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

Erdheim-Chester disease (ECD) is a rare hematologic cancer with varied clinical manifestations. There have been 1,500 cases described since the first report.[1] To date, there has been no investigation of ECD symptoms with validated patient-reported outcomes (PRO). There is increasing evidence that PRO can result in improved decisions about patient-centered care and improve the quality of care[2] especially for patients with rare diseases who often endure heterogeneous and poorly understood symptoms.[3] In patients with cancer, fatigue and pain have a markedly deleterious impact on health-related quality of life and are associated with greater financial stress, increased healthcare utilization, and less employment participation.[4,5] We previously developed a symptom inventory evaluating patient-reported ECD-specific symptoms, their frequency, and severity. In 50 patients, we found that 72% reported fatigue and 58% reported pain,[6] but did not investigate the severity and interference associated with fatigue and pain, nor whether clinical variables modified symptoms or their severity. In the current study, we implemented validated inventories for pain and fatigue to identify factors associated with these prevailing symptoms in a large cohort of ECD patients.

This is an Institutional Review Board-approved registry-based cohort study maintained at Memorial Sloan Kettering Cancer Center (NCT03329274). Participants with ECD who provided informed consent and were enrolled from 2018-2020 with completed PRO assessments were included. The Brief Pain Inventory (BPI)[7] and Brief Fatigue Inventory (BFI)[8] were used to assess pain and fatigue, respectively; these are two validated measures to assess the impact and severity of these symptoms in cancer patients. To elicit an in-depth description of patients' symptomatology in their own words, a subset of patients participated in a qualitative semi-structured interview. Participants were selected in a purposeful approach to represent a diversity of perspectives with respect to age, sex, race, ethnicity, and ECD treatment, with the goal of interviewing at least 12 to achieve thematic saturation.[9]

Clinically relevant fatigue and clinically relevant pain were each categorized *a priori* using a clinically meaningful cutoff of having at least one BFI or BPI item, respectively, scored ≥4 to reflect moderate to severe symptomatology.[10,11] Univariable associations of numeric variables with clinically relevant fatigue or pain were performed with the Wilcoxon rank sum test. Univariable associations of categorical variables with clinically relevant fatigue or pain were identified with the Fisher exact test or χ^2 test as appropriate. Next, in a complementary analysis, recursive partitioning analysis (RPA) was used across all variables to identify subgroups statistically more likely to experience clinically relevant fatigue or pain separately. An internal validation of 10-fold cross-classification was performed to prune each RPA tree to a more parsimonious model. The tree selected minimized both the complexity parameter and the cross-validated error. The Spearman correlation coefficient was used to correlate BFI and BPI scores. Association between clinically relevant fatigue and clinically relevant pain within patients was assessed with the McNemar test. In an exploratory analysis, the association between employment status and RPA-identified groups was investigated descriptively. All tests were two-sided with a statistical level of significance <0.05. Analyses were performed using SAS v9.4 and R v3.6.0.

Qualitative interviews were audio-recorded and transcribed verbatim. Transcripts were analyzed by two coders using a thematic content analysis approach. The codebook consisted of *a priori* codes derived from the domains of the interview guide as well as inductive codes based on recurring patterns in the data. Team members independently coded each transcript, meeting regularly to achieve consensus on emerging concepts. Once transcripts had been coded, the team grouped codes into conceptual categories and identified primary themes. Transcripts were coded using NVivo Pro version 12.0 (QSR International).

There were 127 ECD patients who enrolled in the parent registry protocol and completed PRO assessments. Cohort characteristic distributions are provided in *Online Supplementary Table S1*. Seventy-four percent reported clinically relevant fatigue and 53% reported clinically relevant pain. Twenty-six percent reported only clinically relevant fatigue, 5% reported only clinically relevant pain, and 48% experienced both (*Online Supplementary Table S2*). Among patients with clinically relevant pain, 91% also reported clinically relevant fatigue; and among patients who experienced clinically relevant fatigue, 65% reported clinically relevant pain.

The mean BFI total score was 3.8; 4.2 for BFI severity and 3.6 for BFI interference (with daily activities). The highest individual item mean for the fatigue severity construct was worst fatigue and that for fatigue interference was normal work (Table 1). The mean BPI total score was 2.6; 2.5 for BPI pain severity and 2.6 for BPI pain interference (with daily activities). The highest individual item mean for the pain severity construct was worst pain and that for pain interference was normal work.

The BPI pain severity construct score was moderately cor-

Table 1. Distribution of patient-reported fatigue and pain at enrollment.

