The Influence of Oxidative Stress on Symptom Occurrence, Severity, and Distress During Childhood Leukemia Treatment

Marilyn J. Hockenberry, PhD, RN, PPCNP, FAAN, Olga A. Taylor, MPH, Alice Pasvogel, PhD, Cheryl Rodgers, PhD, RN, CPNP, Kathy McCarthy, BSN, RN, Patricia Gundy, MS, David W. Montgomery, PhD, Phillip Ribbeck, Michael E. Scheurer, PhD, MPH, and Ida M. (Ki) Moore, PhD, RN, FAAN

Purpose/Objectives: To explore the symptom trajectory during the first 16 months of childhood leukemia treatment and any associations with the oxidative stress pathway measured by cerebrospinal fluid (CSF) concentration of oxidized phosphatidylcholine (PC), the predominant glycerophospholipid in the brain and cell membranes.

Design: Prospective, longitudinal design.

Setting: Two cancer centers in the southwestern United States.

Sample: 36 children (aged 3–14 years) newly diagnosed with acute lymphoblastic leukemia.

Methods: Symptoms were measured using the Memorial Symptom Assessment Scale at six specific time points during treatment. Biochemical changes in oxidative stress were measured by oxidized PC in the CSF.

Main Research Variables: Childhood cancer symptoms, oxidized PC.

Findings: Significant differences were found in the number of symptoms experienced during the three phases of treatment. Symptom trajectory changes and influence of the oxidative stress pathway on symptom experiences were identified.

Conclusions: Symptoms experienced during treatment for childhood leukemia are associated with increased oxidative stress.

Implications for Nursing: Children with leukemia experience symptoms throughout treatment. Physiologic measures indicate the influence of oxidative stress on symptoms.

Key Words: fatigue; leukemia/lymphomas/hematology; symptoms

ONF, 41(4), E238–E247. doi: 10.1188/14.ONF.E238-E247

Children with cancer experience multiple symptoms resulting from their disease and treatment. Pain, fatigue, nausea, and vomiting are among the most frequently reported symptoms during childhood cancer treatment (Kestler & LoBiondo-Wood, 2012). Any treatment-related symptom can create significant toxicity leading to complications, therapy-dose reductions, and treatment delays, which compromise long-term survival. Children with cancer report treatment-related symptoms as the worst part of treatment because they create difficulties with completing daily activities and are remembered a long time after treatment ends (Woodgate & Degner, 2003).

To date, most oncology symptom research describes single symptoms related to their occurrence, severity, and distress with limited effort aimed at analyzing factors associated with these symptoms (Henly, Kallas, Klatt, & Swenson, 2003; Van Cleve et al., 2012). Pediatric oncology researchers are now beginning to focus on the interaction and synergy of multiple symptoms. As this work continues to develop, the combined effect of multiple symptoms will provide a more comprehensive picture of the child's cancer treatment experience.

Limited research exists on the role oxidative stress biomarkers may play in evaluating the severity of symptoms experienced by pediatric patients with cancer (Pierce, McCabe, White, & Clancy, 2012). This study advances the understanding of childhood cancer treatment symptoms, their interactions, and changes in symptom severity over time. Even more critical to understanding symptom experiences during childhood leukemia treatment is the need for exploring why individual symptom differences occur; this will allow identification of who may be most susceptible to treatment toxicities. The purpose of this study was to explore the influence of the oxidative stress pathway on symptom severity during the first 16 months of childhood leukemia treatment.

Literature Review

Symptom Severity and Childhood Cancer Treatment

Symptom investigation in pediatric oncology is a relatively new area of exploration. Studies of adults

with cancer provided insight into searching for symptom relationships, concurrence, and underlying dimensions (Chen & Tseng, 2006; Dodd, Miaskowski, & Lee, 2004; Kim et al., 2009; Kim, McGuire, Tulman, & Barsevick, 2005). However, few studies have evaluated specific symptom trajectories in children with cancer. In a study of 144 adolescent patients with cancer treated in Taiwan, five symptom clusters were found: (a) sensory discomfort and body image issues; (b) circulatory and respiratory problems; (c) fatigue, sleep, and depression; (d) body image issues and eating difficulties; and (e) gastrointestinal irritation and pain (Yeh, Chiang, Chien, et al., 2008). A symptom cluster analysis evaluating fatigue, nausea and vomiting, depression, and performance status was evaluated in 67 children receiving chemotherapy (Hockenberry et al., 2010). Aspects of fatigue (e.g., energy, function, mood) and depression clustered together one week after chemotherapy; moderate to severe fatigue was noted in 46% of the sample, whereas 6% had depression and 13% were at risk for depression (Hockenberry et al., 2010). In another study, five clusters were identified in 164 children and adolescents receiving cancer chemotherapy; the most common symptoms found in the clusters were lack of appetite, nausea, nervousness, and lack of energy, with the most distressing symptoms being nausea, hair loss, and vomiting (Atay, 2011; Atay, Conk, & Bahar, 2012).

The current challenge for symptom research is to clearly demonstrate the meaning of the symptoms while addressing patterns of association and interaction (Kim et al., 2005; Miaskowski, Dodd, & Lee, 2004).

Children and adolescents undergoing cancer treatment report frequently feeling depressed, decreased desire to communicate with others, and wanting to be left alone (Hockenberry-Eaton et al., 1998). Earlier studies of short-term, high-dose steroid therapy on behavior, depression, and sleep in pediatric patients with cancer indicated significant negative changes between periods on and off treatment (Hinds et al., 2007). In qualitative studies of children undergoing cancer treatment, patients were acutely aware of emotional changes that occurred during treatment (Gibson, Mulhall, et al., 2005; Hockenberry-Eaton et al., 1998). In a study of health-related quality of life (HRQOL) in 61 children following myelosuppressive chemotherapy, those with poorer functional status and higher symptom burden had significant decreases in HRQOL; on average, the children experienced 10.6 symptoms (Baggott et al., 2010). The most common symptoms included lack of energy, pain, drowsiness, nausea, sadness, and irritability (Baggott et al., 2010). Gibson, Garnett, Richardson, Edwards, and Sepion (2005) evaluated fatigue in children with cancer and found that 57% of parents and healthcare professionals reported observing cancer-related fatigue in the patients. Pediatric patients experience fatigue in the first few days after the start of a chemotherapy cycle (Yeh, Chiang, Lin, et al., 2008). In addition, children and adolescents describe fatigue as a distressing, pervasive symptom with physical, mental, and emotional components characterized by a lack of energy (Gibson, Mulhall, et al., 2005; Hockenberry et al., 2003; Hockenberry-Eaton et al., 1998).

