1). No patients had mixed phenotype such as ECD with Langerhans cell histiocytosis or Rosai-Dorfman disease. *BRAF-V600E* mutation status was determined by immunohistochemistry (n=16), polymerase chain reaction (PCR) [n=7], digital droplet PCR (n=6), or targeted-capture next generation sequencing (NGS) [n=2]. The patients who did not have *BRAF-V600E* mutation testing were excluded. Vemurafenib dosage was considered low-dose if it was less than the FDA-approved dose of 960 mg twice daily. For response criteria, patients were assessed with positron emission tomography (PET) – computed tomography (CT) and we used previously published criteria (5). The median time to assessment of response was 6 months. Radiologic responses were categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The Common Terminology for Adverse Events (CTCAE) version 5.0 was used to assess adverse events (6).

Among 58 ECD patients who met the study inclusion criteria, 31 patients (53%) tested positive for the *BRAF-V600E* mutation status. Of the *BRAF-V600E* positive patients, 23 (74%) were treated with vemurafenib monotherapy. The vemurafenib monotherapy cohort had the following baseline characteristics: male (n=15, 65%), white (n=22, 96%), and the median age of diagnosis was 57 years (range 33–75). Sites of ECD involvement included bone (74%), central nervous system (61%), kidneys (hairly kidney; 57%), and cardiovascular system (43%). The median follow up was 2.5 years (interquartile range (IQR) 1.2–4.7) and 22 patients (96%) were alive at the date of last known follow-up. None of our patients had subsequent malignances diagnosed after their ECD diagnosis. One patient died, but the cause of death was unknown.

Within the vemurafenib cohort, the median duration on vemurafenib therapy was 11 months (IQR 5.0–30). The median time to best response was 6.5 months (IQR 3–7). Eight patients received vemurafenib as first-line therapy while 15 patients (65%) had prior lines of treatment (Table 1). The median number of previous treatments was 2 (range 1–4), and consisted of prednisone (6), anakinra (4), infliximab and methotrexate (3), pegylated interferon-alpha (3), interferon-alpha (2), cladribine (1), cyclophosphamide (1), dabrafenib (1), imatinib (1), infliximab (1), and methotrexate (1). Vemurafenib was initiated at the following doses: 960mg twice daily (n=6, 26%), 720mg twice daily (n=1), 480mg twice daily (n=14, 61%), 240mg twice daily (n=1), and 240mg once daily (n=1). The radiologic responses observed in this cohort included: CR (n=6, 26%), PR (n=15, 65%), and SD (n=1). The patient who received 240 mg twice daily had radiologic PR after 2 months of treatment. The patient who received 240 mg once daily had radiologic PD in the retroperitoneum after 2 months of treatment and was up-titrated to 960 mg twice with radiologic PR after 3 months of treatment. Toxicities were seen in 20 patients (87%). All patients who were started on 960mg twice daily experienced toxicities, while 79% of patients started on 480mg twice daily had toxicities. 15 patients (65%) experienced grade I toxicities, 12 patients (52%) had grade II toxicities, and 2 patients had grade III toxicities. Toxicity details are listed in the Supplementary Appendix.

Dose reduction and discontinuation of vemurafenib occurred in 14 (61%) patients due to toxicities. Eight patients (35%) discontinued vemurafenib completely with the median time to discontinuation being 7.4 months (IQR 4.3–10.8). The median time to requiring the first dose adjustment was 1.3 months (IQR 0.8–4.9) with the median number of dose adjustments being 2 (range 1–6). Among patients who were started on 960mg twice daily, all 6 patients (100%) required either a dose reduction or discontinued therapy; 1 immediately discontinued treatment and 5 required dose reductions with 2 eventually discontinuing therapy. For patients initiated on 480mg twice daily, 7 (50%) required a dose reduction and 4 (29%) discontinued therapy. The reasons for dose reduction, discontinuation of therapy, and initiation of subsequent therapy are outlined in the Table 1. Among those who discontinued vemurafenib, four received subsequent therapy in the form of dabrafenib (2), infliximab and methotrexate (1), and prednisone (1). The average of time to subsequent treatment was 1.7 months (range 0.03–5). See Figure 1 for the duration of time that patients were on for their respective vemurafenib doses until the date of last follow up or date of discontinuation.

Vemurafenib has been touted as having revolutionized the treatment of ECD. While effective, our study, in combination with other institutional studies (2–4), clearly demonstrates that the FDA-approved dose of vemurafenib is not practical or sustainable due to adverse effects leading to discontinuation (2–4). Discontinuation of vemurafenib after a response is achieved is generally not recommended as there is a 75% chance of relapse (7). Based on these data, the latest consensus guidelines on ECD recommend starting vemurafenib at 25–50% of the FDA-approved dose (1). However, there remains a paucity of data on whether lower doses of vemurafenib are truly effective or more tolerable compared to the FDA-approved dose.

Our data suggest that while vemurafenib doses that are 50% of the FDA approval may be adequate in achieving response in patients with ECD, the drug is still not well tolerated in a proportion of patients. While none of our ECD patients treated with vemurafenib at 50% of the FDA-approved dose had PD, 50% of these patients still required further dose reductions and 29% discontinued the medication due to intolerable AEs. Our study did not have a large enough sample size to draw conclusions on comparative efficacy of vemurafenib at <50% of the FDA-approved dose. Furthermore, one patient who was on 12.5% of the FDA-approved dose suffered a radiologic PD.