PRO Item/ Construct	Description	N (%)	Mean	SD	None (0) N (%)	Mild (1-3) N (%)	Moderate (4-6) N (%)	Severe (7-10) N (%)	Unknown N (%)
BFI Item 1	Fatigue right now	123 (97)	3.5	2.9	37 (29)	23 (18)	41 (32)	22 (17)	4 (3)
BFI Item 2	Usual fatigue	123 (97)	3.9	2.7	30 (24)	20 (16)	49 (39)	24 (19)	4 (3)
BFI Item 3	Worst fatigue	123 (97)	5.1	3.4	30 (24)	8 (6)	32 (25)	53 (42)	4 (3)
BFI Item 4	General activity	123 (97)	4.1	3.3	34 (27)	20 (16)	35 (28)	34 (27)	4 (3)
BFI Item 5	Mood	123 (97)	3.3	3.2	43 (34)	31 (24)	23 (18)	26 (20)	4 (3)
BFI Item 6	Walking ability	122 (96)	3.5	3.6	50 (39)	17 (13)	26 (20)	29 (23)	5 (4)
BFI Item 7	Normal work	123 (97)	4.2	3.6	38 (30)	18 (14)	28 (22)	39 (31)	4 (3)
BFI Item 8	Relationships	122 (96)	3.1	3.2	48 (38)	26 (20)	22 (17)	26 (20)	5 (4)
BFI Item 9	Life enjoyment	123 (97)	3.8	3.5	40 (32)	22 (17)	29 (23)	32 (25)	4 (3)
BFI Severity[a] Subscale	Items 1-3	123 (97)	4.2	2.9	30 (24)	21 (17)	48 (38)	24 (19)	4 (3)
BFI Interference[b] Subscale	Items 4-9	123 (97)	3.6	3.1	33 (26)	30 (24)	40 (32)	20 (16)	4 (3)
BFI Total[c]	Items 1-9	123 (97)	3.8	2.9	30 (24)	31 (24)	43 (34)	19 (15)	4 (3)
BPI Item 1	Worst pain	122 (96)	3.7	3.6	49 (39)	15 (12)	20 (16)	38 (30)	5 (4)
BPI Item 2	Least pain	122 (96)	1.6	2.1	63 (50)	41 (32)	12 (9)	6 (5)	5 (4)
BPI Item 3	Average pain	120 (94)	2.5	2.5	49 (39)	26 (20)	36 (28)	9 (7)	7 (6)
BPI Item 4	Right now pain	122 (96)	2.1	2.6	60 (47)	28 (22)	24 (19)	10 (8)	5 (4)
BPI Item 5	General activity	122 (96)	2.9	3.3	57 (45)	17 (13)	23 (18)	25 (20)	5 (4)
BPI Item 6	Mood	122 (96)	2.3	3.0	63 (50)	21 (17)	22 (17)	16 (13)	5 (4)
BPI Item 7	Walking ability	122 (96)	2.8	3.5	62 (49)	17 (13)	17 (13)	26 (20)	5 (4)
BPI Item 8	Normal work	122 (96)	3.0	3.7	63 (50)	14 (11)	16 (13)	29 (23)	5 (4)
BPI Item 9	Relations	122 (96)	1.9	2.9	71 (56)	22 (17)	16 (13)	13 (10)	5 (4)
BPI Item 10	Sleep	122 (96)	2.6	3.3	63 (50)	19 (15)	19 (15)	21 (17)	5 (4)
BPI Item 11	Life enjoyment	121 (95)	2.7	3.4	62 (49)	15 (12)	21 (17)	23 (18)	6 (5)
BPI Severity[d] Subscale	Items 1-4	120 (94)	2.5	2.5	49 (39)	35 (28)	27 (21)	9 (7)	7 (6)
BPI Interference[e] Subscale	Items 5-11	122 (96)	2.6	3.0	53 (42)	28 (22)	26 (20)	15 (12)	5 (4)
BPI Total[f]	Items 1-11	120 (94)	2.6	2.7	49 (39)	31 (24)	32 (25)	8 (6)	7 (6)

