Symptom Prevalence and Physiologic Biomarkers Among Adolescents Using a Mobile Phone Intervention Following Hematopoietic Stem Cell Transplantation

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Purpose/Objectives: To examine symptom reports and physiologic parameters in adolescents using the Eating After Transplant (EAT!) intervention during recovery after hematopoietic stem cell transplantation (HSCT).

Design: Repeated measures design.

Setting: HSCT service at a pediatric teaching institution in the southern United States.

Sample: 16 adolescents recovering from a first-time allogeneic HSCT.

Methods: Use of EAT! was monitored electronically, symptom reports were obtained from a questionnaire, and physiologic parameters were obtained from the medical record at HSCT hospital discharge and 20, 40, and 60 days postdischarge.

Main Research Variables: EAT! use, symptom prevalence, symptom-related distress, and physiologic parameters including weight, body mass index (BMI), pre-albumin, and albumin.

Findings: Symptom prevalence was highest at hospital discharge and steadily declined; however, mean symptom distress scores remained stable. Mean weight and BMI significantly declined during the first 60 days postdischarge; pre-albumin and albumin markers were unchanged. No correlation was noted among use of EAT! and any research variables.

Conclusions: The most frequent symptoms were not always the most distressing symptoms. Weight and BMI significantly declined during HSCT recovery.

Implications for Nursing: Nurses should assess symptom frequency and distress to fully understand patients' symptom experiences. Nurses should monitor weight and BMI throughout HSCT recovery.

Key Words: pediatric oncology; stem cell/marrow transplantation; quantitative nursing research

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Children undergoing hematopoietic stem cell transplantation (HSCT) have reported treatment-related symptoms as the worst part of their cancer experience. Those symptoms create difficulties with other life events and are remembered long after treatment ends (Enskar, Carlsson, Golsater, & Hamrin, 1997; Woodgate & Degner, 2003). Nausea, vomiting, fatigue, pain, anorexia, diarrhea, dry mouth, and taste changes develop immediately after HSCT and persist for months (Barker, Anderson, Sauve, & Butzner, 2005; Rodgers et al., 2008), increasing the need for medical care and negatively affecting patients' development, compliance to treatment, and quality of life (QOL) (Cohen et al., 2012; Erickson et al., 2013). The Eating After Transplant (EAT!) mobile phone application (app) was developed to provide descriptive information and useful strategies to adolescent patients regarding common symptoms and eating issues during the first 100 days post-HSCT (Rodgers, Krance, Street, & Hockenberry, 2013). To meet the expressed needs of patients recovering from HSCT to participate in self-care activities, manage their symptoms, and have available information delivered in a practical method (Larson, 1995), EAT! provides descriptions of common gastrointestinal (GI) problems and self-care strategies in an easily accessible format for mobile phones. The app has demonstrated acceptability and usability, and patients undergoing HSCT were immediately competent with the app following orientation (Rodgers et al., 2013). The current study extends those findings by assessing whether the EAT! app is associated with decreased symptom prevalence and distress or with improved biomarkers, thereby enhancing well-being.

Background

HSCT is a common treatment modality for pediatric illnesses, including a variety of malignancies, hematologic diseases, immunodeficiency disorders, and genetic disorders. About 1,200 allogeneic HSCTs are performed annually in the United States in children younger than age 18 years (National Marrow Donor

Program, 2012). A patient's health status can rapidly change throughout the first year following HSCT as a result of the aggressive treatment and related complications; however, the first 100 days following HSCT are associated with the most complications and QOL issues (Grant, Cooke, Bhatia, & Forman, 2005). Patients often struggle with a variety of physical and psychological symptoms during this time and attempt to learn ways to gain control and relieve uncertainty (Grant et al., 2005). Although children and adolescents have distinct developmental differences, reporting on one single age group is difficult because of the limited amount of age-specific HSCT research.

