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Symptoms, Cytokines, and Quality of Life of Patients with Chronic Graft-versus-Host Disease following Allogeneic Hematopoietic Stem Cell Transplantation

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

by

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Abstract

SYMPTOMS, CYTOKINES, AND QUALITY OF LIFE OF PATIENTS WITH CHRONIC GRAFT-VERSUS-HOST DISEASE FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

By Debra Lynch Kelly, BS

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2014

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Introduction: Chronic graft-versus-host disease (cGVHD) is a serious complication following allo-HSCT characterized by immune dysregulation, organ dysfunction, risk for infection, and distressing symptoms. Complications may include scleroderma, hepatic dysfunction and bronchiolitis obliterans. Advances in allo-HSCT for many hematologic dyscrasias (e.g. acute and chronic leukemias, aplastic anemia, and myelodysplastic syndrome) have improved survival which has generated a renewed focus on survivorship issues. Distressing symptoms are noted as negatively impacting quality of life (QoL). The relationship between inflammation and behavioral responses may impact symptom characteristic thus examining patterns and levels of inflammation with symptoms is relevant. **Objective:** The aims of this study were to examine 1) *levels of symptoms* (cGVHD specific, general symptoms, and cluster symptoms [pain, depression and fatigue]), *inflammation* (cytokines [Interleukin {IL}-1β, IL-6, IL-10, TNF, and INF-γ] and

C-reactive protein [CRP]) and *QoL* in patients diagnosed with cGVHD and 2) relationships between and among symptoms, inflammation and QoL in individuals with cGVHD. Methods: A cross-sectional study design examined 24 individuals (ages 29-79) with cGVHD enrolled from an NCI-designated cancer center after obtaining informed consent. Data were collected using medical record and validated questionnaires. Plasma cytokine levels were measured using BioRad® multiplex assay. C-reactive protein levels were measures using an enzyme-linked immunosorbant assay. Statistical analyses included descriptive statistics and pairwise correlations. **Results:** Participants (58.3% female) with cGVHD had multiple, concurrent symptoms. Several pro-inflammatory cytokines were higher in participants with symptoms versus those without symptoms. IL-6 correlated with lack of energy (r= .42; p= .04) and dry mouth (r= .42; p= .04). IL-10 was correlated with difficulty sleeping (r= .43; p= .03). Sexual dysfunction correlated with social well-being (r= -.44; p=.03). Many symptoms negatively correlated with QoL. **Conclusion:** Findings from this study, one of the first to examine levels of symptoms and inflammatory markers in individuals with cGVHD, demonstrate significant relationships among symptoms, inflammation, and quality of life. The relationship of inflammatory biomarkers with symptoms and symptom severity emphasize the need for further interdisciplinary research. Further understanding mechanisms associated with symptoms is necessary for the development of targeted interventions to improve QoL for individuals with cGVHD.

Chapter 1

Introduction

The focus of inquiry for this dissertation study was prompted by observations made by an experienced oncology certified nurse and though an extensive literature review which revealed gaps in the literature about cGVHD. Individuals with many hematologic dyscrasias such as acute and chronic leukemias, aplastic anemia, and myelodysplastic syndrome may receive hematopoietic stem cell transplantation (bone marrow transplantation) as a life-saving intervention. Receiving stem cells that are not "self" cells is termed an allogeneic donor. A late effect complication that is serious and not uncommon after receiving allogeneic donor cells is cGVHD. Though the etiology of cGVHD is poorly defined, it is marked by immune dysregulation and inflammatory proliferation. Bone marrow transplants have increased greatly over the past ten years (Hahn, 2013). This increase is due, in part, to new treatments prior to transplant that allow patients who once would not be eligible for a transplant to obtain one (Hahn, 2013). As a consequence of both the increase in the number of transplants and conditioning regimens, the number of individuals diagnosed with cGVHD is increasing. Survivorship issues, such as quality of life (QoL), have been gaining attention as the focus of research in cGVHD. Symptoms have been found to influence QoL in cGVHD; however, the literature is limited in its description of the number of symptoms, and various characteristics of symptoms such as frequency, severity and distress (Lynch-Kelly, 2014). Symptoms were therefore chosen as the focus of this study as a way to gain preliminary insight into QoL of

individuals with cGVHD. This researcher's philosophical assumptions are consistent with the biobehavioral framework which holds that biology and behavior are inextricably linked and should be examined concurrently. As cGVHD is a complication involving an over-exaggerated inflammatory response and there is evidence that cytokines (surrogate markers of inflammation) play a role in the development and presentation of symptoms, it was logical to examine cytokines in relation to symptoms of cGVHD (Ratanatharathorn, Ayash, Lazarus, & Uberti, 2001) .

Prior to the establishment of the specific aims for this study, an extensive literature review was conducted to determine what was known about symptoms, cytokines, and quality of life of patients diagnosed with cGVHD. Findings from the review provided evidence about the involvement of symptoms in cGVHD. Symptoms are more pronounced when cGVHD is more severe (Fall-Dickson, 2010). A limitation of the research is that symptoms have been examined in relation to the organ affected by cGVHD and usually with a single measure (Lynch-Kelly, 2014). There was some consistency regarding which cytokines were examined in cGVHD (Lynch-Kelly, 2012). Individuals with cGVHD were found to have lower QoL than other populations (McQuellon et al., 1997). Also, QoL negatively correlated with cGVHD severity (Pidala et al., 2011). What was not known from the literature was an extensive profile of symptoms, if cytokines were related to the symptoms, and how symptoms related to QoL. Thus the specific aims for this study were to: 1) examine *the levels of symptoms* (cGVHD specific, general symptoms, and cluster symptoms [pain, depression and fatigue]), *inflammation* (cytokines [Interleukin {IL}-1β, IL-6, IL-10, TNF, and INF-γ] and C-reactive protein [CRP]) and *QoL* in patients diagnosed with cGVHD and 2) examine the relationships between and among symptoms, inflammation and QoL in individuals with cGVHD. Knowledge about symptoms and biological mechanisms (e.g. increased systemic inflammation expression)

involved in symptom manifestation is important for the development and testing of novel interventions to successfully manage symptoms and improve QoL for patients with cGVHD.

