Published in final edited form as:

Oncol Nurs Forum. 2014 July 1; 41(4): E238–E247. doi:10.1188/14.ONF.E238-E247.

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

Marilyn J. Hockenberry, PhD, RN, PNP, FAAN [Bessie Baker Professor],
Duke School of Nursing, Durham, NC

Olga A. Taylor, MPH [Senior Research Coordinator],
Baylor College of Medicine, Houston, TX

Alice Pasvogel, PhD [Assistant Research Scientist],
University of Arizona College of Nursing, Tucson, AZ

Cheryl Rodgers, PhD, RN, CPNP [Assistant Professor],
Duke School of Nursing, Durham, NC

Kathy McCarthy, BSN, RN [Senior Research Nurse],
Baylor College of Medicine, Houston TX

Patricia Gundy, MS [Senior Research Specialist],
University of Arizona College of Nursing, Tucson, AZ

David W. Montgomery, PhD [Research Professor],
University of Arizona College of Nursing and Research Service, Southern Arizona VA Health Care System, Tucson, AZ

Phillip Ribbeck [Student Intern],
Baylor College of Medicine, Houston, TX

Michael E. Scheurer, PhD, MPH [Associate Professor and Director], and
Epidemiology Center at Texas Children's Cancer & Hematology Centers, Director, Population Sciences Biorepository Baylor College of Medicine, Houston, TX

Ida M. (Ki) Moore, PhD, RN, FAAN [Professor and Director]
Biobehavioral Health Science Division University of Arizona College of Nursing, Tucson, AZ

Abstract

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 cerebral spinal fluid (CSF) concentration of oxidized phosphatidylcholine (PC), the predominant glycerophospholipid in the brain and cell membranes.

Design—Prospective longitudinal design.

Sample and Setting—Thirty-six children with newly diagnosed ALL between 2 years 9 months and 15 years of age at diagnosis 2 cancer centers in the Southwestern United States.

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.

Results—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 Practice—Children with leukemia experience symptoms throughout treatment. Physiologic measures indicate the influence of the oxidative stress on symptoms.

Keywords

children; cancer; symptom frequency, severity and distress; oxidative stress biomarkers

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 and can 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 has ended (Woodgate & Degner, 2003).

To date, most oncology symptom research focuses on describing single symptoms related to their occurrence, severity, and distress with limited effort 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 physiologic biomarkers may play in evaluating the severity of symptoms experienced by pediatric oncology patients (Pierce, McCabe, White, & Clancy, 2012). This study advances the understanding of childhood cancer treatment symptoms, their interactions, and changes in symptom severity over time, all critical aspects that must be incorporated into symptom research. Even more critical to understanding symptom experiences during childhood leukemia treatment is the need for exploration of “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 examine the influence of the oxidative stress pathway on symptom severity during the first 16 months of childhood leukemia treatment.

Review of Literature

Symptom Cluster Severity and Childhood Cancer Treatment

Symptom investigation in pediatric oncology is a relatively new area of exploration. Studies in 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 evaluated specific symptom trajectories in children with cancer. In a study of 144 older pediatric oncology patients treated in Taiwan, five symptom clusters were found; 1) sensory discomfort and body image, 2) circulatory and respiratory problems, 3) fatigue, sleep, and depression, 4) body image and eating difficulties, and 5) gastrointestinal irritation and pain (Yeh et al., 2008a). 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, and mood) and a depression clustered together and one week after chemotherapy; moderate to severe fatigue was noted in 46% of the sample while 6% had depression and 12.5% were “at risk” for depression. In another study, five clusters were identified in 164 children and adolescents receiving cancer chemotherapy; the most common symptoms being lack of appetite, nausea, feeling nervous and lack of energy (Atay, 2011; Atay, Conk & Bahar, 2012). The most distressing symptoms were nausea, hair loss, and vomiting.

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

Children and adolescents undergoing cancer treatment report frequent depression, 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 oncology patients indicated significant negative changes between periods on and off treatment (Hinds et al., 2007). In qualitative studies with children undergoing cancer treatment, patients were acutely aware of emotional changes that occurred during treatment (Gibson et al., 2005b; 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 were associated with significant decreases in HRQOL; children experienced on average, 10.6 symptoms (Baggott et al., 2010). The most common symptoms included lack of energy, pain, feeling drowsy, nausea, and feeling sad and irritable. In a survey of parents of cancer patients and health care professionals concerning cancer-related fatigue, 57% in each group reported fatigue as a frequent symptom (Gibson et al., 2005a). Pediatric patients experience more fatigue in the first few days after the start of a chemotherapy cycle (Yeh et al., 2008b). 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 et al., 2005b; 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 (Robertson et al., 2010). Reactive oxygen species (ROS) are produced as a by-product of oxidative metabolism. ROS are constantly formed in the body as by-products 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; Illingworth & Glover, 1971). Production of ROS during tissue pathogenesis or in response to toxicants induces a complex series of downstream adaptive and reparative responses (Robertson et al., 2010). Several studies used biological markers of oxidative stress to evaluate early changes in the body's protection against oxidation (Amirkhizi, Siassi, Djalali, & Foroushani, 2010; Papageorgiou et al., 2005; Guldiken et al., 2009; 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, Abucoider, Meyerstein, & Kapelushnik, 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, rat brain, and children with ALL (Genestier et al., 2000; Oktem et al., 2006; Rajamani, Muthuvel, Senthilvelan, & Sheeladevi, 2006; Rouse et al., 1995; Sener et al., 2006; Servitja et al., 2000). The brain is particularly vulnerable to oxidative stress due to 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 critically important for the integrity of cellular membranes (Bockkov et al., 2010), and oxidative stress-induced production of lipid peroxides and their by-products 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 known to be 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 the 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, Dodd, & Lee, 2004; Roberts et al., 2010).

Methodology

Design

The study used a prospective, longitudinal design to evaluate symptom severity over six time periods during induction, post-induction 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 clusters during treatment for leukemia. To the author's knowledge, it is the first study to examine the oxidative stress pathway and its influence on the symptom trajectory during childhood leukemia treatment.

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, "Childhood Leukemia and Oxidative Stress: Cognitive Changes and Academic Outcomes." Participants enrolled in the oxidative stress study were recruited to complete six symptom assessments 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 consent was obtained for the addition of symptom assessments to be included in the larger funded study. Children were eligible for the study if they were diagnosed with pre-B acute lymphoblastic leukemia (ALL) or T-cell ALL, were treated according to the Children's Oncology Group Protocols, were between 3 and 15 years of age (the most common time period for ALL presentation) at the time of diagnosis, and spoke English. Children with a pre-existing medical history of neurological 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, post-induction and continuation therapy. Induction therapy, which lasts 1 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 & 29. Children with ALL received central nervous system prophylaxis with standardized doses of IT MTX based on age: 8 mg for children aged 1–1.99 years, 10 mg for children aged 2–2.99 years, 12 mg for children aged 3–8.99 years, and 15 mg for children aged 9 years. Post-

induction therapy, which lasts 6–8 months, involved several courses of treatment that included asparaginase, high- or intermediate-dose intravenous (IV) MTX (depending on ALL protocol assignment), vincristine, doxorubicin, corticosteroid, cytarabine, and mercaptopurine. Continuation therapy, which lasts 2–3 years, consisted of daily mercaptopurine and weekly oral MTX, with monthly pulses 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, 200; 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. Three milliliters of CSF 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 to 6 milliliters). CSF samples were centrifuged at 3000 rpm for 10 min at 4°C to remove debris, and stored at –80°C until assayed.

Glycerophospholipids were extracted from CSF samples using a modified method developed by Folch and others (1957). Lipids were extracted from the aqueous CSF with a chloroform:methanol extraction procedure, vortexed for 1 minute, and centrifuged at 10,000 rpm for 20 minutes. The organic phase was collected and stored on ice. A second extraction of the aqueous phase to insure complete extraction 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 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 chromatic 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 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 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 subjects 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 7 (n=18) and parents for children younger than 7 (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, post-induction and during 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 6 symptom assessment time periods. Pearson correlation was used to determine the association between oxidized PC and symptom occurrence, distress and severity during induction, post-induction 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 time 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 over the six time points are found in Table 2. The most frequently reported symptoms during all 6 time periods, occurring in at least 25% of the children, included lack of energy, pain, being irritable, nausea, feeling nervous, cough, and lack of appetite. Immediately after induction (T1), 11 symptoms were reported in more than 30% of the children. In addition, hair loss, lack of energy, pain, being irritable, sweats and feeling of sadness occurred in 50% of these children. At T2, 14 symptoms were reported in over 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, feeling nervous, 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 to 8 symptoms, respectively. Four symptoms were observed more frequently at T3 when compared to the previous two assessments: being irritable, feeling nervous, 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, being irritable, 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.

Symptom severity scores ranged between “*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 over time. Results from the GLM Repeated Measures ANOVA showed a significant difference in the mean number of symptoms across the six symptom assessment time periods [$F(5, 135) = 6.76$; $p < .001$]. Tests of within-subject contrasts showed significant differences in the mean number of symptoms at T1-T3 than at T6. Mean symptom severity scores ranged from 1.81 ($SD = 0.50$) at T3 (post-induction) 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-subject contrasts showed that oxidized PC peak area was significantly greater at day 8, induction, and post-induction compared to peak area at diagnosis.

Table 4 summarizes oxidized PC peak area correlations with symptom measures. Mean oxidized PC peak area at diagnosis was significantly correlated with symptom measures. Mean and highest oxidized PC peak area during induction were also significantly correlated with T1 symptom distress and symptom severity. Mean oxidized PC peak area during post-induction 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 symptom, 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 et al., 2005a; Gibson et al., 2005b; Hinds et al., 2007; Hockenberry et al., 2010; Hockenberry et al., 2003; Hockenberry-Eaton et al., 1998; Yeh et al., 2008a; Yeh et al., 2008b) with similar symptoms (e.g., lack of energy, pain, being irritable, nausea, feeling nervous, lack of appetite, and difficulty concentrating) being reported in >30% of the children at 5 of the 6 time periods assessed. Baggott and colleagues (2010) explored changes in symptom occurrence and severity in 66 children followed over 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 & Hockenberry, 2011). This study supports these 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 due to vincristine and for many, the addition of an anthracycline. Interestingly, children tolerated these symptoms well. During post-induction (T2 and T3), the most intense time of leukemia treatment, children experienced numerous gastro-intestinal symptoms often associated with chemotherapeutic agents administered during this time. During post-induction the highest distress and severity score ranges occurred, which confirms the intensity of therapy given during this time. Interestingly, difficulty concentrating was

frequently observed during T2-6, 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 (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, post-induction, 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 (Battistti, et al, 2008; Hileman, et al, 2004).

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

Findings in this study contribute to the evidence that pediatric leukemia chemotherapy drugs can trigger ROS production as by-products of cellular destruction (Mazor, Abucoider, Meyerstein, & Kapelushnik, 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, and memory and concentration difficulties (Baggott et al., 2010; Leonard & Maes, 2012; Maes, 2011). As oxidative stress biological 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 larger childhood cancer centers. The data was 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).

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 author's 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 post-induction 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.

Acknowledgement

Funded in part by the National Institute of Nursing Research Institute (R01NR010889)

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Knowledge Translation

- Children with leukemia continue to experience symptoms throughout treatment.
- Physiologic measures indicate the influence of the oxidative stress pathway on symptom occurrence, severity and distress during the post-induction and continuation phases of therapy
- In the future, as oxidative stress biological markers continue to develop, it will be possible to determine individual susceptibility to oxidative stress and its influence on clinical outcomes and symptom severity.