PRO: patient-reported outcome; BFI: Brief Fatigue Inventory; BPI: Brief Pain Inventory; N: number; SD: standard deviation. [a]The BFI severity subscale comprises three items rated on a numerical scale of 0-10 concerning fatigue severity: right now, usual, and worst. [b]The BFI interference subscale comprises six items rated on a numerical scale of 0-10 concerning interference of fatigue with daily living: general activity, mood, walking ability, normal work, relationships, and enjoyment of life. [c]The BFI total comprises all nine items: three from the BFI severity subscale and six from the BFI interference subscale. [d]The BPI severity subscale comprises four items rated on a numerical scale of 0-10 concerning pain severity: worst, least, average, and right now. [e]The BPI interference subscale comprises seven items rated on a numerical scale of 0-10 concerning interference of pain with daily living: general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life. [f]The BPI total comprises all 11 items: four from the BPI severity subscale and seven from the BPI interference subscale.

related with BFI fatigue severity construct score (r=0.58) and BPI interference severity construct score was moderately correlated with BFI interference severity construct score (r=0.53). Finally, BPI total score was moderately correlated with BFI total score (r=0.56). Within patients, clinically relevant fatigue was statistically significantly correlated with clinically relevant pain (P<0.0001) (*Online Supplementary Table S2*).

In univariable analysis, patients who were *BRAF*^{V600E}-wild-type were more likely to report clinically relevant fatigue (P=0.04) (Table 2). RPA did not identify any subgroups more likely to report clinically relevant fatigue. The only individual

variable associated with clinically relevant pain was lines of prior therapy (*P*=0.04) (Table 2). RPA identified subgroups associated with clinically relevant pain (Figure 1). Patients who were ≥70 years at ECD diagnosis were least likely to report clinically relevant pain whereas patients <70 years at ECD diagnosis with an ECD duration of 9.3 months or longer who were anemic (hemoglobin <13 g/dL) were most likely to report clinically relevant pain (*P*<0.0001).

We further explored the distribution of current employment status for the RPA-identified group most likely to report clinically relevant pain. Among these patients, 100% reporting unemployment also reported clinically relevant pain. Among patients in the other four RPA-identified groups who were less likely to report clinically relevant pain, only 47% reporting unemployment also reported clinically relevant pain.

Table 2. Clinically relevant fatigue and pain by variables of interest.

Variable	Level	BPI Total: Any Item 4+			BFI Total: Any Item 4+		
		No	Yes	*P* value*	No	Yes	*P* value*
Median age, years		56.2	54.6	0.20	56.0	55.7	0.37
Median duration of diagnosed ECD illness, years		4.8	4.9	0.12	5.1	4.8	0.94
Brain parenchyma involvement, N (%)	No	15 (52)	14 (48)	0.63	10 (32)	21 (68)	0.50
	Yes	23 (58)	17 (43)		10 (25)	30 (75)	
Neurological involvement, N (%)	No	8 (44)	10 (56)	0.29	8 (40)	12 (60)	0.17
	Yes	30 (59)	21 (41)		12 (24)	39 (76)	
Median number of sites of disease		4	4	0.72	4	4	0.56
Sites of disease, N (%)	1	1 (25)	3 (75)	0.28	1 (25)	3 (75)	0.88
	2	1 (25)	3 (75)		2 (40)	3 (60)	
	3	6 (50)	6 (50)		4 (31)	9 (69)	
	> 3	30 (61)	19 (39)		13 (27)	36 (73)	
Lines of prior therapy, N (%)	0 or 1	29 (58)	21 (42)	0.04	12 (24)	38 (76)	0.67
	2+	28 (39)	43 (61)		20 (27)	53 (73)	
BRAF^{V600E} status, N (%)	*BRAF*^{V600E} wildtype	17 (37)	29 (63)	0.07	7 (15)	40 (85)	0.04
	BRAF^{V600E} mutated	38 (54)	32 (46)		22 (31)	48 (69)	
Anemia, N (%)	No	33 (52)	30 (48)	0.38	17 (27)	47 (73)	0.80
	Yes	16 (43)	21 (57)		9 (24)	28 (76)	
Elevated CRP, N (%)	No	9 (31)	20 (69)	0.19	9 (31)	20 (69)	0.19
	Yes	5 (17)	25 (83)		5 (17)	25 (83)	
Treatment, N (%)	None	19 (54)	16 (46)	0.31	7 (19)	29 (81)	0.29
	Any	38 (44)	48 (56)		25 (29)	62 (71)	
	None	19 (54)	16 (46)	0.51	7 (19)	29 (81)	0.41
	Conventional	4 (36)	7 (64)		2 (17)	10 (83)	
	Targeted	34 (45)	41 (55)		23 (31)	52 (69)	
	Targeted middle, reduced, or intermittent	18 (50)	18 (50)	0.56	13 (36)	23 (64)	0.27
	Targeted high or reduced high	16 (43)	21 (57)		9 (24)	28 (76)	