Symptoms

Four studies have described the physical symptom profile following HSCT among adult patients. During the first year following HSCT, 118 adults reported that tiredness, poor appetite, taste alterations, dry mouth, and nausea decreased in frequency but persisted throughout the year (Iestra, Fibbe, Zwinderman, van Staveren, & Kromhout, 2002). In addition, a majority of the patients (66%) reported eating difficulties at 50 days post-HSCT, and 22% at one year post-HSCT. Immediately before HSCT discharge and for two weeks following, 16 adult patients reported appetite loss, nausea, vomiting, diarrhea, and sleep disturbances as significantly affecting their QOL, and six of those patients reported ongoing symptoms, such as fatigue, affecting their QOL at six weeks postdischarge (Hacker & Ferrans, 2003). In Bevans, Mitchell, and Marden's (2008) study, 76 adults reported a high prevalence of fatigue, worry, anorexia, nausea and vomiting, pain, and insomnia throughout the first 100 days following HSCT. In addition, during the first 100 days after autologous or allogeneic HSCT, 164 adult patients reported physical weakness, sleep disturbance, lack of appetite, fatigue, and drowsiness as the most severe symptoms, with allogeneic HSCT associated with more severe symptoms than autologous HSCT (Cohen et al., 2012).

Pediatric populations have received less attention with only three studies evaluating prevalence and duration of symptoms during HSCT recovery. In the largest study, 132 children and adolescents reported that mucositis, vomiting, abdominal pain, and odynophagia were common at 100 days post-HSCT (Barker et al., 2005). A longitudinal cohort study of GI symptoms and anthropometric measurement changes in 35 children and adolescents through the first four months post-HSCT found lack of appetite, nausea, vomiting, diarrhea, dry mouth, and taste changes common throughout the study period (Rodgers et al., 2008). Finally, a qualitative study of 13 adolescents' eating experiences at 50 and 100 days post-HSCT described a slow return of the patients' appetites as well as eating barriers that consisted of nausea, vomiting, taste changes, dry mouth, and bad smells (Rodgers, Young, Hockenberry, Binder, & Symes, 2010). Missing from previous work among children and adolescents have been assessments of the multidimensional nature of symptoms that tap not only prevalence but also severity and distress (Erickson et al., 2013), findings that would empower healthcare providers to develop interventions that diminish symptoms and improve QOL (Reid, McKenna, Fitzsimons, & McCance, 2009).

Biomarkers

Given the symptom profile described, patients are at risk of impaired nutritional status. Nutritional well-being of patients post-HSCT has been measured relatively simply as body mass index (BMI) using height and weight, muscle mass, and fat tissue using mid-arm circumference and skinfold triceps measurements (Muscaritoli, Grieco, Capria, Iori, & Fanelli, 2002), bioelectrical impedance (Jaime-Pérez et al., 2013), or whole-body dual-energy x-ray absorptiometry (Kyle et al., 2005). Among adults in two studies, significant weight loss of 12 kg occurred between transplantation and engraftment (Jaime-Pérez et al., 2013), and significant lean BMI loss of 1 kg/m^2 and a body fat mass loss of 1.2 kg/m^2 occurred during six months that was not regained by one year post-HCST (Kyle et al., 2005), respectively. Children and adolescents experienced significant declines in weight, skinfold triceps measurement, and mid-arm circumference measurements from baseline to four months post-HSCT, illustrating a significant loss of muscle mass and fat tissue (Rodgers et al., 2008).

Laboratory measurements such as serum protein markers (albumin and pre-albumin) also have been used to assess patients' nutritional status following HSCT, with mixed findings. Jaime-Pérez et al. (2013) studied albumin levels between HSCT and engraftment in 77 adult patients and found no significant change. Uderzo et al. (1991) studied albumin and pre-albumin levels during total parenteral nutrition (TPN) supplementation after HSCT in 25 pediatric patients. Although albumin levels did not fluctuate, pre-albumin level showed a statistically significant rise about one week after starting TPN. Protein markers have not been studied longitudinally among adolescents during HSCT recovery.