Oxidative Stress and Symptom Severity

Oxidative metabolism is the body's first line of defense against environmental attack (Roberts et al., 2010). Reactive oxygen species (ROS) are produced as a byproduct of oxidative metabolism and are constantly formed in the body as byproducts of cellular metabolism and as cellular regulators. ROS are removed by antioxidant defenses, substances that have the ability to significantly delay or prevent ROS oxidation of substrates. An excessive production of ROS can lead to oxidative stress and disease (Girotti, 1998). Production of ROS during tissue pathogenesis or in response to toxicants induces a complex series of downstream adaptive and reparative responses (Roberts et al., 2010). Several studies used biologic markers of oxidative stress to evaluate early changes in the body's protection against oxidation (Amirkhizi, Siassi, Djalali, & Foroushani, 2010; Guldiken et al., 2009; Papageorgiou et al., 2005; Suresh, Annam, Pratibha, & Prasad, 2009). The total antioxidant capacity (TAC) biomarker was evaluated in 20 children with cancer at the time of diagnosis and during the first three cycles of chemotherapy and revealed significant decreases in TAC over time, suggesting an oxidative stress additive effect that could impact response to treatment, disease course, and prognosis (Papageorgiou et al., 2005). In a study of 13 children with leukemia and various solid tumors, TAC was impaired in both groups; however, higher oxidative stress occurred in the leukemia group (Mazor, Abucoider, Meyerstein, & Kapelushnik, 2008).

Growing evidence shows that alkylating agents and antimetabolites (common pediatric leukemia chemotherapy drugs) increase production of ROS (Mazor et al., 2008). Methotrexate decreases the effectiveness of antioxidant defense systems resulting in an increase in oxidative stress. Methotrexate-induced oxidative stress has been observed in tumor tissue, HeLa cell cultures, the brains of rats, and children with acute lymphoblastic leukemia (ALL) (Genestier, Paillot, Quemeneur, Izeradjene, & Revillard, 2000; Oktem et al., 2006; Rajamani, Muthuvel, Senthilvelan, & Sheeladevi; 2006; Rouse, Nwokedi, Woodliffe, Epstein, & Klimberg, 1995; Sener et al., 2006; Servitja, Masgrau, Pardo, Sarri, & Picatoste, 2000). The brain is particularly vulnerable to oxidative stress because of limited antioxidant capacity, higher energy requirements, and higher amounts of lipids (Adibhatia & Hatcher, 2008; Dringen, 2000; Floyd & Hensley, 2002). Glycerophospholipids are a class of lipids that are critically important for the integrity of

cellular membranes, and oxidative stress-induced production of lipid peroxides and their byproducts leads to the loss of membrane functions and integrity (Chauhan & Chauhan, 2006). Phosphatidylcholine (PC) is the most prevalent glycerophospholipid in cell membranes and brain tissue. Oxidized lipids are known to play a crucial role in human inflammatory diseases, and oxidized PC has been established as a marker for neuroinflammation in multiple sclerosis (Qin, Goswami, Balabanov, & Dawson, 2007). To date, no studies have evaluated oxidative stress biomarkers in relation to symptom frequency, severity, and distress among pediatric patients with cancer. The current study measured changes in cerebrospinal fluid (CSF) levels of oxidized PC during the course of ALL treatment and explored the association with the symptom experience.

Conceptual Model

Dynamic models are needed to explain the complexities of symptoms during cancer treatment (Stenzel et al., 2010; Xiao, 2010). The oxidative stress pathway is dynamic and interactive and may result in significant cellular damage and toxicity (Girotti, 1998; Roberts et al., 2010). The conceptual framework for this study (see Figure 1) identifies the oxidative stress response to leukemia treatment, the subsequent increase in oxidized PC, and the influence in number and severity of symptoms during childhood cancer therapy. Chemotherapy agents commonly used for childhood leukemia (e.g., methotrexate) can increase ROS production as a result of altered folate metabolism and decreased antioxidant enzyme production (Girotti, 1998; Miaskowski et al., 2004; Roberts et al., 2010).

Methods

Design

The study used a prospective, longitudinal design to evaluate symptom severity along six time periods (T1–T6) during the induction, postinduction, and continuation phases of leukemia treatment. The study also evaluated the association between CSF levels of oxidized PC with symptom occurrence, severity, and distress. This research design provides a unique opportunity to characterize symptoms and identify patients who are more likely to experience adverse symptom trajectories during treatment for leukemia. To the authors' knowledge, this is the first study to examine the oxidative stress pathway and its influence on the symptom trajectory during treatment for childhood leukemia.

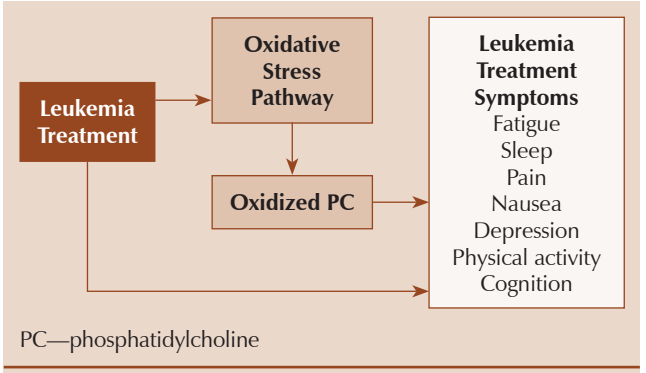

Figure 1. Oxidative Stress Pathway and Symptoms

Setting and Sample

The sample included 36 children newly diagnosed with acute lymphoblastic leukemia (ALL) who were participating in a National Institute of Nursing Research–funded study, "Childhood Leukemia and Oxidative Stress: Cognitive Changes and Academic Outcomes." Participants enrolled in the oxidative stress study were recruited to complete symptom assessments at six time points during the first 16 months of leukemia treatment. CSF collection occurred with each therapeutic lumbar puncture for the larger study. Participants were from two cancer centers in the southwestern United States. Each of the centers' institutional review boards approved the study, and both parent and patient consent were obtained for the addition of symptom assessments to the larger funded study. Children were eligible for the study if they were diagnosed with pre-B cell ALL or T cell ALL, were treated according to the Children's Oncology Group Protocols, were aged 3–15 years (the most common time period for ALL presentation) at the time of diagnosis, and spoke English. Children with a preexisting medical history of neurologic disorders (i.e., seizures), psychiatric disorders, or a traumatic brain injury associated with an alteration of consciousness were excluded. Children with a developmental disability, such as Down Syndrome, also were excluded.