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Variable	Level	BPI Total: Any Item 4+			BFI Total: Any Item 4+		
		No	Yes	*P* value*	No	Yes	*P* value*
Diabetes mellitus, N (%)	No	53 (48)	56 (51)	0.44	30 (27)	80 (73)	0.73
	Yes	4 (36)	7 (64)		2 (17)	10 (83)	
Diabetes insipidus, N (%)	No	20 (48)	22 (52)	0.74	12 (29)	30 (71)	0.73
	Yes	16 (52)	15 (48)		8 (25)	24 (75)	
Hypertension, N (%)	No	33 (49)	34 (51)	0.67	20 (30)	47 (70)	0.32
	Yes	24 (45)	29 (55)		12 (22)	43 (78)	
Clinical response, N (%)	Complete response	5 (83)	1 (17)	0.13	4 (67)	2 (33)	0.10
	Partial response	26 (46)	31 (54)		14 (24)	44 (76)	
	Stable disease	4 (33)	8 (67)		3 (25)	9 (75)	
Best response on PET, N (%)	Complete response	6 (50)	6 (50)	0.49	5 (42)	7 (58)	0.34
	Partial response	21 (49)	22 (51)		9 (20)	35 (80)	
	Stable disease	4 (31)	9 (69)		3 (23)	10 (77)	
BPI RPA**	Age ≥70 years	12 (92)	1 (8)	<0.0001			
	Age <70 years, ECD duration <9.3 months	11 (85)	2 (15)				
	Age <70 years, ECD duration ≥9.3 months, Hb ≥13 g/dL, Intermittent or high targeted treatment	8 (89)	1 (11)				
	Age <70 years, ECD duration ≥9.3 months, Hb ≥13 g/dL, All other treatments	13 (37)	22 (63)				
	Age <70 years, ECD duration ≥9.3 months, Hb <13 g/dL	6 (19)	25 (81)				

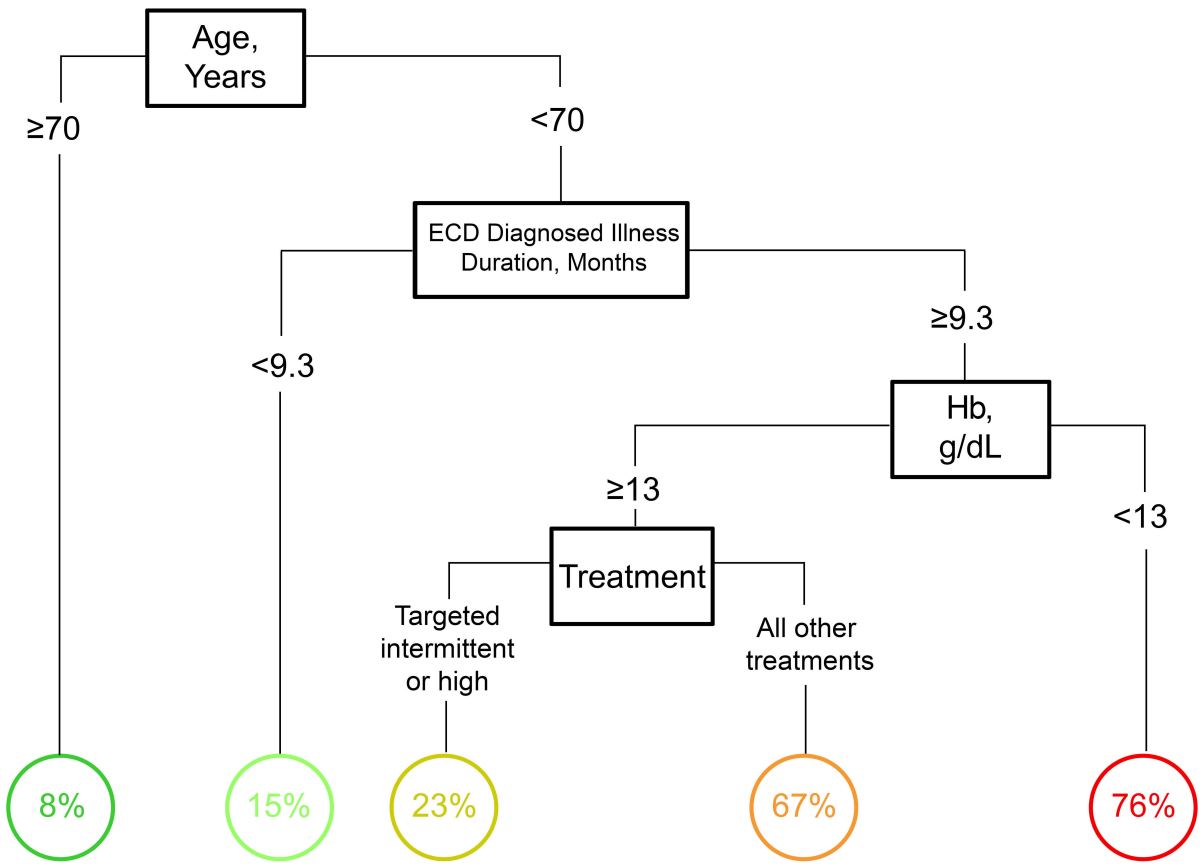
BPI: Brief Pain Inventory; BFI: Brief Fatigue Inventory; ECD: Erdheim-Chester disease; CRP: C-reactive protein; PET: positron emission tomography; RPA: recursive partitioning analysis; Hb: hemoglobin. *Tests of association were performed using the χ^2 test, Fisher test, or Wilcoxon rank sum test, depending on the type and distribution of the variable. **The RPA identified subgroups of patients who were more likely to report clinically relevant pain but did not identify subgroups of patients who were more likely to report clinically relevant fatigue.