Figure 1.
Oxidative Stress Pathway and Symptoms

Figure 2.
Oxidized PC Peak Area

Table 1

Demographic Characteristics of the Sample (N=36)

Age at diagnosis (years)	
Mean (SD)	7.36 (3.6)
Range	3.37-14.74
Gender	
Male	17 (47.2%)
Female	19 (52.8%)
Ethnicity	
Caucasian	16 (44.4%)
Hispanic	15 (41.7%)
African American	2 (5.6%)
Native American	1 (2.8%)
Other	2 (5.6%)

Table 2

Symptoms Frequency, Severity and Distress

Symptom Classification	Mean (SD) Range	Statistic
Symptom Total		F(5,135)=6.76; p<.001
T1	9.50 (4.2) 1-16	T1 > T6; p=.001 T2 > T6; p=.001 T3 > T6; p=.03
T2	9.82 (5.1) 2-19	
T3	8.54 (4.6) 0-18	
T4	6.96 (4.8) 0-20	
T5	6.61 (3.8) 1-14	
T6	5.39 (3.3) 0-11	
Symptom Severity		F(5,120)=1.76; p=.13
T1	1.57 (0.4) 1.00-2.29	
T2	1.65 (0.4) 1.00-2.64	
T3	1.79 (0.5) 1.00-3.00	
T4	1.61 (0.6) 1.00-3.00	
T5	1.55 (0.4) 1.00-2.80	
T6	1.51 (0.5) 1.00-2.90	
Symptom Distress		F(5,120)=0.78; p=.57
T1	1.01 (0.6) 0-3.21	
T2	1.17 (0.8) 0-2.64	
T3	1.17 (0.9) 0-3.07	
T4	1.02 (0.9) 0-3.40	
T5	0.92 (0.9) 0-3.00	
T6	0.98 (0.7) 0-2.90	

Table 3

Symptom Frequency Rates (%) Over Time

Symptom	T1 Induction	T2 Post Induction	T3 Post Induction	T4 Continuation	T5 Continuation	T6 Continuation
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
Feeling of sadness	50	28.6	25	28.6	25	14.3
Changes in the way food tastes	46.4	57.1	42.9	42.9	28.6	14.3
A feeling of being drowsy	42.9	32.1	21.4	28.6	25	14.3
Nausea or feeling like you could vomit	35.7	71.4	42.9	39.3	35.7	21.4
Feeling of being nervous	32.1	35.7	42.9	39.3	35.7	25
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, bowel movements are less often	28.6	21.4	21.4	14.3	17.9	3.6
Vomiting or throwing up	25	46.4	21.4	17.9	17.9	14.3
Diarrhea or loose bowel movement	25	28.6	14.3	10.7	7.1	7.1
Lack of appetite or not wanting to eat	25	67.9	35.7	39.3	39.3	53.6
Mouth sores	25	35.7	28.6	17.9	0	10.7
"I don't look like myself"	25	21.4	21.4	14.3	10.7	0
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

Table 4

Oxidized PC correlations with Symptom Data (1 tail test)

	Total Symptoms T1	Symptom Distress T1	Symptom Severity T1	Total Symptoms T2	Total Symptoms T3	Symptom Distress T3	Symptom Severity T3
Diagnosis Oxidized PC	r = 0.359 p = 0.046	r = 0.479 p = 0.010	r = 0.323 p = 0.066				
Mean Induction Oxidized PC	NS	r = 0.521 p = 0.003	r = 0.446 p = 0.010				
Highest Induction Oxidized PC	NS	r = 0.489 p = 0.005	r = 0.458 p = 0.008				
Mean Post induction Oxidized PC				r = 0.328 p = 0.047			
Mean Continuation Oxidized PC					r = 0.482 p = 0.021	r = 0.445 p = 0.032	r = 0.409 p = 0.046
Highest Continuation Oxidized PC				r = 0.518 p = 0.014			