LETTER TO THE EDITOR

Patient-reported fatigue and pain in Erdheim-Chester disease: a registry-based, mixed methods study

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Supplementary Table 1. Cohort Characteristics.

Characteristic	Category	N (%)	Median (SD)	Range
Sex	Male	75 (59)		
	Female	52 (41)		
Age at PRO assessment, years	Continuous	127 (100)	55.9 (12.2)	18.9-80.0
Length of undiagnosed illness, months	Continuous	127 (100)	10 (40.0)	0-247.3
Duration of diagnosed ECD illness, years	Continuous	127 (100)	4.8 (5.8)	0.08-38.8
Duration of diagnosed ECD illness, years	< 2	31 (24)		
	2-5	45 (35)		
	6-10	30 (24)		
	> 10	21 (17)		
Treating Institution	MSKCC	84 (66)		
	Other	43 (34)		
Information on sites of disease available	No	53 (42)		
	Yes	74 (58)		
Sites of disease (N=74)	Bone	72 (97)		
	Neurologic[1]	54 (73)		
	Brain parenchyma[1]	42 (57)		
	Cardiovascular	38 (51)		
	Pulmonary	8 (11)		
	Retroperitoneum	39 (53)		
	Abdomen	14 (19)		
	Skin or subcutaneous	25 (34)		
	Lymph nodes	6 (8)		
	Other	15 (20)		
Number of sites (N=74)	1	4 (5)		
	2	5 (7)		
	3	15 (20)		
	> 3	50 (68)		
Lines of prior therapy	0	14 (11)		
	1	38 (30)		
	2	36 (28)		
	> 2	39 (31)		
Prior steroids	No	64 (50)		
	Yes	60 (47)		
	Unknown	3 (2)		
Mutational status	*BRAF*V600E	72 (57)		
	*BRAF*V600E only	71 (56)		
	*BRAF*V600E and other[2]	1 (1)		
	*BRAF*V600E-wildtype	49 (39)		
	*BRAF*non-V600[3]	2 (2)		
	ARAF[4]	2 (2)		
	RAS isoforms[5]	5 (4)		

	MAP2K1/*MAP2K2*[6]	11 (9)		
	Kinase fusion[7]	4 (3)		
	Other mutations[8]	4 (3)		
	Multiple mutations[9]	2 (2)		
	No mutation identified	19 (15)		
	No sequencing performed	6 (5)		
Hemoglobin	Continuous	104 (82)	13.4 (1.9)	8.4-18.0
Hemoglobin (g/dL)	No anemia (men: ≥13.5, women: ≥12)	66 (52)		
	Mild anemia (men: 10-<13.5, women: 10-<12)	31 (24)		
	Moderate anemia (7.0-<10.0)	7 (6)		
	Severe anemia (<7.0)	0 (0)		
	Unknown Hb	23 (18)		
CRP (mg/dL)	Continuous	42 (33)	7.4 (42.4)	0.4-215.0
Treatment	None	39 (31)		
	Conventional[10]	12 (9)		
	Targeted other	2 (2)		
	Targeted *BRAF MEK*[11]	74 (58)		
	Intermittent dosing	3 (4)		
	Targeted High	17 (23)		
	Targeted Reduced High	21 (28)		
	Targeted Middle	14 (19)		
	Targeted Reduced	19 (26)		
Hypertension	No	70 (55)		
	Yes	56 (44)		
	Unknown	1 (1)		
Diabetes	No	114 (90)		
	Yes	12 (9)		
	Unknown	1 (1)		
Disease Status				
Clinical Response	CR	6 (5)		
	PR	58 (46)		
	SD	12 (9)		
	NE[12]	37 (29)		
	No treatment or treatment on hold but PR	2 (2)		
	Unknown	12 (9)		
Best Response on PET	CR	11 (9)		
	PR	45 (35)		
	SD	13 (10)		
	NE[12]	37 (29)		
	No treatment or treatment on hold but CR	2 (2)		

	Unknown	19 (15)		

Abbreviations: N Number; SD Standard Deviation; PRO Patient-Reported Outcome; ECD Erdheim-Chester Disease; CR Complete response; PR partial response; SD stable disease; NE Not-evaluable.

[1]Neurologic sites refer to those with involvement of neurologic structures (including spine and orbit), while brain parenchyma indicates the central nervous system.

[2]*BRAF*V600E and *JAK2*V617F

[3]*BRAF*V471F, *BRAF*M484_P490delins

[4]*ARAF*S412A, *ARAF*S214F

[5]*KRAS*G12S, *KRAS*L19F, *KRAS*R149G, *KRAS*A146V, *KRAS*Q61c.180_182del

[6]*MAP2K1*Q56P (two patients), *MAP2K1* P105_I107 indel, *MAP2K2*Y134H, *MAP2K1*G128D, *MAP2K1*P124Q, *MAP2K1*F53L, *MAP2K1*F68L, *MAP2K1* p.I103-A106del, *MAP2K1*E102_I103del (two patients)

[7]*ANP32A-BRAF* fusion, *BRAF-PICALM* fusion, *KI5FB-ALK* fusion, *FLT3-MEF2C* fusion

[8]*JAK2*, *CSF1R*, *TP53*R156C, MAP3K6 splice variant

[9]*ARAF*S216A and *KRAS*G12S for one patient and *RAF1*T491l and *KRAS*Y64D for another patient.

[10]Chemotherapy, interferon, or immunosuppression.

[11]Targeted (*BRAF*/*MEK*) inhibitors were further characterized by dose as (1) high (full dose of an inhibitor such as vemurafenib 960mg twice daily) (2) reduced high (reduced dose but higher than 50% of full dose) (3) middle (50% of full dose) (4) reduced (lower than 50% of full dose) or (5) intermittent (alternating days or weeks on and off treatment).

[12]Patients who were off treatment when they completed the BFI and BPI were considered not evaluable for clinical or PET response.

Supplementary Table 2. Association of Clinically-Relevant Fatigue with Clinically-Relevant Pain.

	Clinically-Relevant Pain (Any BPI Item 4+)		
Clinically-Relevant Fatigue (Any BFI Item 4+)	**No**	**Yes**	**P-value**
No	25 (21%)	6 (5%)	<0.0001
Yes	31 (26%)	58 (48%)	

Abbreviations: BPI Brief Pain Inventory; BFI Brief Fatigue Inventory.

Supplementary Table 3. Qualitative Interviews and Representative Quotations

Fatigue	
Severity and pervasiveness	"Fatigue is like—I can't even describe it. It's like, um, the most exhausting thing ever, and you didn't really do anything."
	Lack of energy. Just don't want to get out the bed. Want to stay in bed. Everything takes extra effort, like, uh, everything feels going uphill. Nothing is just smooth. Everything takes an effort to do, to get up. And I'm like, "Oh. Do I really want to get up?"
Variable interference	Uh, I would say that, overall, I'm able to do what I want to do. Uh, my stamina over that period has decreased slightly and continues to decrease slightly, but I'm able to do what I want to do. Maybe not quite as long, but I can do whatever I want to do.
	I really have to pace myself with what I do, um, you know, to determine—I-I can't—I just can't do as much. Like, today, I'm doing this and this, and then, I have to wait till tomorrow to do something else because I don't want to overdo it. Because if I overdo it then, tomorrow is a whole day wasted because I'm having to rest.
Pain	
Variable pain quality	Um, so I'm getting, like, this electrical—literally, that's what it feels like. I don't know if you've ever had anything like that before. But in my left arm, I'm getting, like, this electrical, um, like, feeling from my elbow to my hand. Like, I'll hear like a-a shooting electrical pain.
and	It's no sharp pain or anything. It's more so with exertion. When I walk, after a certain period of time, my bottom calves tighten up and it starts aching. That over the timeframe of the disease has probably developed not only in the bottom legs, but now in the top, upper thigh muscles start to ache. Uh, I don't have muscle pain or any discomfort in—above my waist.
Fatigue exacerbates pain	It's a diffused pain. It's an all-over pain. You know, it is—it comes and goes. And what I mean with that, if I overdo it, I'm really fatigued, the pain is worse. The pain at night, and I wake up in the morning with pain. And I'm taking Neurontin at bedtime and that helps me get through the night. However, it takes me a lot in the morning to get around some mornings… I

	don't always schedule early morning appointments because I'm just—I'm late. You know? And that's not-that's not like me.
Pain location	I'm having shoulder pain, a lot of joint pain. Joints, my ankles, my shoulders, my elbows […] My ankle, it feels like this nerve pain, and so does my elbows. It feels like an electric shock, something like that.
Variable time course of pain	Um, it fluctuates. When it comes it lasts for maybe, like, two-two, three days. It's just, like, constant, like, and I can block it out sometimes and sometimes I can't. So yeah.
Pain is side effect of treatment	Now I know that it has its own set of side effects. Now, it—now, I have the same—not the same but, you know, similar side effects as the other medications where the hair is, you know, thinning and falling out and the fatigue and the pain, those things. Because before, it was just combatting what the other ones had made me go through. So it was a better version, I guess. And it didn't seem like it was as harsh.
	So, um, but the pain, you know—when I was on the Zelboraf the pain was—it was really bad. And that's why I quit working, I overdo it. It's just too much.
	Yes. It, probably, didn't cause the pain. Well, the Zelboraf did, but I still have the pain when I was—when I do too much.