Thematic saturation was achieved after 13 patients had been interviewed. In the theme related to physical symptom burden, ten patients (77%) described pain and nine (69%) described fatigue. *Online Supplementary Table S3* contains illustrative quotes on the nature of pain and fatigue. Pain was characterized as “diffuse” or “electrical” neuropathic pain. A few patients specifically mentioned joint pain as a treatment side effect. Patients generally described pain as worse at night and amplified by fatigue. Fatigue was described as a “constant” lack of energy and exacerbated by physical exertion.

This is the first study to identify specific subgroups of ECD patients who may benefit most from pain and fatigue interventions. While no other studies have detailed patient-reported pain and fatigue, some have detailed general symptomatology in patients with ECD.[6,12,13] Our current estimate of pain prevalence sits at the higher end of those previously reported for clinical presentation and our fatigue prevalence is three times that reported by Estrada-Veras *et al.*[12] We hypothesize that eliciting patient-reported symptoms, rather than gleaning symptoms documented by healthcare providers, may demonstrate a greater frequency of symptoms. We further hypothesize that these symptoms may become more severe over time, therefore more frequently reported in a patient population that spans time since ECD diagnosis, and this is supported by our RPA results.

The finding that *BRAF*^{V600E}-wildtype patients reported more fatigue is intriguing, but difficult to interpret because few differences in disease phenotype or biology have been noted between *BRAF*^{V600E}-mutated and wildtype patients. However, it is plausible that *BRAF* inhibitors have positively affected symptomatology of *BRAF*^{V600E}-mutated patients. The observed association between fatigue and pain also raises the question of whether unmanaged pain interrupts sleep or rest and contributes to fatigue, underscoring the importance of optimal pain management.

We observed that pain was more frequent in younger patients, which has not been observed in a large meta-analysis of characteristics associated with cancer pain[14] but has



Final recursive partitioning analysis model for clinically relevant pain. Five subgroups and their associated predicted probabilities of having clinically relevant pain are shown. The following variables were entered into the recursive partitioning analysis model: age (continuous), sex (male/female), hypertension at enrollment (yes/no/unknown), presence of diabetes mellitus at enrollment (yes/no/unknown), *BRAF*^{V600E} mutational status (mutated/wildtype/unknown), steroid treatment prior to enrollment (yes/no/unknown), individual organ system involvement (yes/no): bone, neurological, brain/parenchyma, cardiovascular, pulmonary, retroperitoneum, abdomen, lymph nodes, other, or unknown, presence of diabetes insipidus at enrollment (yes/no/unknown), number of prior lines of systemic treatment (continuous), undiagnosed Erdheim-Chester disease (ECD) duration from first symptom to official ECD diagnosis (continuous), diagnosed ECD duration from official ECD diagnosis until assessment of patient-reported outcomes (continuous), C-reactive protein (elevated/not elevated/unknown), hemoglobin (Hb; g/dL) at enrollment (continuous), clinical status at the time of survey completion (resolved/improved but not resolved/stable/not evaluable), ECD disease status as measured by positron emission tomography (resolved/improved but not resolved/stable/not evaluable), treatment at enrollment (none/conventional/targeted high dose/targeted reduced high dose/targeted middle dose/targeted reduced dose/targeted intermittent/targeted other), and anemia at enrollment (none/mild/moderate/severe/unknown).

been observed in one meta-analysis of breast cancer patients.[15] We also observed that patients were more likely to report pain if they were anemic. Pain and anemia are most likely correlates of overall disease burden rather than mechanistically related. Altogether, our study suggests that ECD pain is highly prevalent, is likely persistent despite treatment, and should be discussed with all patients but particularly with individuals younger than 70. This is of great importance as pain in this group can be so debilitating as to prohibit gainful employment, with significant implications for disability program qualifications. In exploratory analysis, all patients who were most likely to report pain based on RPA were also unemployed, suggesting that pain is disruptive with respect to employment.

Our study has some limitations. This registry-based, cross-sectional cohort is heterogeneous by design. We did not collect information on medications for pain or fatigue management. Furthermore, the rarity of this disease also precludes the external validation of the RPA results.

Using a registry-based study design of ECD patients with PRO-based methodology, we found that fatigue and pain were prevalent, severe, and interfered in the daily lives of patients. Fatigue and pain were moderately associated, raising the notion that these may potentiate the impact of one another. Fatigue and pain were unrelated to treatment response emphasizing the importance of PRO assessments when evaluating the impact of therapies. Future investigations of the evolution of fatigue and pain over time may yield additional information about how best to evaluate and manage these symptoms.

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Contributions

ASR conceived the study, was responsible for the formal statistical analysis, interpreted the research , and drafted the manuscript. DB, JJB and AMS conceived the study, collected and interpreted data and drafted the manuscript. DF, KB, GG, JC, CEA, KLM, TMA, and JJM conceived the study, interpreted the research, and drafted the manuscript. SG conceived the study and drafted the manuscript. KAL and KSP conceived and supervised the study, interpreted the research and drafted the manuscript. ELD conceived and supervised the study, collected and interpreted data and drafted the manuscript. All authors reviewed and edited the final version of the manuscript and agreed with the submission.

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Data-sharing statement

For original data, please contact diamone1@mskcc.org.

References

1. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. Blood. 2020;135(16):1311-1318.
2. Kotronoulas G, Kearny N, Maguire R, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, process of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol. 2014;32(24):1480-1501.
3. Slade A, Isa F, Kyte D, et al. Patient reported outcome measures in rare diseases: a narrative review. Orphanet J Rare Dis. 2018;13(1):61.
4. Thong MSY, van Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. Curr Treat Options Oncol. 2020;21(2):17.
5. Neufeld NJ, Elnahal SM, Alvarez RH. Cancer pain: a review of epidemiology, clinical quality and value impact. Future Oncol. 2017;13(9):833-841.
6. Diamond EL, Reiner AS, Buthorn JB, et al. A scale for patient-reported symptom assessment for patients with Erdheim-Chester disease. Blood Adv. 2019;3(7):934-938.
7. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Sing. 1994;23(2):129-138.
8. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999;85(5):1186-1196.
9. Guest G, Bunce A, Johnson L. How many interviews are enough? An experiment with data saturation and variability. Field Method. 2006;18(1):59-82.
10. Mao H, Bao T, Shen X, et al. Prevalence and risk factors for fatigue among breast cancer survivors on aromatase inhibitors. Eur J Cancer. 2018;101:47-54.
11. Romero SAD, Jones L, Bauml JM, Li QS, Cohen RB, Mao JJ. The association between fatigue and pain symptoms and decreased physical activity after cancer. Support Care Cancer. 2018;26(10):3423-3430.
12. Estrada-Veras JI, O'Brien KJ, Boyd LC, et al. The clinical spectrum of Erdheim-Chester disease: an observational cohort study. Blood Adv. 2017;1(6):357-366.
13. Cavalli G, Guglielmi B, Berti A, Bampochiaro C, Sabbadini MG, Dagna L. The multifactorial clinical presentations and manifestations of Erdheim-Chester disease: comprehensive review of the literature and of 10 new cases. Ann Rheum Dis. 2013;72(10):1961-1965.
14. MH van den Beuken-van Everdingen, Hochstenbach LM, Joosten EAJ, Tjan-Heijnen VCG, Janssen DJA. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016;51(6):1070-1090.
15. Wang L, Guyatt GH, Kennedy SA, et al. Predictors of persistent pain after breast cancer surgery: a systematic review and meta-analysis of observational studies. CMAJ. 2016;188(14):E352-E361.