Children with ALL receive chemotherapy in three phases—induction, postinduction, and continuation therapy. Induction therapy, which lasts one month, included weekly treatment with vincristine and daunomycin (for high-risk ALL), a corticosteroid, and a dose of PEG-asparaginase, and two intrathecal methotrexate (IT MTX) treatments on days 1 and 29. Children with ALL received central nervous system prophylaxis with standardized doses of IT MTX based on age: 8 mg for children aged 1 year, 10 mg for children aged 2 years, 12 mg for children aged 3–8 years, and 15 mg for children aged 9 years or older. Postinduction therapy, which lasts 6–8 months, involved several courses of treatment that included asparaginase, high- or intermediate-dose IV MTX (depending on ALL protocol assignment),

Table 1. Sample Characteristics (N = 36)			
Characteristic	**X̄**	**SD**	**Range**
Age at diagnosis (years)	7.36	3.6	3.37–14.74
Characteristic			**n**
Gender			
Male			17
Female			19
Ethnicity			
Caucasian			16
Hispanic			15
African American			2
Native American			1
Other			2

vincristine, doxorubicin, corticosteroid, cytarabine, mercaptopurine, and IT MTX. Continuation therapy, which lasts 2–3 years, consisted of daily mercaptopurine and weekly oral MTX, with monthly infusions of vincristine and a corticosteroid, and an IT MTX treatment every 12 weeks.

Measurement Variables and Instruments

Symptom occurrence, severity, and distress were measured with the **Memorial Symptom Assessment Scale** (**MSAS 10-18**). The MSAS 10-18 questionnaire was used for all participants in the study to maintain consistency with symptom assessments. MSAS 10-18 was chosen because, unlike the MSAS 7-12, which queries only eight symptoms and provides minimal information about symptom severity and distress, the MSAS 10-18 assesses 30 symptoms evaluating occurrence, severity, and distress for each symptom. Children aged 7–9 years completed the MSAS 10-18 with a parent or research assistant available for assistance, if needed; however, none experienced difficulties completing the questionnaire. Parents served as the proxy for completing the scale with children younger than seven years of age.

If the patient was younger than 7 years at time of first assessment, and then turned 7 during the study period, the parents continued to complete the MSAS at each assessment. The MSAS has excellent reliability and validity (Collins et al., 2000; Portenoy et al., 1994). Collins et al. (2000) reported strong agreement between child and parent report ($p < 0.05$) for most of the symptoms on the MSAS.

CSF was obtained as part of the oxidative stress study during scheduled therapeutic lumbar punctures performed during the 16 months when symptoms were assessed. CSF (3 ml) was required for the oxidative stress studies and did not require additional CSF to be removed because an adequate volume of CSF must be removed prior to instillation of the chemotherapy (5–6 ml). CSF samples were centrifuged at 3,000 rpm for 10 minutes at 4°C to remove debris, and then stored at -80°C until assayed.

Glycerophospholipids were extracted from CSF samples using a modified method developed by Folch, Lees, and Sloane Stanley (1957). Lipids were extracted from the aqueous CSF with a chloroform:methanol extraction procedure, vortexed for one minute, and centrifuged at 10,000 rpm for 20 minutes. The organic phase was collected and stored on ice. A second extraction was done to ensure complete recovery of the less polar phospholipids. The organic fractions were combined, evaporated to dryness under nitrogen, and resuspended in hexane-isopropanol. This method recovers 98% of phospholipids, which then can be separated by high-performance liquid chromatography (HPLC).

Mawatari and Murakami (1998) developed an HPLC method for detecting peroxidation of phospholipids in a single elution. HPLC is the method of choice for the analysis of a wide variety of compounds. This is accomplished by injection of a small amount of liquid sample into a moving stream of liquid (mobile phase) that passes through a stationary phase column. Separation of a mixture into its components and, therefore, its retention time on the column, depends on its reaction with the mobile and stationary phase. In the resulting

Table 2. Symptom Frequency, Severity, and Distress			
Classification	**X̄**	**SD**	**Range**
Symptom total*[a]			
Time 1	9.5	4.2	1–16
Time 2	9.82	5.1	2–19
Time 3	8.54	4.6	0–18
Time 4	6.96	4.8	0–20
Time 5	6.61	3.8	1–14
Time 6	5.39	3.3	0–11
Symptom severity[b]			
Time 1	1.57	0.4	1–2.29
Time 2	1.65	0.4	1–2.64
Time 3	1.79	0.5	1–3
Time 4	1.61	0.6	1–3
Time 5	1.55	0.4	1–2.8
Time 6	1.51	0.5	1–2.9
Symptom distress*[c]			
Time 1	1.01	0.6	0–3.21
Time 2	1.17	0.8	0–2.64
Time 3	1.17	0.9	0–3.07
Time 4	1.02	0.9	0–3.4
Time 5	0.92	0.9	0–3
Time 6	0.98	0.7	0–2.9

* $p < 0.001$; ** $p = 0.13$; *** $p = 0.57$
[a] $F(5,135) = 6.76$
[b] $F(5,120) = 1.76$
[c] $F(5,120) = 0.78$

Table 3. Symptom Frequency Rates[a] Over Time

	Induction	Postinduction		Continuation		
Symptom	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
Hair loss	78.6	67.9	64.3	32.1	28.6	10.7
Lack of energy	64.3	57.1	46.4	39.3	32.1	28.6
Pain	60.7	42.9	35.7	32.1	32.1	32.1
Feelings of being irritable	57.1	50	60.7	46.4	32.1	35.7
Sweats	53.6	21.4	25	25	21.4	28.6
Feelings of sadness	50	28.6	25	28.6	25	14.3
Changes in taste	46.4	57.1	42.9	42.9	28.6	14.3
Feeling drowsy	42.9	32.1	21.4	28.6	25	14.3
Nausea	35.7	71.4	42.9	39.3	35.7	21.4
Feeling nervous	32.1	35.7	42.9	39.3	35.7	21.4
Changes in skin	32.1	21.4	32.1	17.9	14.3	10.7
Cough	28.6	35.7	39.3	28.6	60.7	67.9
Difficulty sleeping	28.6	21.4	28.6	35.7	25	32.1
Shortness of breath	28.6	21.4	10.7	7.1	7.1	7.1
Itching	28.6	28.6	21.4	17.9	21.4	14.3
Weight loss	28.6	53.6	25	21.4	14.3	3.6
Constipation	28.6	21.4	21.4	14.3	17.9	3.6
Vomiting	25	46.4	21.4	17.9	17.9	14.3
Diarrhea	25	28.6	14.3	10.7	7.1	7.1
Lack of appetite	25	67.9	35.7	39.3	39.3	53.6
Mouth sores	25	35.7	28.6	17.9	–	10.7
"I don't look like myself."	25	21.4	21.4	14.3	10.7	–
Difficulty concentrating	21.4	35.7	42.9	42.9	50	39.3
Worrying	17.9	25	28.6	7.1	14.3	28.6

[a] Given as percentages

chromatogram, the area under a peak (peak area count) is a measure of the concentration of the compound it represents. This area value is integrated and calculated automatically by the computer data station.

The current study's researchers modified Mawatari and Murakami's (1998) method to optimize detection using normal-phase HPLC for separation of phospholipid classes by polarity. Oxidized and unoxidized glycerophospholipids absorb UV light at different wavelengths, but can be monitored simultaneously. Standards and CSF extracts were separated by normal phase HPLC using a Model 126 Solvent System and 168 Diode Array Detector with a silica column (Ultrasphere Si-5). The mobile phase in a gradient system changes over time in the amount of water present in the system, run at a constant flow rate and specified time, returning to its original composition. Unoxidized PC standard was used to determine retention time because this is the same for both unoxidized and oxidized PC. Results are reported in peak area.

Procedure

Parents of potential participants who were currently enrolled in the oxidative stress study and children who were old enough to give assent (aged 6 years or older) were introduced to the study by the clinical pediatric oncologist or nurse practitioner responsible for the child's care. If interested in participation, the principal investigator (PI) or the PI's research staff provided a detailed description of the symptom study and answered questions. Written consent was obtained from the parent and assent from the child (within his or her level of understanding) prior to study participation.

Children aged older than seven (n = 18) and parents for children younger than seven (n = 18) completed symptom assessments during routine follow-up clinic visits. Symptom assessments occurred at six time periods during the first 16 months of leukemia treatment (average of 45, 142, 241, 338, 424, and 510 days from diagnosis, respectively), spanning induction, postinduction, and continuation therapy.

Data Analysis

All data were analyzed using SPSS®, version 20. Descriptive statistics were used to summarize sample characteristics and symptom occurrence and severity. General linear model (GLM) for repeated measures analysis of variance (ANOVA) was used to test for significant differences in symptom occurrence, distress, and severity across the assessment time period. Pearson correlation was used to determine the association between oxidized PC and symptom occurrence, distress, and severity during induction, postinduction, and continuation therapy.

Results

Demographic and clinical characteristics of the participants are found in Table 1. Completed data from all 36 participants were available for the first four time points, data from 33 participants were available for the first five time points, and measures on 28 participants existed for all six time points. Missing data for the last time point is because of participant removal from the study for clinical reasons or loss to follow-up. To assess the limitations of using a proxy report for children aged younger than seven years for the MSAS, results from the parent proxy reports were compared with the self-report from the younger children using a two-sample t test. Results were similar at all times points for total number of symptoms, symptom severity, and symptom distress, except for two measures. At T1 ($t = 2.045$, $p = 0.048$) the mean score for total number of symptoms was higher for proxy compared to the self-report, and mean symptom severity at T4 ($t = –0.2311$, $p = 0.028$) was higher in the self-report group versus proxy.

Descriptive statistics for symptoms, severity, and distress experienced during the six time points are found in Table 2. The most frequently reported symptoms during all six time periods, occurring in at least 25% of the children, included lack of energy, pain, being irritable, feeling nervous, cough, and lack of appetite (see Table 3). Immediately after induction (T1), 11 symptoms were reported in more than 30% of the children. In addition, hair loss, lack of energy, pain, irritability, sweats, and sadness occurred in greater than 50% of these children. At T2, 14 symptoms were reported in more than 30% of the children. Nine symptoms observed in children at T2 had increased in frequency compared to T1, including nausea, lack of appetite, changes in food taste, weight loss, vomiting, mouth sores, nervousness, difficulty concentrating, and cough. During the next three assessments (T3–T5), the number of symptoms experienced by more than 30% of the children decreased from 11 to 10 and then to 8 symptoms, respectively. Four symptoms were observed more frequently at T3 when compared to the previous two assessments, including irritability, nervousness, difficulty concentrating, and cough. At T4, difficulty sleeping occurred more frequently than during the previous three assessments. At T5, difficulty concentrating and cough occurred more frequently than at other assessments.

At the last assessment (T6), six symptoms were experienced by more than 30% of the children. These symptoms included cough, lack of appetite, difficulty concentrating, irritability, difficulty sleeping, and pain. At this last symptom assessment, five symptoms (difficulty sleeping, lack of appetite, cough, difficulty concentrating, and worrying) were reported even more frequently than at the first symptom assessment after induction therapy.

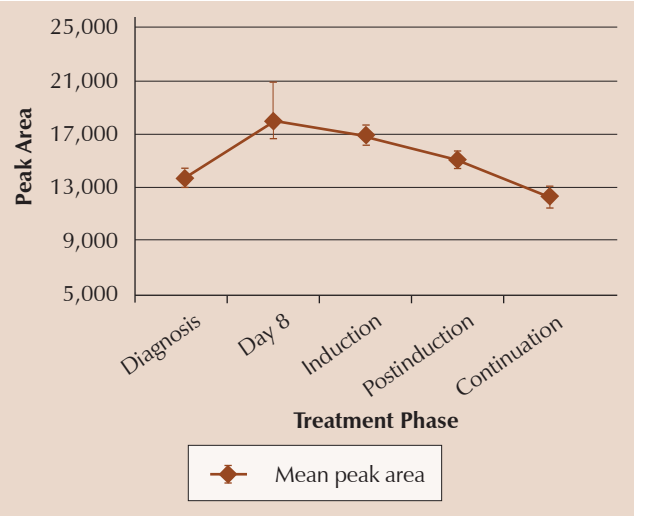

Figure 2. Oxidized Phosphatidylcholine Peak Area

Symptom severity scores ranged from "slight" to "severe," with mean scores remaining within the "slight" category during the six time periods. The highest severity score ranges occurred during T3 and T4. Symptom distress scores ranged between "a little bit" to "quite a bit," with mean scores remaining in the "a little bit" category during the six time periods. The highest distress score ranges occurred during T2 and T3.

Significant decreases in symptom occurrence were noted across time. Results from the GLM Repeated Measures ANOVA showed a significant difference in the mean number of symptoms across the six time periods for symptom assessment ($F[5,135] = 6.76$; $p < 0.001$). Tests of within-participant contrasts showed significant differences in the number of symptoms from T1–T3 than at T6. Mean symptom severity scores ranged from 1.81 (SD = 0.5) at T3 (postinduction) to 1.55 (SD = 0.48) at T6 (continuation). Results from the GLM Repeated Measures ANOVA showed no significant effect of time ($F[5, 120] = 1.76$; $p = 0.127$) for mean symptom severity scores. Mean ratings on symptom distress ranged from 1.17 (SD = 0.88) at T2 (induction) to 0.92 (SD = 0.89) at T5 (continuation). No significant difference existed in symptom distress ratings across time ($F[5, 120] = 0.78$; $p = 0.568$).

Results from GLM one-way ANOVA showed a significant change in oxidized PC peak area over time ($F[2.319, 6.193]$; $p = 0.003$) (see Figure 2). Tests of within-participant contrasts showed that oxidized PC peak area was significantly greater at day 8, induction, and postinduction compared to peak area at diagnosis.

Table 4 summarizes oxidized PC correlations with symptom measures. Mean oxidized PC peak area at diagnosis was significantly correlated with total symptoms and symptom distress at T1. Mean and highest oxidized PC peak areas during induction also were

Table 4. Oxidized Phosphatidylcholine (PC) Correlations With Symptom Data[a]

	Time 1			Time 2	Time 3		
Oxidized PC	Total Symptoms	Symptom Distress	Symptom Severity	Total Symptoms	Total Symptoms	Symptom Distress	Symptom Severity
Diagnosis	r = 0.359 p = 0.046	r = 0.479 p= 0.01	r = 0.323 p = 0.066	–	–	–	–
Mean induction	NS	r = 0.521 p = 0.003	r = 0.446 p = 0.01	–	–	–	–
Highest induction	NS	r = 0.489 p = 0.005	r = 0.458 p = 0.008	–	–	–	–
Mean postinduction	–	–	–	r = 0.328 p = 0.047	–	–	–
Mean continuation	–	–	–	–	r = 0.482 p = 0.021	r = 0.445 p = 0.032	r = 0.409 p = 0.046
Highest continuation	–	–	–	r = 0.518 p = 0.014	–	–	–

[a] One-tailed test
NS—not significant

significantly correlated with T1 symptom distress and symptom severity. Mean oxidized PC peak area during postinduction and highest oxidized PC peak area during continuation were significantly correlated with total symptoms at T2. Finally, mean oxidized PC peak area was significantly correlated with T3 total symptoms, symptom distress, and symptom severity.

Discussion

Childhood leukemia survival rates have greatly increased over the last three decades. However, symptoms experienced during treatment often result in complications that may compromise therapy, negatively influence quality of life, and, even more notably, jeopardize chances for long-term survival. This study was designed to provide perspective on the symptom trajectory experienced during the first 16 months of childhood leukemia treatment. Study findings support the previous work of other symptom researchers (Gibson, Garnett, et al., 2005; Gibson, Mulhall, et al., 2005; Hinds et al., 2007; Hockenberry et al., 2003, 2010; Hockenberry-Eaton et al., 1998; Yeh, Chiang, Chien, et al., 2008; Yeh, Chiang, Lin, et al., 2008), with similar symptoms (i.e., lack of energy, pain, irritability, nausea, nervousness, lack of appetite, and difficulty concentrating) being reported in greater than 30% of the children at five of the six time periods assessed. Baggott et al. (2010) explored changes in symptom occurrence and severity in 66 children during one cancer chemotherapy cycle, with more than 30% of their sample experiencing 10 or more symptoms at all measured time points. Multiple symptoms also were observed in 39 hospitalized children with cancer; nausea, pain, and fatigue were the most prevalent symptoms experienced during one hospital stay (Miller, Jacob, & Hockenberry, 2011). This study supports those findings and enhances the understanding of the childhood leukemia treatment symptom trajectory throughout ALL therapy.

During induction (T1), children experienced numerous symptoms that are known side effects of leukemia treatment; for example, steroids are associated with sweats, irritability, lack of energy, and feelings of sadness. Hair loss occurs in most children during induction because of the use of vincristine and, for many, the addition of an anthracycline. Interestingly, children tolerated these symptoms well. During postinduction (T2 and T3), the most intense time of leukemia treatment, children experienced numerous gastrointestinal symptoms often associated with chemotherapeutic agents administered during this time. During postinduction, the highest distress and severity scores occurred, which confirms the intensity of therapy given during this time. Interestingly, difficulty concentrating was frequently observed during T2–T6, with nervousness and irritability also commonly experienced.

The continuation phase of treatment, with intermittent courses of vincristine and prednisone or dexamethasone, most likely contributed to the prevalence of emotional symptoms and supports the need for continued assessment and attention to the child's psychological well-being throughout treatment. This last phase of treatment is a time when children with leukemia have returned to "normal" activities of daily living and limited attention is focused on symptom

experiences. Symptoms continue to be experienced after the most intensive phase of therapy (post-induction) is completed. With five symptoms (i.e., difficulty sleeping, lack of appetite, cough, difficulty concentrating, and worrying) observed more frequently at T6 than at T1, increased awareness occurs showing that the symptom trajectory continues throughout leukemia treatment, regardless of the phase of therapy. Cough was a frequently observed symptom and increased considerably during T5 and T6. Why this symptom occurred so often is unclear, and more attention is needed to evaluate this finding in the future.

This study examined the influence of the oxidative stress pathway, measured by oxidized PC, on symptom occurrence, severity, and distress during the six time points. Oxidized PC, a biomarker of oxidative stress, significantly correlated with the symptom occurrence and severity at diagnosis and during induction, postinduction, and continuation treatment phases. Leukemia cells are known to induce oxidative stress, and the elevated oxidized PC levels at diagnosis found in this study demonstrate this effect. Growing evidence shows that cancer cells produce high levels of ROS and are constantly under oxidative stress (Battisti et al., 2008; Hileman et al., 2004).

Children with highest CSF concentrations of oxidized PC experienced symptoms that were more frequent and severe, particularly during postinduction. Postinduction therapy includes several courses of treatment (depending upon the treatment arm), and common agents include asparaginase, methotrexate, vincristine, doxorubicin, corticosteroids, cytarabine, mercaptopurine, and IT MTX.

Findings in this study contribute to the evidence that pediatric leukemia chemotherapy drugs can trigger ROS production as byproducts of cellular destruction (Mazor et al., 2008). Oxidative metabolism is the body's first line of defense against environmental attack (Roberts et al., 2010). The oxidative stress pathway is interactive and may result in significant cellular damage and toxicity. The current study's findings add to the evidence that activation of the oxidative stress pathway can induce numerous somatic symptoms that include fatigue, depression, pain, muscle aches, flu-like malaise, as well as memory and concentration difficulties (Baggott et al., 2010; Leonard & Maes, 2012; Maes, 2011). As oxidative stress biologic markers continue to be identified and described, it may be possible to determine individual susceptibility to oxidative stress and its influence on clinical outcomes and symptom severity.

Limitations

This study used a small sample size from two large childhood cancer centers. The data were collected for only the first 16 months of therapy and explored only one biomarker, oxidized PC, as a measure of oxidative stress. The use of the MSAS 10-18 in children aged 7–9 years has not been validated. Children completed the questionnaire without difficulty and with the assistance of a parent or research assistant. Because the MSAS 10-18 is more comprehensive than the eight-item MSAS 7-12 version, future research on its use in younger children would be of benefit. Parent proxy was used for children aged younger than seven years and may be less reliable for symptoms that are less readily observed (e.g., difficulty concentrating, lack of energy, nervousness).

Knowledge Translation

Children with leukemia experience symptoms throughout treatment.

Physiologic measures indicate the influence of the oxidative stress pathway on symptom occurrence, severity, and distress.

As oxidative stress biologic markers continue to develop, individual susceptibility to oxidative stress can be determined.

Nursing Implications

Study findings provide important information for nurses, which confirm that the symptom trajectory continues throughout childhood leukemia treatment, regardless of the phase of therapy. Although symptom identification is most evident to nurses during the early phases of treatment (induction and postinduction), the current study confirms that children continue to experience symptoms even during the last phase of treatment. Nurses involved in the care of children in remission for leukemia must be aware of the importance of continuing symptom assessment during clinic visits when the child may appear asymptomatic and healthy.

Symptom trajectory experiences throughout childhood leukemia treatment are emphasized further by elevated oxidized PC levels occurring within each treatment phase. This biomarker of oxidative stress can be elevated by cancer cells that produce high levels of ROS, as well as by the chemotherapy agents given to treat the disease. Nurses should become more knowledgeable of the role oxidative stress biologic markers may play in determining a child's unique susceptibility to oxidative stress and its influence on clinical outcomes and symptom severity. As treatment for childhood leukemia continues to improve, measures for optimizing cure while minimizing treatment toxicities will become more critical. The use of biomarkers such as oxidized PC may assist in symptom severity assessment in the future.

Conclusion

To the authors' knowledge, this study is the first to report that children with leukemia continue to experience symptoms during all phases of leukemia treatment. Physiologic measures indicate the influence of the oxidative stress pathway on symptom occurrence, severity, and distress during the postinduction and continuation phases of therapy. Findings suggest that continued assessment must occur throughout leukemia treatment. Future studies should focus on symptom interventions during specific phases of leukemia therapy.

Marilyn J. Hockenberry, PhD, RN, PPCNP, FAAN, is a Bessie Baker Professor in the School of Nursing at Duke University in Durham, NC; Olga A. Taylor, MPH, is a senior research coordinator in the College of Medicine at Baylor University in Houston, TX; Alice Pasvogel, PhD, is an assistant research scientist in the College of Nursing at the University of Arizona in Tucson; Cheryl Rodgers, PhD, RN, CPNP, is an assistant professor in the School of Nursing at Duke University; Kathy McCarthy, BSN, RN, is a senior research nurse in the College of Medicine at Baylor University; Patricia Gundy, MS, is a senior research specialist and David W. Montgomery, PhD, is a research professor, both in the College of Nursing at the University of Arizona; Phillip Ribbeck is a student intern in the College of Medicine at Baylor University; Michael E. Scheurer, PhD, MPH, is an associate professor and director of the epidemiology center at Texas Children's Cancer and Hematology Centers and director of the Population Sciences Biorepository in the College of Medicine at Baylor University; and Ida M. (Ki) Moore, PhD, RN, FAAN, is a professor and director of the Biobehavioral Health Science Division in the College of Nursing at the University of Arizona. This research was supported, in part, by a grant from the National Institute of Nursing Research (No. R01NR010889). Hockenberry can be reached at marilyn.hockenberry@duke.edu, with copy to editor at ONFEditor@ons.org. (Submitted September 2013. Accepted for publication December 11, 2013.)