Our study raises several important questions that may need to be addressed. First, there is a need to determine whether the strategies that are applicable for managing BRAF-inhibitor toxicities in melanoma studies can be applied on ECD patients to ensure drug adherence (8). In our study, corticosteroids were not utilized among patients who had fatigue, and that may be one approach to consider. In practice, some clinicians may prefer “drug holidays” over dose reductions, and that approach may need to be evaluated as well. Second, there may be a role for using dabrafenib among patients who do not tolerate vemurafenib well, as highlighted by two cases in our study as well as another case series (9). Third, given that BRAF-inhibitor treatment is needed to be given indefinitely to prevent disease relapses (7), it is important that future studies further investigate ways to improve vemurafenib tolerability without sacrificing efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Gordon Ruan designed the research study, performed the research, analyzed the data, and wrote the first draft of the manuscript.

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Figure 1. Total duration of time on different dosages of vemurafenib in Erdheim-Chester disease.

^aPatient remains on vemurafenib at the date of last follow-up.

^bPatient experienced toxicities.

^cPatients who discontinued vemurafenib.

^dPatients who discontinued vemurafenib and underwent subsequent therapy.

^ePatient died at date of last follow-up.

BID= twice daily, QD=once daily.

Table 1.

Baseline characteristics of ECD patients on Vemurafenib Monotherapy.

Patient ID	Age at diagnosis (years)	Prior treatment	Line of Tx on Vem	Starting dose (mg/day)	Final dose (% of FDA-dose)	Toxicities (CTCAE grade)	Duration of Tx, Months	Best response	Reason for discontinuation (CTCAE grade) [Subsequent Treatment]
1	57	P; MTX + Inflix + P	3	1920	960 (50)	Pancreatitis (II)	11.3	CR	Pancreatitis (II) [None]
2	76	P; A	3	1920	1920 (100)	Fatigue (II)	6.1	PR	Fatigue (II) [D]
3	58	None	1	1920	960 (50)	Actinic keratosis (I), papilloma (II), maculo-papular rash (II), pruritus (III)	4.0	PR	Rash (III) and pruritus (III) that improved with oral prednisone [D]
4	57	None	1	1920	960 (50)	Arthralgia (I), dry skin (I), fatigue (II), papilloma (I), paresthesias (I)	23.9	PR	N/A
5	51	None	1	1920	240 (12.5)	Alopecia (II), hand-foot syndrome (II), dyesthesias (I)	62.7	CR	N/A
6	64	Inflix + MTX	2	1920	720 (37.5)	Diarrhea (I), fatigue (II)	66.2	CR	N/A
7	54	IFN; PEG; A	4	1440	1440 (75)	Actinic keratosis (I)	9.3	Unknown	Yes but unknown
8	60	P	2	960	960 (50)	None	26.0	CR	N/A
9	65	P	2	960	960 (50)	Maculopapular rash (I)	20.4	PR	N/A
10	58	PEG	2	960	960 (50)	Diarrhea (I)	38.3	CR	N/A
11	34	Inflix + MTX	2	960	960 (50)	Pancreatitis (III)	0.03	PR	Pancreatitis (III) [Inflix + MTX, then D + T]
12	51	P	2	960	960 (50)	None	6.7	PR	N/A
13	62	None	1	960	960 (50)	Cutaneous erythema (I)	7.1	PR	N/A
14	68	P; Inflix; Cyclophosphamide; Cladribine	5	960	960 (50)	None	3.8	PR	N/A
15	75	IFN	2	960	720 (37.5)	Arthralgia (II), hearing loss (I), hoarseness (I), myalgia (I)	30.9	PR	N/A
16	44	None	1	960	480 (25)	Arthralgia (I), diarrhea (I), fatigue (I-II), myalgia (I)	4.0	PR	N/A
17	65	IFN	2	960	480 (25)	Diarrhea (II), nausea (I), pruritus (I)	5.0	PR	Diarrhea (II), nausea (I), pruritus (I) [P]
18	57	PEG	2	960	480 (25)	Actinic keratosis (I), blurred vision (I), diarrhea (I), fatigue (II), gait disturbance (II)	8.7	SD	Fatigue (II), gait disturbance (II) [None]

Patient ID	Age at diagnosis (years)	Prior treatment	Line of Tx on Vem	Starting dose (mg/day)	Final dose (% of FDA-dose)	Toxicities (CTCAE grade)	Duration of Tx, Months	Best response	Reason for discontinuation (CTCAE grade) [Subsequent Treatment]
19	62	None	1	960	240 (12.5)	gynecomastia (I), nausea (I), photosensitivity (I)	4.0	CR	N/A
20	56	None	1	960	240 (12.5)	Arthralgia (I), fatigue (I), photosensitivity (I)	25.6	PR	N/A
21	46	None	1	960	* ₂₄₀	Arthralgia (I), cognitive disturbance (II), fatigue (II), maculo-papular rash (I), myalgia (I), seborrheic keratosis (II)	28.3	CR	Myalgias (I) [None]
22	65	Im; A	3	480	240 (12.5)	Dyspnea (I), fatigue (I)	56.8	PR	N/A
23	55	P; MTX; D; A	5	240	960 (50)	Photosensitivity (II)	56.5	PR	N/A

Abbreviations:

A=anakinra; C=cobimetinib; D=dabrafenib; PEG=pegylated interferon-alpha; IFN=interferon-alpha; Im=imatinib; Infix=Infliximab; MTX=methotrexate; P=prednisone; T=trametinib;

* This patient was taking 240mg three times a week.