Findings from this study lend evidence about symptoms individuals diagnosed with cGVHD may be experiencing. It also provides information about median cytokine and CRP levels as well as some comparison cytokine levels between individuals with a certain symptom and individuals not experiencing that certain symptom. A mean QoL score is also provided. This study also provides insight into relationships that may exist among and between symptoms, inflammation and QoL. In this study, many individuals were experiencing multiple symptoms concurrently and had varying levels of frequency, severity, and distress. There were significant relationships among symptoms and cytokines and CRP as well as among symptoms and QoL. Information gained from this study serves as a starting point by providing preliminary information about symptoms, cytokines and QoL of cGVHD. This information may be used to move the science forward in this challenging population and may eventually lead to the development and testing of novel interventions to mitigate symptoms thereby increasing the QoL for individuals living with cGVHD.

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Chapter 2

Symptoms, Cytokines, and Quality of Life of Patients with Chronic Graft-Versus-Host Disease: An Integrative Review

Hematopoietic stem cell transplantation has become the standard treatment for many hematologic cancers including acute leukemia, chronic myelogenous leukemia, and multiple myeloma. There has been a 165% increase in the number of allogeneic hematopoietic stem cell transplants (alloHSCT) from 1994-2005 and survival rates post 100 days transplant have increased nearly 86% (Hahn et al., 2013). Patients receiving an alloHSCT are at risk for developing a serious, potentially life-threatening complication known as chronic graft-versus-host disease (cGVHD). This is a complex, multisystem issue involving immune dysregulation and immunodeficiency, impaired organ function, and decreased survival (Baird and Pavletic, 2006). This phenomenon occurs in as many as 90% of all alloHSCT recipients who survive greater than 100 days post-transplant (Lee, Cook, Soiffer, & Antin, 2002; Lee, Vogelsang, & Flowers, 2003). Any of the body systems can be affected by cGVHD. Cutaneous and ocular cGVDH occur most often and pulmonary and hepatic cGVHD pose the greatest risk for mortality. In addition to being the most serious complication of alloHSCT, cGVHD is also the most common (Pidala et al., 2011; Vogelsang, 2011). Debilitating consequences of cGVHD include loss of sight, pulmonary disease, and joint contractures as well as death due to chronic immune suppression secondary to prolonged immunosuppressive therapy (Filipovich et al., 2005).

Understandnig the frequency and severity of symptoms and the interplay between symptoms and inflammation, as indicated by levels of cytokines, may be major factors contributing to the quality of life of patients with cGVHD. Patients with cGVHD may experience similar symptoms as other cancer survivors such as pain, depressive symptoms, and fatigue; however, due to the lack of literature aimed at helping patients with cGVHD manage their symptoms, adequate management of symptoms is a barrier to caring for these patients and is a major issue (Lee et al., 2002; Perez-Simon, Sanchez-Abarca, Diez-Campelo, Caballero, & San Miguel, 2006; Williams et al., 2007). Biological factors such as cytokines are speculated to influence the frequency and severity of symptoms that are common among cancer patients and are also associated with other autoimmune and chronic conditions similar to cGVHD (Baird & Montine, 2008; Bazzichi et al., 2007; Klimiuk et al., 2003; Seruga, Haibo, Bernstein, &Tannock, 2008). Research in the past has focused on survivorship. Advances such as earlier transplantation, better human leukocyte antigen matching between donor and recipient and improvements in transplant conditioning have increased survivorship (Perez-Simon, Sanchez-Abarca, Diez-Campelo, Caballero, & San Miguel, 2006).

Due to increased survivorship of patients with cGVHD, improving quality of life is of growing importance (Flowers et al., 2008; Lee et al., 2002; Lee et al., 2003). Quality of life is altered due to many factors among which are symptoms (Monga et al., 2007). Among patients surviving hematopoietic stem cell transplantation, quality of life returned to pre transplant levels within one to two years except for patients experiencing cGVHD (Baker and Fraser, 2008). The National Institutes of Health (NIH) Chronic Graft-Versus-Host Disease Consortium put forth a series of papers in which it was concluded the need for the development and validation of biomarkers includes examining both biological and behavioral (patient-reported) measures

objectively with quality of life as a possible endpoint to measure success of research testing novel interventions for supportive care (Filipovich et al., 2005;). The aims of this integrative review are to determine what is known about the symptoms and cytokine patterns and levels of patients with cGVHD and to examine the impact of cGVHD on quality of life. The goal is to identify areas for future research leading to the development and testing of interventions to mitigate distressing symptoms of patients with cGVHD thereby improving quality of life.

Symptoms

Symptoms are a major source of distress and discomfort for patients with cancer and are a major barrier in caring for patients with cGVHD (Lee et al., 2002; Perez-Simon et al., 2006; Theobald, Kirsh, Holtsclaw, Donaghy, & Passik, 2003;). The National Institutes of Health (2002) reported that the most commonly experienced symptoms among patients with cancer are pain, depression, and fatigue. Insomnia is also frequently reported as a symptom associated with cancer (Fox & