Original Article

Self-Reported Fatigue in Children With Advanced Cancer: Results of the PediQUEST Study

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BACKGROUND: Pediatric cancer-related fatigue is prevalent and significantly impairs health-related quality of life, yet its patterns and correlates are poorly understood. The objectives of this study were to describe fatigue as prospectively reported by children with advanced cancer and to identify the factors associated with fatigue and associated distress. **METHODS**: Children (age ≥2 years) with advanced cancer (N = 104) or their parents at 3 academic hospitals reported symptoms at most weekly over 9 months using the computer-based Pediatric Quality of Life Evaluation of Symptoms Technology (PediQUEST) system. PediQUEST administered a modified version of the Memorial Symptom Assessment Scale (PQ-MSAS) as part of a randomized controlled trial. Clinical information was abstracted from medical records. Primary outcomes were: 1) fatigue prevalence (yes/no response to PQ-MSAS fatigue item) and 2) fatigue distress (composite score of severity, frequency, and bother). Multivariable models were constructed to identify factors independently associated with fatigue prevalence and scores reflecting fatigue distress (ie, burden). **RESULTS**: Of 920 reports, 46% (n = 425) noted fatigue. When reported, fatigue was of high frequency in 41% of respondents (n = 174), severity in 25%of respondents (n = 107), and bother in 34%of respondents (n = 143). Most reports (84%; n = 358) were associated with scores indicating fatigue distress. In multivariable analyses, fatigue was associated with older age, lower hemoglobin, and distress from particular symptoms (anorexia, nausea, sleep disturbance, sadness, and irritability). In contrast, fatigue distress was associated with distress from nausea, cough, and pain. **CONCLUSIONS**: Fatigue is common among children with advanced cancer and is often highly distressing. Interventions focused on uncontrolled symptoms may ease fatigue distress in children with advanced cancer. ***Cancer* 2018;124:3776-3783**. *© 2018 American Cancer Society.*

KEYWORDS: fatigue, palliative care, patient-reported outcomes, pediatric cancer, symptoms.

INTRODUCTION

Fatigue is 1 of the most common symptoms experienced by children who have advanced (relapsed, progressive) cancer.[1–8] These patients describe fatigue as a debilitating symptom with physical, cognitive, and emotional components that are detrimental to their health-related quality of life (HRQL).[9–15] For many, fatigue is 1 of the most distressing symptoms they experience.[14,16–18] Parents of children with advanced cancer view it as a source of significant suffering for their children[6,7,19] and identify it as 1 of the symptoms of most concern to them.[4,20]

Despite the significant impact of fatigue, our understanding of its patterns, correlates, and potential causes among children with advanced cancer is limited. Consequently, strategies with proven efficacy to mitigate this complex symptom are lacking, and it remains undertreated.[6–8] To develop effective interventions aimed at treating fatigue and easing suffering in this population, it is imperative to understand which factors that potentially contribute to fatigue may be targeted.

Studies of pediatric cancer-related fatigue to date are largely limited by retrospective design,[1–4,6–8] reliance on proxy report,[1,3,4,6–8,19] and a focus on the end-of-life period as opposed to earlier stages of advanced cancer.[1–4,6–8] Quantitative studies, especially fatigue as reported by children themselves, are lacking. Research addressing the difference between the

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presence of fatigue and fatigue distress (ie, high fatigue burden or impact on the child) is similarly limited. Given the complex, multifactorial nature of fatigue, studies addressing how patient-reported factors (eg, symptoms), child factors (eg, age), and clinical factors (eg, cancer-directed therapy), taken together, contribute to fatigue and fatigue distress are especially needed. Elucidating these factors may inform the development of effective interventions to mitigate fatigue. Understanding the prevalence and factors associated with fatigue also may create a better framework in which to test the effectiveness of future fatigue interventions.

The objective of the current study was to therefore describe patterns of both fatigue and distress associated with fatigue in pediatric advanced cancer. We used a multicenter cohort of children with advanced cancer who primarily self-reported symptoms to comprehensively evaluate the factors associated with fatigue during 9 months of follow-up.

MATERIALS AND METHODS

Design and Setting

The setting and data-collection methods have been previously detailed.[21–23] Briefly, Pediatric Quality of Life Evaluation of Symptoms Technology (PediQUEST) is a computer-based data-collection system that prospectively collects child-reported (or parent proxy-reported, when necessary) symptom and HRQL outcomes and can generate feedback reports for clinicians and families. Data were collected in the context of a pilot randomized controlled trial assessing the effect of PediQUEST reports on symptoms and HRQL.[21] The study (clinicaltrials.gov identifier NCT01838564) was conducted at 3 large pediatric cancer centers: Boston Children's Hospital/Dana-Farber Cancer Institute, Seattle Children's Hospital, and the Children's Hospital of Pennsylvania. The institutional review board of each participating site approved the study.

Participants

Eligible children were at least 2 years of age, were receiving cancer care at a study site, and had at least a 2-week history of advanced cancer (ie, not responsive to therapy, progressive, or recurrent) or for whom there was a decision to not pursue cancer-directed therapy. Children who had an isolated, relapsed solid tumor and received radiation or surgery alone or who had the first relapse of a hematologic malignancy and were proceeding to stem cell transplantation were excluded. One eligible parent per enrolled child was selected by the family to participate. Eligible parents had written command of English and the ability to complete self-administered surveys.

Study Instruments

Participants were regularly presented age-specific and respondent-specific PediQUEST surveys on tablet computers. PediQUEST surveys included the PediQUEST Memorial Symptom Assessment Scale (PQ-MSAS). PQ-MSAS is an adapted version of the Memorial Symptom Assessment Scale (MSAS), which is the only multidimensional and multisymptom instrument that has been validated for use in children with cancer.[24–27] Three PQ-MSAS versions allowed the assessment of 24 physical and psychological symptoms across the study age range: the PQ-MSAS 7-12 for children aged 7 to 12 years, which is comprised of a self-report version assessing 8 symptoms, including fatigue, and a parent supplemental version asking about the remaining 16 symptoms; the PQ-MSAS 13-18 for adolescents aged ≥13 years; and the PQ-MSAS proxy-full for parents whose child was too young (age <7 years) or was not able/willing to respond.

The PQ-MSAS asks about the presence, frequency, severity, and bother of symptoms that the child experienced in the preceding week. Response options use a 4-point (PQ-MSAS 7-12) or 5-point (PQ-MSAS 13-18 and PQ-MSAS proxy-full) Likert-type scale.[24–26] PQ-MSAS symptom scores reflecting burden/distress for individual symptoms were calculated as the average of the 3 subitems, according to the authors' recommendations. Subitem scores were standardized using a scale from 0 to 100 (with 100 considered the worst score). Equivalence across age groups and respondents was assumed. Whenever a child answered, the administration was considered self-report, even if it was a combined child-parent report. A full description of the PQ-MSAS is available elsewhere.[21,22,27]

Study Procedures

Eligible children who assented (if developmentally able) and had informed permission (consent) from a parent who also consented to participate were enrolled sequentially. One hundred four children were enrolled from December 2004 to June 2009 and were followed until death or the end of data collection. Children completed the PediQUEST in clinic or in the inpatient ward at most once each week and at least once a month. Children at least 7 years of age were asked to complete the PediQUEST using the corresponding PQ-MSAS version. If the child was unable or unwilling to do so,

then the parent completed a proxy version on the child's behalf.

Demographic and clinical data were abstracted from medical records. For each PediQUEST administration, detailed data were collected from the corresponding clinical encounter and for the preceding 10 days. Abstracted encounter data included disease status, receipt and type of cancer-directed treatment (chemotherapy, procedures, radiation, and surgery), laboratory data (hemoglobin [Hb] level), and treatment for symptoms (eg, opioids).

Statistical Analysis

All analyses were conducted using the SAS statistical software package (version 9.4; SAS Institute, Inc, Cary, NC). Because the intervention did not significantly affect PQ-MSAS scores, data from the arms were pooled.[21] These analyses include reports generated over 9 months of follow-up. Because PediQUEST assessments were not tied to specific clinical events or precisely defined intervals of time and anchors for measurements over time were not available, an analytic approach was chosen in which PediQUEST administrations were considered the unit of analysis.

For the purpose of analysis, fatigue subitem scores were classified as follows: high frequency (scores ≥66; medium amount/a lot/almost always), high severity (scores ≥66; medium amount/severe/very severe), and high bother (scores ≥50; somewhat/quite a bit/very much). Fatigue distress was defined as a fatigue score (composite of severity, frequency, and bother subitem scores) ≥44 (PQ-MSAS 7-12) and ≥33 (PQ-MSAS-13-18, PQ-MSAS proxy-full). Symptom distress was defined similarly for other symptoms. The rationale for these cutoff points and dichotomization is presented in detail elsewhere.[21,22]

The primary outcomes of interest were report of fatigue (as indicated by response to the PQ-MSAS fatigue item) and among, the reports of fatigue, fatigue distress (ie, a high degree of fatigue burden). High fatigue frequency, severity, and bother and fatigue distress frequencies also were reported. Factors hypothesized to be associated with fatigue outcomes (including age [continuous variable], diagnosis, disease status, time since diagnosis, receipt of cancer-directed treatment, cancer treatment [chemotherapy, radiation, surgery, other procedures as part of cancer treatment], opioid therapy, Hb level [continuous variable], distress from other specific symptoms) were selected a priori based on the existing cancer fatigue literature and clinical experience.[7,28–32] Generalized mixed linear models (logit link and binomial distribution) were used to evaluate associations between these factors and fatigue or fatigue distress, taking into account intervention arm and patient-level clustering. All factors associated with fatigue outcomes on univariate analysis were entered into multivariable models ($P \leq .1$ for variable entry) and then eliminated by backward selection (retention criterion, $P \leq .1$). All models included patient as a random effect (to account for the repeated measurements from single patients) and study arm as fixed to account for a potential small intervention effect.

RESULTS

Over the course of the study, 147 eligible children were approached, and 104 (71%) enrolled. Among those who enrolled, nearly one-half were adolescents (48% were age≥13 years), and nearly one-half were female (49%; n = 51).(Table 1) Slightly over one-half (56%; n = 58) had a diagnosis of solid tumor, and relatively few (10%; n = 10) had brain tumors. Twenty-six children (25%) died during follow-up.

Over the course of 9 months of follow-up, 920 PediQUEST administrations were completed, with a median of 8 administrations (interquartile range, 4-12 administrations) per child. The vast majority of administrations for children aged ≥7 years (ie, children able to self-report) were completed by the child. Specifically, among reports representing the group aged 7 to 12 years, 238 of 248 (96%) were self-reports, and in the group aged ≥13 years, 453 of 456 (99%) were self-reports.

Patterns of Fatigue and Fatigue Distress

Among the 104 children, 90 reported fatigue at least once; and, of those 90 children, 87 reported fatigue distress at least once. Among the 920 PediQUEST administrations,

TABLE 1. Baseline Characteristics of the Study Sample, n = 104

Characteristic	No. of Patients (%)
Site of care	
Site 1	24 (23)
Site 2	59 (57)
Site 3	21 (20)
Female	51 (49)
Age: Median [IQR], y	12.1 [6.8-17.1]
White non-Hispanic	93 (89)
Diagnosis	
Hematologic malignancy	36 (34)
Solid tumor	58 (56)
Brain tumor	10 (10)
Time from diagnosis to enrollment: Median [IQR], mo	27 [17-51]
Time from last disease progression to enrollment: Median [IQR], mo	5.9 [3.4-9.4]
Intervention arm	51 (49)

Abbreviations: IQR, interquartile range; SD, standard deviation.

fatigue was reported in almost one-half (46%; n = 425). Among those 425 who reported fatigue, 41% (n = 174) reported fatigue of high frequency, 25% (n = 107) reported fatigue of high severity, and 34% (n = 143) reported fatigue of high bother. The average ± standard deviation fatigue distress score was 46.8 ± 16.6. Most participants (84%; n = 358) had fatigue scores above the prespecified cutoff point indicating fatigue distress (Fig. 1).

Factors Associated With Fatigue

Some variables representing clinical factors (including receipt of opioids in the previous 10 days and lower Hb) and reports of distressing symptoms (except cough) were significantly associated with fatigue on univariate analysis, whereas other variables (diagnosis, time from diagnosis, disease status) were not (Table 2). Older children and those undergoing a procedure were marginally associated with fatigue. In the multivariable model, older age, lower Hb, other distressing physical (anorexia, nausea, difficulty sleeping) and psychological (sadness, irritability) symptoms were associated with fatigue (Table 3).

Factors Associated With Fatigue Distress

In the subgroup of surveys in which fatigue was noted, female sex was associated with fatigue distress. Other variables, including diagnosis, disease status, receipt of cancer treatment, and Hb level, were not (Table 2). Older child age, receipt of opioids, and undergoing a procedure were marginally associated with fatigue distress. Both distressing physical (nausea, cough, pain) and psychological (worry) symptoms were associated with fatigue distress. In multivariate analyses, only distressing nausea, cough, and pain were associated with fatigue distress (Table 3).

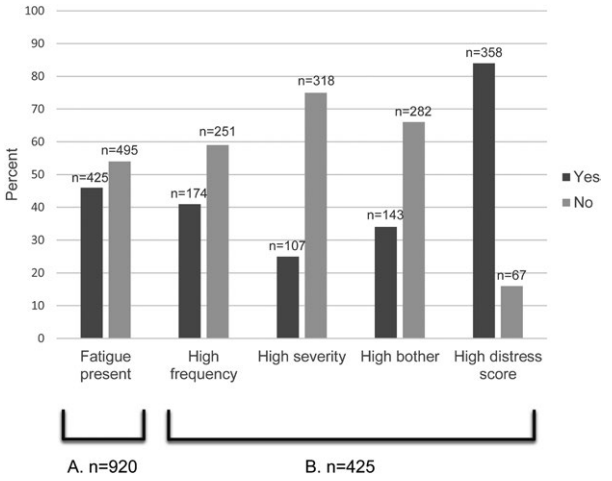

Figure 1. The frequencies of reports of fatigue, fatigue dimensions, and fatigue distress are illustrates, including data from (A) surveys that reported fatigue among all 920 surveys and (B) surveys that reported high frequency, high severity, high bother, and high distress scores among all 425 surveys that reported fatigue. Fatigue subitem scores were classified as follows: high frequency (score ≥66; medium amount/a lot/almost always), high severity (score ≥66; medium amount/severe/very severe), and high bother (score ≥50; somewhat/quite a bit/very much). High fatigue distress scores (composite of severity, frequency, and bother subitem scores) were defined as scores ≥44 on a Pediatric Quality of Life Evaluation of Symptoms Technology (PediQUEST)-modified version of the Memorial Symptom Assessment Scale (PQ-MSAS) 7-12 for children ages 7 to 12 years and a score ≥33 either on the PQ-MSAS 13-18 for adolescents aged ≥13 years or on the PQ-MSAS proxy-full (for parents with children too young [aged <7 years] or not able/willing to respond).

DISCUSSION

This sizeable, multicenter cohort, children with advanced cancer reported fatigue nearly 50% of the time. Moreover, a substantial proportion of their fatigue reports revealed high fatigue frequency, severity, or bother; and the majority had fatigue distress. These data support the conclusion that, when present, fatigue may present a significant burden to children with advanced cancer.

Fatigue was associated with older age, lower Hb, and distress from multiple symptoms. Prior studies of children with earlier stage cancer and adults with advanced cancer have revealed associations between fatigue and a range of similar factors, including patient factors (eg, age),[5,33] clinical factors (eg, anemia),[34] and symptoms.[7,32,35] Our findings, in conjunction with those of others, underscore the complex and multifactorial nature of fatigue.

The factors we observed to be associated with fatigue in this advanced cancer setting differ from those associated with earlier stage fatigue. For example, we noted that neither anemia nor recent receipt of any cancer treatment in the prior 10 days was associated with fatigue. This stands in contrast to findings from other studies of children/adolescents with earlier stage cancer who were more likely to report fatigue if they were anemic, were receiving treatment, or had recently received treatment.[11,14,17,29,33,34,36,37] The cause of this difference may be that, for children with advanced cancer, symptom distress figures more prominently than other factors like cancer-directed therapy or anemia.

We observed that fatigue is experienced as distressing when it occurs in association with other uncontrolled physical symptoms, such as nausea, cough, pain, and possibly worry. The mechanism by which a child with a high burden of other symptoms is more likely to experience

TABLE 2. Factors Associated With Reports of Fatigue and High Fatigue Distress: Univariate Analysis

	All Reports, n = 920			Fatigue Reports, n = 425		
	No. of Patients (%)			No. of Patients (%)		
Variable	No Fatigue, n = 495	Fatigue, n = 425	*P*[a]	Low Distress, n = 67[a]	High Distress, n = 358A	*P*[a]
Demographic characteristics						
Site of care			.31			.53
Site 1	105 (61)	67 (39)		15 (22)	52 (78)	
Site 2	257 (51)	248 (49)		38 (15)	210 (85)	
Site 3	133 (55)	110 (45)		14 (13)	96 (87)	
Female	215 (49)	222 (51)	.32	24 (11)	198 (89)	.03
Age at enrollment: Median [IQR], y	11.7 [6.7-16.7]	14.7 [8.7-17.2]	.05	10.4 [6.5-16.4]	15.4 [(8.7-17.6]	.05
White non-Hispanic	441 (54)	372 (46)	.55	61(16)	311 (84)	.34
Disease characteristics						
Diagnosis			.80			.72
Hematologic malignancy	165 (54)	141 (46)		25 (18)	116 (82)	
Solid tumor	277 (52)	256 (48)		36 (14)	220 (86)	
Brain tumor	53 (65)	28 (35)		6 (21)	22 (78)	
Time from diagnosis to enrollment: Median [IQR], mo	25 [15-50.6]	30.6 [20-50.6]	.14	26.3 [17.9-54.1]	30.7 [20.5-50.4]	.96
Disease status active/progressive	323 (55)	267 (45)	.63	48 (18)	219 (82)	.12
Time since last disease progression Median [IQR], mo	6.1 [3.7-9.5]	5.6 [3.2-9.4]	.38	5.4 [3.2-9.4]	6.1 [3.4-8.7]	.28
Treatment in past 10 d						
Cancer-directed treatment, any	256 (53)	231 (47)	.12	39 (17)	192 (83)	.42
Type of cancer treatment						
Chemotherapy	245 (53)	214 (47)	.23	38 (18)	176 (82)	.24
Procedure	36 (44)	47 (56)	.07	13 (28)	34 (72)	.05
Surgery	3 (27)	8 (73)	.21	1 (12)	7 (88)	.21
Radiation therapy	14 (36)	25 (64)	.13	0	25 (100)	.13
Opioid therapy	56 (40)	85 (60)	.02	6 (7)	79 (93)	.07
Hemoglobin: Mean ± SD, g/dL	10.9 ± 1.7	10.7 ± 1.9	< .01	10.7 ± 2.4	10.7 ± 1.9	.94
Physical symptoms: High distress[b]						
Anorexia	67 (29)	168 (71)	< .001	17 (10)	151 (90)	< .01
Nausea	63(28)	160 (72)	< .001	6 (4)	154 (96)	< .001
Cough	74 (46)	86 (54)	.06	4 (5)	82 (95)	< .01
Diarrhea	72 (37)	123 (63)	< .001	15 (12)	108 (88)	.49
Pain	155 (43)	205 (57)	< .01	14 (7)	191 (93)	< .001
Difficulty sleeping	62 (31)	140 (69)	< .001	15 (11)	125 (89)	.27
Psychological symptoms: High distress[b]						
Sadness	60 (38)	100 (62)	< .001	10 (10)	90 (90)	.1
Irritability	104 (42)	141 (58)	< .001	20 (14)	121 (86)	.52
Worry	63 (39)	99 (61)	< .01	5 (5)	94 (95)	< .01

Abbreviations: CI, confidence interval; IQR, interquartile range; SD, standard deviation.

[a]Analyses were adjusted for intervention arm and respondent clustering (patient-level clustering).

[b]For symptom distress scores, high distress was defined as a score ≥44 on the Pediatric Quality of Life Evaluation of Symptoms Technology (PediQUEST)-modified version of the Memorial Symptom Assessment Scale (PQ-MSAS) 7-12 for children ages 7 to 12 years and a score ≥33 on either the PQ-MSAS 13-18 for adolescents aged ≥13 years or the PQ-MSAS proxy-full (for parents with children too young [aged <7 years] or not able/willing to respond).

fatigue distress is not well understood but has been previously described.[35] Suffering from a different symptom may reduce a child's threshold for experiencing fatigue distress (and vice versa). Treatment of other symptoms (ie, polypharmacy) also may lead to fatigue. Clinical experience suggests that suffering from uncontrolled symptoms is exhausting; these data provide evidence for this important observation.

Our findings have important implications for the care of children with advanced cancer. First, fatigue may present a high degree of burden for some children, and interventions targeting their fatigue are warranted. Second, relief of fatigue distress may be within grasp, because treatments exist to relieve many other distressing symptoms that contribute to fatigue (eg, nausea). An important corollary of this is that fatigue need not simply be accepted by clinicians

TABLE 3. Factors Associated With Reports of Fatigue and Fatigue Distress: Multivariate Models

Variable	OR	95%CI	*P*[a]
Fatigue			
Age	1.06	1.0-1.13	.04
Hemoglobin	0.79	0.69-0.91	.001
High distress symptoms[b]			
Anorexia	3.37	1.96-5.79	< .001
Nausea	3.29	1.97-5.5	< .001
Difficulty sleeping	2.93	1.70-5.03	< .001
Sadness	1.96	1.06-3.64	.03
Irritability	1.96	1.10-3.50	.02
Fatigue distress[b]			
High distress symptoms[a]			
Nausea	5.01	1.99-12.57	< .001
Cough	4.25	1.41-12.81	.01
Pain	2.3	1.13-4.70	.02
Worry	2.52	0.89-7.11	.08

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Analyses were adjusted for intervention arm and respondent clustering (patient-level clustering).

[b]For symptom distress scores, high distress was defined as a score ≥44 on the Pediatric Quality of Life Evaluation of Symptoms Technology (PediQUEST)-modified version of the Memorial Symptom Assessment Scale (PQ-MSAS) 7-12 (for children ages 7-12 years) and a score ≥33 on the PQ-MSAS 13-18 (for adolescents aged ≥13 years) or on the PQ-MSAS proxy-full (for parents with children too young [aged <7 years] or not able/willing to respond).

or patients. We need communication about a child's fatigue and the strategies we may have in hand to relieve it.

Third, although a differential diagnosis for fatigue and the identification and treatment of nonsymptom factors often are emphasized, optimal fatigue treatment should be focused primarily on concomitant, uncontrolled symptoms. The co-occurrence of fatigue with other bothersome symptoms may explain why single interventions aimed at fatigue, such as methylphenidate, have had variable success in relieving fatigue.[38–41] This also may explain why intensive, multimodal treatment of multiple concurrent symptoms is known to reduce fatigue, fatigue distress, and interference with functioning for adults with advanced cancer,[42,43] as do global approaches such as coaching interventions that promote self-care.[44]

The current study has several strengths. First, the vast majority of symptom reports were self-reported by the child. Second, the multicenter design and sizeable sample (relative to other studies in this population) increases the generalizability of findings. Third, the MSAS permitted a deeper examination of the symptom, fatigue's various dimensions, and the burden experienced by the child, which are not 1 and the same.[35,45] Finally, we evaluated fatigue and fatigue distress in a comprehensive manner, assessing an array of child, clinical, and symptom factors together, as a child would experience them, to better understand the nature of pediatric advanced cancer fatigue.

Our findings must be interpreted in light of the study's limitations. First, limited diversity of the study population may have precluded the detection of associations between fatigue or fatigue distress and race or ethnicity. Second, fatigue assessments were not systematically tied to chemotherapy cycles, limiting the analysis of fatigue variation throughout the treatment course. Third, at times (albeit infrequently), fatigue outcomes were based on parent proxy report; however, parents are generally the proxy of choice, and their use prevented otherwise nonrandom loss of data. Because parent reports of child outcomes can be influenced by the parent's state,[45,46] future efforts involving parent proxy reporting of child symptoms would be strengthened by concomitant assessments of parents. In addition, analyses were focused on factors hypothesized a priori to be associated with fatigue; other factors that were not included might still have an impact on fatigue. Finally, future efforts in this vein also might use an instrument dedicated to fatigue assessment, thereby providing an even deeper understanding of this complex symptom.

Children with advanced cancer experience a high burden from fatigue. It is noteworthy that fatigue and associated distress are primarily related to other symptoms, which may be amenable to treatment. Therefore, future interventions to mitigate suffering from fatigue should focus on overall symptom control. Such a strategy may well strengthen our ability to mitigate fatigue and improve the overall well being of children with advanced cancer.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Christina K. Ullrich: Data curation, formal analysis, funding acquisition, investigation, methodology, software, validation, visualization, writing–original draft; and writing–review and editing. **Veronica Dussel:** Conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, validation, and writing–review and editing. **Liliana Orellana:** Data curation, formal analysis, methodology, software, validation, and writing–review and editing. **Tammy I. Kang:** Investigation, project administration, resources, and writing–review and editing. **Abby R. Rosenberg:** Investigation, project

administration, resources, and writing–review and editing. **Chris Feudtner:** Investigation, project administration, resources, and writing–review and editing. **Joanne Wolfe:** Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing–original draft, and writing–review and editing.

REFERENCES

1. Jalmsell L, Kreicbergs U, Onelov E, Steineck G, Henter JI. Symptoms affecting children with malignancies during the last month of life: a nationwide follow-up. *Pediatrics.* 2006;117:1314-1320.
2. Wolfe J, Grier HE, Klar N, et al. Symptoms and suffering at the end of life in children with cancer. *N Engl J Med.* 2000;342:326-333.
3. Theunissen JM, Hoogerbrugge PM, van Achterberg T, Prins JB, Vernooij-Dassen MJ, van den Ende CH. Symptoms in the palliative phase of children with cancer. *Pediatr Blood Cancer.* 2007;49:160-165.
4. Pritchard M, Burghen E, Srivastava DK, et al. Cancer-related symptoms most concerning to parents during the last week and last day of their child's life. *Pediatrics.* 2008;121:e1301-e1309.
5. Van Cleve L, Munoz CE, Savedra M, et al. Symptoms in children with advanced cancer: child and nurse reports. *Cancer Nurs.* 2012;35:115-125.
6. von Lutzau P, Otto M, Hechler T, Metzing S, Wolfe J, Zernikow B. Children dying from cancer: parents' perspectives on symptoms, quality of life, characteristics of death, and end-of-life decisions. *JPalliat Care.* 2012;28:274-281.
7. Ullrich CK, Dussel V, Hilden JM, et al. Fatigue in children with cancer at the end of life. *JPain Symptom Manage.* 2010;40:483-494.
8. van der Geest IM, Darlington AS, Streng IC, Michiels EM, Pieters R, van den Heuvel-Eibrink MM. Parents' experiences of pediatric palliative care and the impact on long-term parental grief. *JPain Symptom Manage.* 2014;47:1043-1053.
9. Gibson F, Mulhall AB, Richardson A, Edwards JL, Ream E, Sepion BJ. A phenomenologic study of fatigue in adolescents receiving treatment for cancer. *Oncol Nurs Forum.* 2005;32:651-660.
10. Ream E, Gibson F, Edwards J, Seption B, Mulhall A, Richardson A. Experience of fatigue in adolescents living with cancer. *Cancer Nurs.* 2006;29:317-326.
11. Erickson JM, Beck SL, Christian B, et al. Patterns of fatigue in adolescents receiving chemotherapy. *Oncol Nurs Forum.* 2010;37:444-455.
12. Hicks J, Bartholomew J, Ward-Smith P, Hutto CJ. Quality of life among childhood leukemia patients. *JPediatr Oncol Nurs.* 2003;20:192-200.
13. Hinds PS, Hockenberry-Eaton M, Gilger E, et al. Comparing patient, parent, and staff descriptions of fatigue in pediatric oncology patients. *Cancer Nurs.* 1999;22:277-288; quiz 288-279.
14. Enskar K, von Essen L. Prevalence of aspects of distress, coping, support and care among adolescents and young adults undergoing and being off cancer treatment. *Eur J Oncol Nurs.* 2007;11:400-408.
15. Rosenberg AR, Orellana L, Ullrich C, et al. Quality of life in children with advanced cancer: a report from the PediQUEST Study. *JPain Symptom Manage.* 2016;52:243-253.
16. Moody K, Meyer M, Mancuso CA, Charlson M, Robbins L. Exploring concerns of children with cancer. *Support Care Cancer.* 2006;14:960-966.
17. Walker AJ, Gedaly-Duff V, Miaskowski C, Nail L. Differences in symptom occurrence, frequency, intensity, and distress in adolescents prior to and 1 week after the administration of chemotherapy. *JPediatr Oncol Nurs.* 2010;27:259-265.
18. Hedstrom M, Ljungman G, von Essen L. Perceptions of distress among adolescents recently diagnosed with cancer. *JPediatr Hematol Oncol.* 2005;27:15-22.
19. Wolfe J, Hammel JF, Edwards KE, et al. Easing of suffering in children with cancer at the end of life: is care changing? *JClin Oncol.* 2008;26:1717-1723.
20. Hendricks-Ferguson V. Physical symptoms of children receiving pediatric hospice care at home during the last week of life. *Oncol Nurs Forum.* 2008;35:E108-E115.
21. Wolfe J, Orellana L, Cook EF, et al. Improving the care of children with advanced cancer by using an electronic patient-reported feedback intervention: results from the PediQUEST randomized controlled trial. *JClin Oncol.* 2014;32:1119-1126.
22. Wolfe J, Orellana L, Ullrich C, et al. Symptoms and distress in children with advanced cancer: prospective patient-reported outcomes from the PediQUEST Study. *JClin Oncol.* 2015;33:1928-1935.
23. Dussel V, Orellana L, Soto N, et al. Feasibility of conducting a palliative care randomized controlled trial in children with advanced cancer: assessment of the PediQUEST Study. *JPain Symptom Manage.* 2015;49:1059-1069.
24. Collins JJ, Byrnes ME, Dunkel IJ, et al. The measurement of symptoms in children with cancer. *JPain Symptom Manage.* 2000;19:363-377.
25. Collins JJ, Devine TD, Dick GS, et al. The measurement of symptoms in young children with cancer: the validation of the Memorial Symptom Assessment Scale in children aged 7-12. *JPain Symptom Manage.* 2002;23:10-16.
26. Drake R, Frost J, Collins JJ. The symptoms of dying children. *JPain Symptom Manage.* 2003;26:594-603.
27. Tomlinson D, Hinds PS, Bartels U, Hendershot E, Sung L. Parent reports of quality of life for pediatric patients with cancer with no realistic chance of cure. *JClin Oncol.* 2011;29:639-645.
28. Hinds PS, Nuss SL, Ruccione KS, et al. PROMIS pediatric measures in pediatric oncology: valid and clinically feasible indicators of patient-reported outcomes. *Pediatr Blood Cancer.* 2013;60:402-408.
29. Perdikaris P, Merkouris A, Patiraki E, Tsoumakas K, Vasilatou-Kosmidis E, Matziou V. Evaluating cancer related fatigue during treatment according to children's, adolescents' and parents' perspectives in a sample of Greek young patients. *Eur J Oncol Nurs.* 2009;13:399-408.
30. Spathis A, Booth S, Grove S, Hatcher H, Kuhn I, Barclay S. Teenage and young adult cancer-related fatigue is prevalent, distressing, and neglected: it is time to intervene. A systematic literature review and narrative synthesis. *JAdolesc Young Adult Oncol.* 2015;4:3-17.
31. Atay S, Conk Z, Bahar Z. Identifying symptom clusters in paediatric cancer patients using the Memorial Symptom Assessment Scale. *Eur J Cancer Care (Engl).* 2012;21:460-468.
32. Smith AW, Bellizzi KM, Keegan TH, et al. Health-related quality of life of adolescent and young adult patients with cancer in the United States: the Adolescent and Young Adult Health Outcomes and Patient Experience Study. *JClin Oncol.* 2013;31:2136-2145.
33. Hinds PS, Hockenberry M, Tong X, et al. Validity and reliability of a new instrument to measure cancer-related fatigue in adolescents. *JPain Symptom Manage.* 2007;34:607-618.
34. Miller E, Jacob E, Hockenberry MJ. Nausea, pain, fatigue, and multiple symptoms in hospitalized children with cancer. *Oncol Nurs Forum.* 2011;38:E382-E393.
35. Perdikaris P, Merkouris A, Patiraki E, Papadatou D, Vasilatou-Kosmidis H, Matziou V. Changes in children's fatigue during the course of treatment for paediatric cancer. *Int Nurs Rev.* 2008;55:412-419.
36. Erickson JM, Beck SL, Christian BR, et al. Fatigue, sleep-wake disturbances, and quality of life in adolescents receiving chemotherapy. *JPediatr Hematol Oncol.* 2011;33:e17-e25.
37. Bruera E, Yennurajalingam S, Palmer JL, et al. Methylphenidate and/or a nursing telephone intervention for fatigue in patients with advanced cancer: a randomized, placebo-controlled, phase II trial. *JClin Oncol.* 2013;31:2421-2427.
38. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. *JClin Oncol.* 2006;24:2073-2078.
39. Escalante CP, Meyers C, Reuben JM, et al. A Randomized, double-blind, 2-period, placebo-controlled crossover trial of a sustained-release methylphenidate in the treatment of fatigue in cancer patients. *Cancer J.* 2014;20:8-14.

40. Roth AJ, Nelson C, Rosenfeld B, et al. Methylphenidate for fatigue in ambulatory men with prostate cancer. *Cancer.* 2010;116:5102-5110.
41. de Raaf PJ, de Klerk C, Timman R, Busschbach JJ, Oldenmenger WH, van der Rijt CC. Systematic monitoring and treatment of physical symptoms to alleviate fatigue in patients with advanced cancer: a randomized controlled trial. *JClin Oncol.* 2013;31:716-723.
42. Given B, Given CW, McCorkle R, et al. Pain and fatigue management: results of a nursing randomized clinical trial. *Oncol Nurs Forum.* 2002;29:949-956.
43. Ream E, Richardson A, Alexander-Dann C. Supportive intervention for fatigue in patients undergoing chemotherapy: a randomized controlled trial. *JPain Symptom Manage.* 2006;31:148-161.
44. Poder U, Ljungman G, von Essen L. Parents' perceptions of their children's cancer-related symptoms during treatment: a prospective, longitudinal study. *JPain Symptom Manage.* 2010;40:661-670.
45. Parsons SK, Shih MC, Duhamel KN, et al. Maternal perspectives on children's health-related quality of life during the first year after pediatric hematopoietic stem cell transplant. *JPediatr Psychol.* 2006;31:1100-1115.