Given the dearth of research on the symptom and biologic marker profiles of adolescent patients and the feasibility of the EAT! app as a symptom management intervention during recovery from HSCT, the current study used Symptom Management Theory (SMT) (Dodd et al., 2001) as a framework for testing two research questions: (a) What are the symptom prevalence, symptom-related distress, and biomarker profiles of adolescent patients at hospital discharge and 20, 40, and 60 days post-discharge following HSCT? and (b) Is the use of

Knowledge Translation

Adolescents experience multiple symptoms through recovery from hematopoietic stem cell transplantation (HSCT) that vary in frequency and distress.

Weight and body mass index can decline during the recovery period after HSCT and should be monitored closely.

Use of a mobile phone application for HSCT symptom management should be investigated further with a variety of outcome measures.

the EAT! app related to better or worse symptom experiences or nutrition status (weight, BMI, serum albumin, or serum pre-albumin) in the sample? The SMT states that with a full understanding of symptom experiences (research question 1), symptom management strategies can be used to create either positive or negative outcomes (research question 2) (Dodd et al., 2001).

Methods

The current study used a repeated measures design, as previously reported (Rodgers et al., 2013). Briefly, data were collected at four time points (initial HSCT hospital discharge and 20, 40, and 60 days post-hospital discharge) from September 2011 to September 2012 from patients within the HSCT service at Texas Children's Hospital in Houston. Sixteen consecutively discharged adolescents who were aged 11–18 years, English-speaking, and discharged within 50 days of a first-time allogeneic HSCT, participated. Adolescents who received an autologous HSCT or a repeat allogeneic HSCT or had neurologic or developmental delays were excluded. The study was approved by the institutional review board at Baylor College of Medicine in Houston, TX. Informed consent by the parent or legal guardian and patient assent were obtained if the patient was younger than age 18 years, and patient consent was obtained if the patient was aged 18 years or older.

Development and feasibility of the EAT! intervention have been described previously (Rodgers et al., 2013). EAT! is a touch screen app that includes descriptions and strategies regarding appetite, choosing foods, nausea and vomiting, taste changes, dry mouth, control of eating, and returning to normal following HSCT. The app allowed patients to access the information at any time between its introduction prior to HSCT hospital discharge and the conclusion of the 60-day study period.

Research Variables

Symptoms were assessed using the Memorial Symptom Assessment Scale 10-18 (MSAS 10-18) (Portenoy et al., 1994), a 30-item patient-rated instrument adapted from the original MSAS questionnaire to accommodate a reading and comprehension age of 10 years (Collins et al., 2000). Items refer to presence or absence of a specific symptom in the past week and, if present, assessed frequency and severity on a four-point Likert-type scale and distress on a five-point Likert-type scale. Symptom frequencies were totaled to measure symptom prevalence, and symptom distress scores were averaged for an overall symptom distress score. Higher scores signify more frequent symptoms and more distress from symptoms. Validity and reliability of the MSAS 10-18 has been assessed by Collins et al. (2000). Cronbach alpha coefficient of the MSAS 10-18 ranged from 0.83 for psychological symptoms to 0.87 for physical symptoms. Test-retest reliability has been mixed: correlation was significant for 26 of the 30 symptoms ($p < 0.005$), but four symptoms (e.g., pain, nervousness, drowsiness, and constipation) lacked correlation, possibly caused by instability of symptoms over time. Convergent and discriminate validity of the MSAS 10-18 has shown significant correlations to the pediatric Memorial Pain Assessment Card and nausea visual analog scales ($p < 0.01$).

Physiologic markers included BMI calculated from weight and height, pre-albumin, and albumin. Weight in kilograms and height in centimeters were obtained from the patient's medical record on each of the four days that the symptom questionnaire was completed; BMI was calculated as height in meters squared divided by weight in kilograms. Pre-albumin levels in milligrams per deciliter were obtained from the patient's medical record, based

Table 1. Sample Characteristics (N = 16)

Characteristic	n
Age (years)	
11–12	5
13–14	3
15–16	5
17–18	3
Gender	
Male	9
Female	7
Ethnicity	
Hispanic	9
Caucasian	5
African American	1
Asian	1
Diagnosis	
Leukemia	11
Lymphoma	2
Immunologic disease	2
Myelodysplastic syndrome	1
HSCT conditioning regimen	
Chemotherapy and radiation	12
Chemotherapy alone	4

HSCT—hematopoietic stem cell transplantation

on serum blood drawn within two days of symptom assessments at each data collection time point, due to pre-albumin's approximate two-day half-life (Rzepecki, Barzal, Sarosiek, & Szczylik, 2007). Albumin levels in grams per deciliter also were based on serum blood data from the patient's medical record, drawn within seven days following symptom assessments over time, given albumin's half-life of 20 days (Rzepecki et al., 2007). TPN and appetite-stimulant medications may affect the physiologic markers because of fluid volume variations or oral intake; therefore, use of either of these variables was monitored from the patient's medical record and recorded as either receiving or not receiving. Use of the EAT! application was measured in seconds and recorded individually for each patient. To avoid any potential influence on the use of the app, patients were unaware of the monitoring, and the principal investigator (PI) downloaded the information remotely from a secure website.

Procedure

After consent/assent, adolescents were introduced and oriented to the EAT! intervention via a mobile phone provided to them for the duration of the study (n = 14) or downloaded onto their own smart phones (n = 2). All adolescents were recruited to the study prior to hospital discharge, which occurred 18–28 days post-HSCT. Next, patients completed the MSAS 10-18 questionnaire, and the PI documented the patient's physiologic parameters and TPN/appetite-stimulant medication use from their medical record. If predischarge pre-albumin results were not available within the previous two days or albumin results were not available within the past seven days, the PI ordered the testing to be done with the next blood draw (later that day or the following morning). At 20, 40, and 60 days post-HSCT hospital discharge, patients again completed the MSAS 10-18 questionnaire during a routine clinic visit, and the PI recorded the patient's time using the EAT! app and obtained the patient's physiologic parameters and TPN/appetite-stimulant medication use from the patient's medical record. Upon completion of the study, patients returned the mobile phone or deleted the app from their mobile phone, and were given a small monetary incentive for their participation in the study.

Statistical Analysis

Descriptive statistics, including measures of central tendency and variability, were used to evaluate symptom reports from the MSAS 10-18 and physiologic markers. Friedman repeated measures analyses of variance were used to examine the differences in symptom scores and physiologic markers across time. If differences were noted, pairwise comparison testing was conducted using a Wilcoxon test that controlled for type 1 errors, using a 5% significance level. Correlation between use of EAT! and symptom prevalence and distress was evaluated

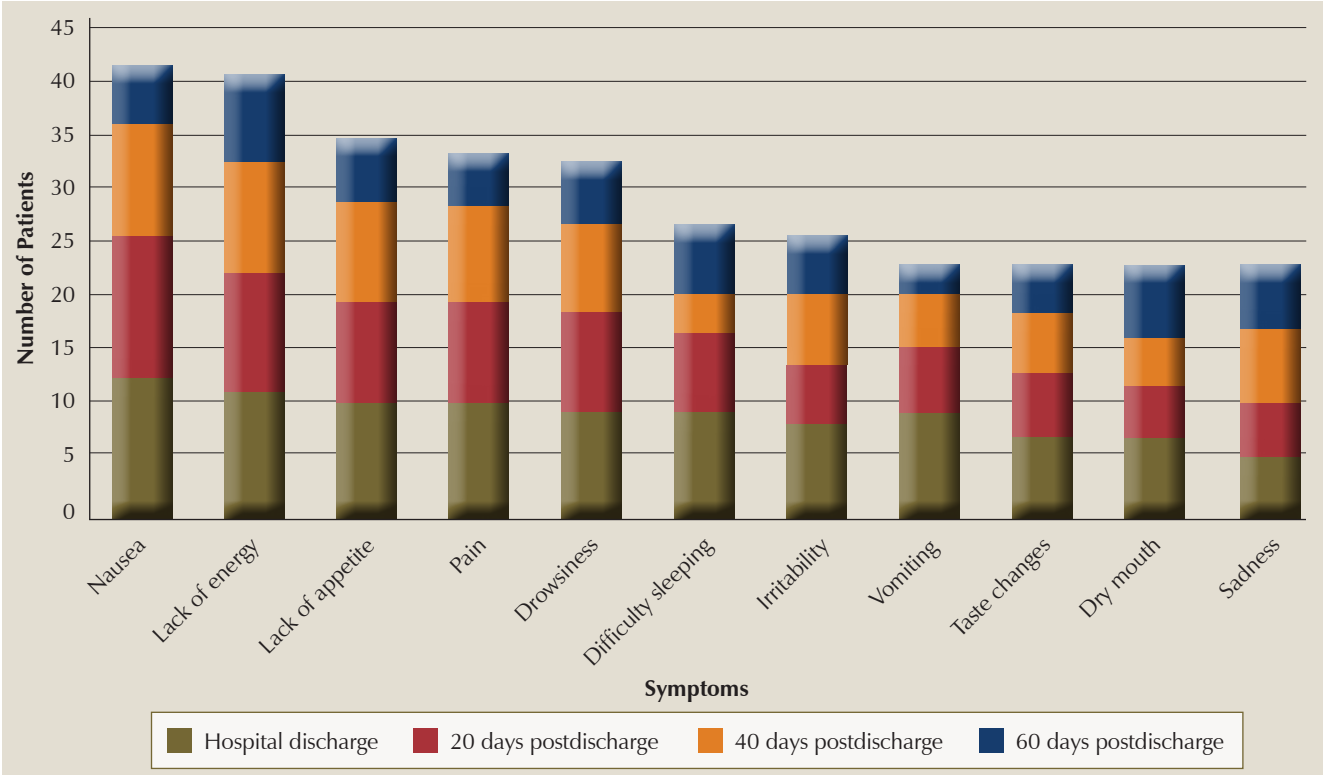
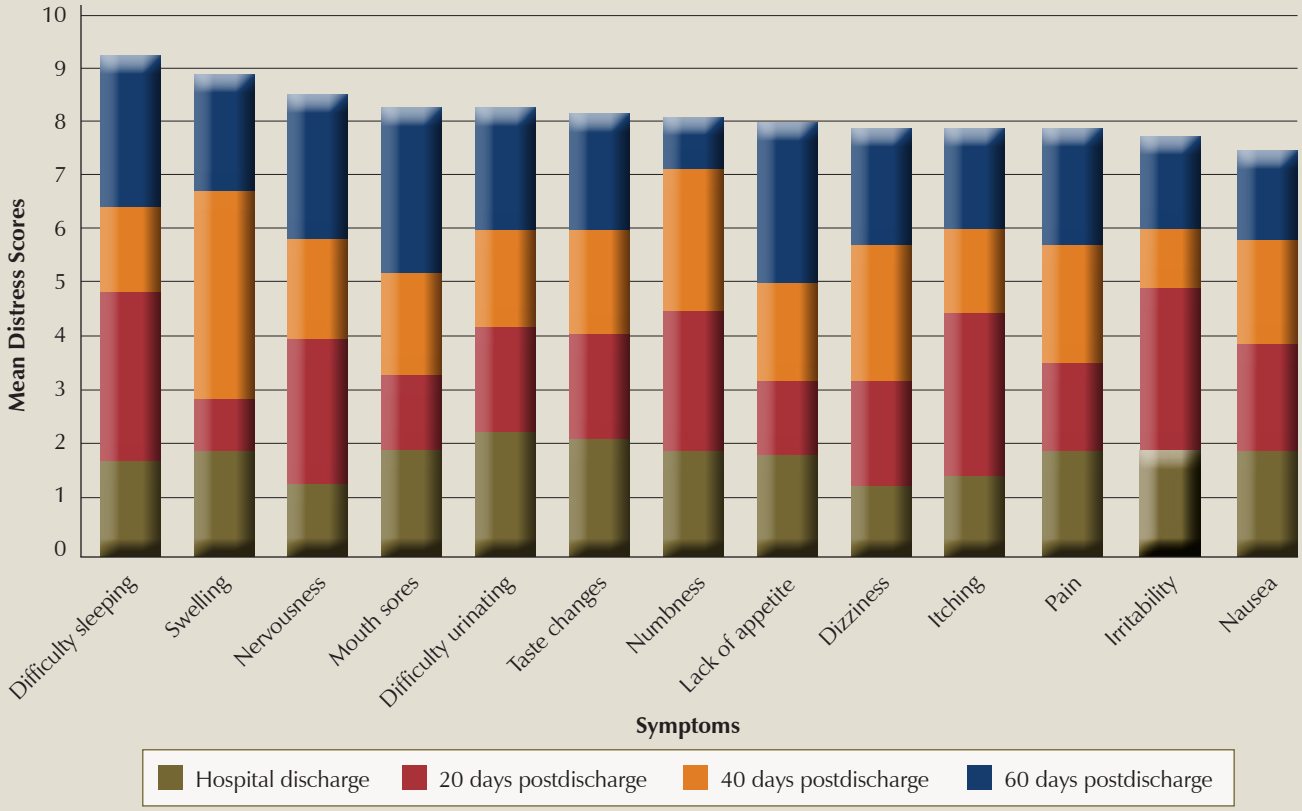


Figure 1. Prevalence of Patient-Reported Symptoms Over Time (N = 16)



Note. Patients rated the amount of distress associated with each symptom on the Memorial Symptom Assessment Scale using a four-point Likert-type scale, with 0 indicating no distress and 4 indicating very much distress.

Figure 2. Mean Distress of Patient-Reported Symptoms Over Time (N = 16)

with Spearman rank testing, and correlation between the use of EAT! and physiological markers was evaluated with Pearson correlation coefficient testing.

Results

As previously reported (Rodgers et al., 2013), patients completed data at all collection times except for one patient who relapsed prior to completion of the 60-day post-HSCT assessment. The majority of patients were male, Hispanic, had a diagnosis of leukemia, and received chemotherapy and radiation as part of their HSCT conditioning regiment (see Table 1). All patients accessed the EAT! app initially, and its use declined significantly over time (Rodgers et al., 2013).

Symptoms

All 30 symptoms in the MSAS 10-18 were reported by at least one participant at each time point. The total prevalence of all symptoms significantly decreased over time ($p = 0.006$): at hospital discharge ($n = 217$), at 20 days post-hospital discharge ($n = 153$), at 40 days post-hospital discharge ($n = 147$), and at 60 days post-hospital discharge ($n = 121$). The most prevalent symptoms ($n = 11$) are illustrated in Figure 1.

At least one patient reported some degree of distress with all 30 symptoms at all four time points, with one exception: two patients reported no distress with "not looking like myself" at 60 days post-hospital discharge. Mean distress scores of the most prevalent 11 symptoms are illustrated in Figure 2. Four of the most prevalent symptoms (difficulty sleeping, taste changes, lack of appetite, and nausea) were among the symptoms reported as most distressing. Symptom distress scores did not show a linear decline over time, and no statistically significant difference was noted over time ($p = 0.22$). Overall mean symptom distress scores were lowest at hospital discharge ($\bar{X} = 1.5$), increased at 20 days post-hospital discharge ($\bar{X} = 1.8$), then decreased at 40 days post-hospital discharge ($\bar{X} = 1.7$) and 60 days post-hospital discharge ($\bar{X} = 1.6$). Use of the EAT! intervention was not correlated with symptom prevalence or symptom distress at any time during HSCT recovery (see Table 2).

Physiologic Markers

A statistically significant decline occurred in the overall mean weight and BMI from the start to the end of the study ($p = 0.029$ and 0.002, respectively), despite the slight increase in weight and BMI noted at the end

Table 2. Correlation of EAT! With Symptoms and Physiologic Markers by Days Postdischarge

	20 Days			40 Days			60 Days		
Variable	r	rs	p	r	rs	p	r	rs	p
Symptom prevalence	–	0.369	0.159	–	–0.442	0.086	–	0.372	0.172
Symptom distress	–	0.289	0.278	–	–0.304	0.253	–	0.366	0.18
Weight	0.331	–	0.211	–0.199	–	0.459	0.201	–	0.472
Body mass index	0.38	–	0.147	0.12	–	0.659	0.196	–	0.484

EAT!—Eating After Transplant

of the study (see Figure 3). Use of the EAT! intervention was not correlated with weight or BMI changes at any time during HSCT recovery (see Table 2).

Mean albumin and pre-albumin levels remained in the normal range throughout the course of the study (see Table 3). No statistically significant changes for either of the serum proteins were reported over time. The majority of patients (n = 12) were receiving TPN at HSCT hospital discharge, four of whom were receiving an additional oral medication to stimulate their appetite. The number of patients receiving TPN decreased over time, but the use of appetite stimulants remained the same.

Discussion

As expected, symptom prevalence was highest at hospital discharge and steadily declined over time, likely corresponding to overall HSCT recovery. This study reported similar symptom prevalence during the first 100 days post-HSCT as did adult HSCT studies, including reports of nausea, fatigue, and lack of appetite, despite the mean age in the current study being only 14 years. Age may not be a significant factor in symptom prevalence during HSCT recovery but should be evaluated further with various age groups, including adolescents and young adults. In addition, reports of symptom prevalence in this study overlapped with many of the symptoms reported by adolescents receiving cancer treatment, according to a literature review by Erickson et al. (2013). Fatigue, sleep disturbances, nausea and eating problems, pain, mood disturbances, and appearance changes were common symptoms found in 12 studies evaluating symptoms in adolescents during cancer treatment. This comparable symptom prevalence may be from the fact that many patients undergoing HSCT receive similar chemotherapy agents as patients undergoing cancer treatment. Additional evaluations should be performed to identify symptom trajectories related to specific chemotherapy medications.

The most frequent symptoms were not always the most distressing symptoms reported in this study. Nausea was the most frequently reported symptom, yet ranked the 11th most distressing score. Difficulty sleeping was the most distressing symptom, yet the sixth most frequently reported. Symptom-related distress is not routinely reported in symptom assessment studies, but should be evaluated as results may differ from symptom prevalence. A thorough evaluation of symptoms should be performed to fully understand the

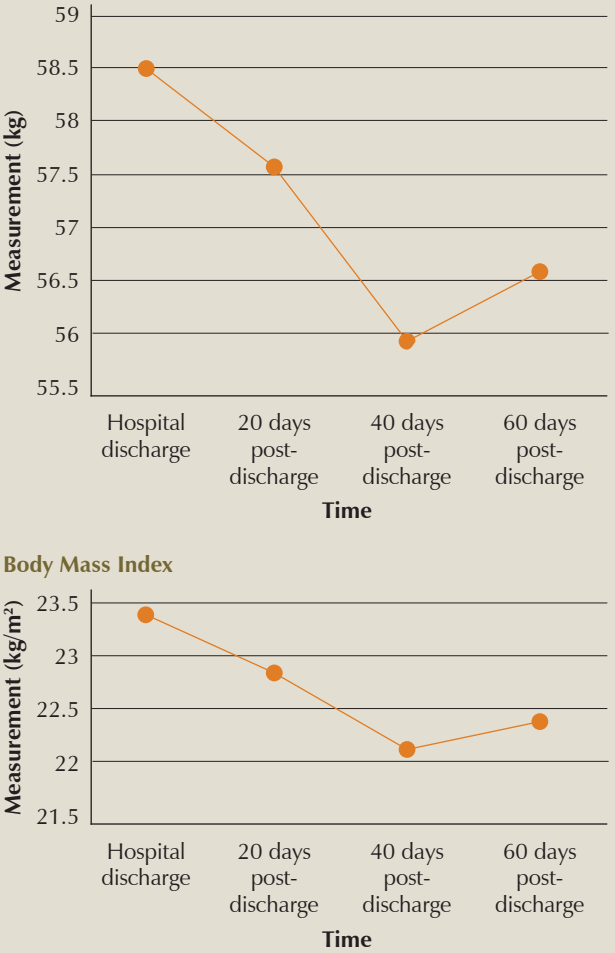


Figure 3. Mean Weight and Body Mass Index Changes Over Time

experience of and appropriate support for patients recovering from HSCT.