References

Adibhatia, R.M., & Hatcher, J.F., (2008). Phospholipase A2, reactive oxygen species, and lipid peroxidation in CNS pathologies. *Biochemistry and Molecular Biology Report, 41,* 560–567.

Amirkhizi, F., Siassi, F., Djalali, M., & Foroushani, A.R. (2010). Evaluation of oxidative stress and total antioxidant capacity in women with general and abdominal adiposity. *Obesity Research and Clinical Practice, 4,* e209–e216.

Atay, S. (2011). Symptom characteristics and clustering in children and adolescents undergoing or being off cancer chemotherapy. *Journal of Balkan Union of Oncology, 16,* 751–758.

Atay, S., Conk, Z., & Bahar, Z. (2012). Identifying symptom clusters in paediatric cancer patients using the Memorial Symptom Assessment Scale. *European Journal of Cancer Care, 21,* 460–468. doi:10.1111/j.1365-2354.2012.01324.x

Baggott, C., Dodd, M., Kennedy, C., Marina, N., Matthay, K.K., Cooper, B.A., & Miaskowski, C. (2010). Changes in children's reports of symptom occurrence and severity during a course of myelosuppressive chemotherapy. *Journal of Pediatric Oncology Nursing, 27,* 307–315. doi:10.1177/1043454210377619

Battisti, V., Maders, L.D., Bagatini, M.D., Santos, K.F., Spanevello, R.M., Maldonado P.A., . . . Morsch, V.M. (2008). Measurement of oxidative stress and antioxidant status in acute lymphoblastic leukemia patients. *Clinical Biochemistry, 41,* 511–518.

Chauhan, A., & Chauhan, V. (2006). Oxidative stress in autism. *Pathophysiology, 13,* 171–181.

Chen, M.L., & Tseng, H.C. (2006). Symptom clusters in cancer patients. *Supportive Care in Cancer, 14,* 825–830.

Collins, J.J., Byrnes, M.E., Dunkel, I.J., Lapin, J., Nadel, T., Thaler, H.T., . . . Portenoy, R.K. (2000). The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management, 19,* 363–377.

Dodd, M.J., Miaskowski, C., & Lee, K.A. (2004). Occurrence of symptom clusters. *Journal of the National Cancer Institute. Monographs, 32,* 76–78.

Dringen, R. (2000). Metabolism and functions of glutathione in brain. *Progress in Neurobiology, 62,* 649–671.

Floyd, R.A., & Hensley, K. (2002). Oxidative stress in brain aging: Implications for therapeutics of neurodegenerative diseases. *Neurobiology of Aging, 23,* 795–807.

Folch, J., Lees, M., & Sloane Stanley, G.H. (1957). A simple method for the isolation and purification of total lipids from animal tissues. *Journal of Biological Chemistry, 225,* 497–509.

Genestier, L., Paillot, R., Quemeneur, L., Izeradjene, K., & Revillard, J.P. (2000). Mechanisms of action of methotrexate. *Immunopharmacology, 47,* 247–257.

Gibson, F., Garnett, M., Richardson, A., Edwards, T., & Sepion, B. (2005). Heavy to carry: A survey of parents' and healthcare professionals' perceptions of cancer-related fatigue in children and young people. *Cancer Nursing, 28,* 27–35.

Gibson, F., Mulhall, A.B., Richardson, A., Edwards, J.L., Ream, E., & Sepion, B.J. (2005). A phenomenologic study of fatigue in adolescents receiving treatment for cancer. *Oncology Nursing Forum, 32,* 651–660 doi:10.1188/05.ONF.651-660

Girotti, A.W. (1998). Lipid hydroperoxide generation, turnover, and effector action in biological systems. *Journal of Lipid Research, 39,* 1529–1542.

Guldiken, B., Demir, M., Guldiken, S., Turgut, N., Turgut, B., & Tugrul A. (2009). Oxidative stress and total antioxidant capacity in diabetic and nondiabetic acute ischemic stroke patients. *Clinical and Applied Thrombosis/Hemostasis, 15,* 695–700. doi:10.1177/1076029608323087

Henly, S.J., Kallas, K.D., Klatt, C.M., & Swenson, K.K. (2003). The notion of time in symptom experiences. *Nursing Research, 52,* 410–417.

Hileman, E.O., Liu, J., Albitar, M., Keating, M.J., & Huang, P. (2004). Intrinsic oxidative stress in cancer cells: A biochemical basis for therapeutic selectivity. *Cancer Chemotherapy and Pharmacology, 53,* 209–219.

Hinds, P.S., Hockenberry, M.J., Gattuso, J.S., Srivastava, D.K., Tong, X., Jones, H., . . . Pui, C.H. (2007). Dexamethasone alters sleep and fatigue in pediatric patients with acute lymphoblastic leukemia. *Cancer, 110,* 2321–2330.

Hockenberry, M., Hooke, M.C., Gregurich, M., McCarthy, K., Sambuco, G., & Krull, K. (2010). Symptom clusters in children and adolescents receiving cisplatin, doxorubicin, or ifosfamide [Online exclusive]. *Oncology Nursing Forum, 37,* E16–E27. doi:10.1188/10.ONF.E16-E27

Hockenberry, M.J., Hinds, P.S., Barrera, P., Bryant, R., Adams-McNeill, J., Hooke, C., . . . Manteuffel, B. (2003). Three instruments to assess fatigue in children with cancer: The child, parent and staff perspectives. *Journal of Pain and Symptom Management, 25,* 319–328.

Hockenberry-Eaton, M., Hinds, P.S., Alcoser, P., O'Neill, J.B., Euell, K., Howard, V., . . . Taylor, J. (1998). Fatigue in children and adolescents with cancer. *Journal of Pediatric Oncology Nursing, 15,* 172–182.

Kestler, S.A., & LoBiondo-Wood, G. (2012). Review of symptom experiences in children and adolescents with cancer. *Cancer Nursing, 35,* E31–E48. doi:10.1097/NCC.0b013e3182207a2a

Kim, E., Jahan, T., Aouizerat, B.E., Dodd, M.J., Cooper, B.A., Paul, S.M., . . . Miaskowski, C. (2009). Changes in symptom clusters in patients undergoing radiation therapy. *Supportive Care in Cancer, 17,* 1383–1391.