Patients with high symptom prevalence and distress might be expected to use the EAT! intervention more frequently than patients with lower symptom prevalence and distress; however, this was not supported. All patients frequently used the intervention directly after HSCT hospital discharge and less frequently over time. This may be from adolescents being interested in using a novel intervention to receive information (Rodgers et al., 2013). Expanded options on this phone app could provide a more effective mechanism for patient education and engagement of adolescents in their health care and well-being.

Table 3. Mean Serum Protein Markers and Frequency of Nutritional Supplements

	Albumin		Pre-Albumin		
Time	$\bar{X}$	SD	$\bar{X}$	SD	Frequency[a]
Hospital discharge	3.6	0.6	26.4	6.9	12/4
20 days post-hospital discharge	3.8	0.5	24.6	10.5	5/4
40 days post-hospital discharge	3.7	0.6	27	10.8	2/5
60 days post-hospital discharge	3.8	0.5	25.1	10.7	0/3

[a] Total parenteral nutrition/appetite stimulant frequency

Weight and BMI declined significantly during the study. These changes correspond to the frequency patterns of anorexia and nausea, which likely results in limited oral intake during early HSCT recovery. Adolescents typically need 45 days post-HSCT to regain 50% of their appetite (Cunningham et al., 1983). Despite weight loss, mean albumin and pre-albumin levels remained essentially the same throughout the study. The stable albumin levels are similar to findings in studies of adults (Jaime-Pérez et al., 2013; Uderzo et al., 1991). This may be related to the use of supplemental nutrition, such as TPN, commonly used during HSCT recovery, which maintains adequate serum protein levels. The majority of the patients in this study (n = 12) were discharged with TPN. Additional studies should evaluate the influence of nutritional supplements on the nutritional well-being of patients during HSCT recovery.

Limitations

Limitations of the study include a small sample size from a single institution. A larger and more diverse sample would provide more generalizable conclusions concerning symptom trajectories and physiologic markers throughout HSCT recovery. Adolescents' symptom reports may have been influenced by the receipt of a mobile phone to use for the duration of the study. Although patients were told that their symptom reports had no influence over availability of the phone or app, some adolescents may still have altered their symptom reports.

Implications for Nursing

Patients in this study reported a high prevalence of symptoms at hospital discharge, with symptom frequency and distress decreasing but not diminishing by 100 days post-HSCT. Awareness of symptom trajectories throughout HSCT recovery illustrates the importance of performing a thorough symptom assessment with patients, including separate queries of incidence and distress of symptoms known to occur during HSCT recovery. These assessments can increase awareness of symptoms that might otherwise be overlooked and not addressed.

A thorough understanding of symptom experiences during HSCT recovery allows healthcare providers to educate patients about techniques to assist in relieving frequent and distressing symptoms that may decrease the need for additional medical treatment and, ultimately, improve well-being (Baggott, Dodd, Kennedy, Marina, & Miaskowski, 2009). Patients may be unaware of self-initiated strategies that can be used to minimize symptoms. Sharing strategies such as deep breathing and avoidance of noxious smells to relieve nausea may allow patients to increase their ability to eat that will minimize the need for nutritional supplements. Sharing strategies, such as relaxation techniques and avoidance of daytime naps to minimize difficulty sleeping at night, may allow patients to be more active during the day and help reduce the potential for further medical complications.

Conclusions

Only through a comprehensive understanding of symptom experiences will caregivers be able to develop robust interventions to educate patients on effective symptom interventions. Use of a mobile phone app should be considered for future interventions, particularly with symptom management, as it has the ability to guide a number of individuals through the ease of accessibility. Adolescent patients are particularly comfortable using mobile phone technology to obtain information and communicate with others. This valuable tool can be used as a way to educate and empower patients to use effective strategies to minimize symptoms and to create a more positive experience during HSCT recovery that will promote well-being.

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