Kim, H.J., McGuire, D.B., Tulman, L., & Barsevick, A.M. (2005).

Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing, 28,* 270–282.
Leonard, B., & Maes, M. (2012). Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neuroscience Biobehavioral Review, 36,* 764–785. doi:10.1016/j.neubiorev.2011.12.005
Maes, M. (2011). An intriguing and hitherto unexplained co-occurrence: Depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35,* 784–794.
Mawatari, S., & Murakami, K. (1998). Analysis of membrane phospholipid peroxidation by isocratic high-performance liquid chromatography with ultraviolet detection. *Annals of Biochemistry, 264,* 118–123.
Mazor, D., Abucoider, A., Meyerstein, N., & Kapelushnik, J. (2008). Antioxidant status in pediatric acute lymphocytic leukemia (ALL) and solid tumors: The impact of oxidative stress. *Pediatric Blood and Cancer, 51,* 613–615. doi:10.1002/pbc.21665
Miaskowski, C., Dodd, M., & Lee, K. (2004). Symptom clusters: The new frontier in symptom management research. *Journal of the National Cancer Institute. Monographs, 32,* 17–21.
Miller, E., Jacob, E., & Hockenberry, M.J. (2011). Nausea, pain, fatigue and multiple symptoms in hospitalized children with cancer [Online exclusive]. *Oncology Nursing Forum, 38,* E382–E393. doi:10.1188/11.ONF.E382-E393
Oktem, F., Yilmaz, H.R., Ozguner, F., Olgar, S., Ayata, A., Uzar, E., & Uz, E. (2006). Methotrexate-induced renal oxidative stress in rats: The role of a novel antioxidant caffeic acid phenethyl ester. *Toxicology and Industrial Health, 22,* 241–247.
Papageorgiou, M., Stiakaki, E., Dimitriou, H., Malliaraki, N., Notas, G., Castanas, E., & Kalmanti, M. (2005). Cancer chemotherapy reduces plasma total antioxidant capacity in children with malignancies. *Leukemia Research, 29,* 11–16.
Pierce, J.D., McCabe, S., White, N., & Clancy, R. (2012). Biomarkers: An important clinical assessment tool. *American Journal of Nursing, 112,* 52–58.
Portenoy, R.K., Thaler, H.T., Kornblith, A.B., Lepore, J.M., Friedlander-Klar, H., Kiyasu, E., . . . Scher, H. (1994). The Memorial Symptom Assesment Scale: An instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer, 30a,* 1326–1336.
Qin, J., Goswami, R., Balabanov, R., & Dawson, G. (2007). Oxidized phosphatidylcholine is a marker for neuroinflammation in multiple sclerosis brain. *Journal of Neuroscience Research, 85,* 977–984. doi:10.1002/jnr.21206
Rajamani, R., Muthuvel, A., Senthilvelan, M., & Sheeladevi, R. (2006). Oxidative stress induced by methotrexate alone and in the presence of methanol in discrete regions of the rodent brain, retina and optic nerve. *Toxicology Letters, 165,* 265–273.
Roberts, R.A., Smith, R.A., Safe, S., Szabo, C., Tjalkens, R., & Robertson, F.M. (2010). Toxicological and pathophysiological roles of reactive oxygen and nitrogen species. *Toxicology, 276,* 85–94. doi:10.1016/j.tox.2010.07.009
Rouse, K., Nwokedi, E., Woodliffe, J.E., Epstein, J., & Klimberg, V.S. (1995). Glutamine enhances selectivity of chemotherapy through changes in glutathione metabolism. *Annals of Surgery, 221,* 420–426.
Sener, G., Ekisioglu-Demiralp, E., Cetiner, M., Ercan, F., Sirvanci, S., Gedik, M., & Yegen, B.C. (2006). L-Carnatine ameliorates methotrexate-induced oxidative organ injury and inhibits leukocyte death. *Cell Biology and Toxicology, 22,* 47–60.
Servitja, J.M., Masgrau, R., Pardo, R., Sarri, E., & Picatoste, F. (2000). Effects of oxidative stress on phospholipid signaling in rat cultured astrocytes and brain slices. *Journal of Neurochemistry, 75,* 788–794. doi:10.1046/j.1471-4159.2000.0750788.x
Stenzel, S.L., Krull, K.R., Hockenberry, M., Jain, N., Kaemingk, K., Miketova, P., & Moore, I.M. (2010). Oxidative stress and neurobehavioral problems in pediatric acute lymphoblastic leukemia patients undergoing chemotherapy. *Journal of Pediatric Hematology/Oncology, 32,* 113–118. doi:10.1097/MPH.0b013e3181c9af84
Suresh, D.R., Annam, V., Pratibha, K., & Prasad, B.V. (2009). Total antioxidant capacity-a novel early bio chemical marker of oxidative stress in HIV infected individuals. *Journal of Biomedical Science, 16,* 61–65. doi:10.1186/1423-0127-16-61
Van Cleve, L., Muñoz, C.E., Savedra, M., Riggs, M., Bossert, E., Grant, M., & Adlard, K. (2012). Symptoms in children with advanced cancer. *Cancer Nursing, 35,* 115–125.
Woodgate, R., & Degner, L. (2003). Expectations and beliefs about children's cancer symptoms: Perspective of children with cancer and their families. *Oncology Nursing Forum, 30,* 479–491. doi:10.1188/03.ONF.479-491
Xiao, C. (2010). The state of science in the study of cancer symptom clusters. *European Journal of Oncology Nursing, 14,* 417–434. doi:10.1016/j.ejon.2010.05.011
Yeh, C.H., Chiang, Y.C., Chien, L.C., Lin, L., Yang, C.P., & Chuang, H.L. (2008). Symptom clustering in older Taiwanese children with cancer. *Oncology Nursing Forum, 35,* 273–281. doi:10.1188/08.ONF.273-281
Yeh, C.H., Chiang, Y.C., Lin, L., Yang, C.P., Chien, L.C., Weaver, M.A., & Chuang, H.L. (2008). Clinical factors associated with fatigue over time in paediatric oncology patients receiving chemotherapy. *British Journal of Cancer, 99,* 23–29. doi:10.1038/sj.bjc.6604434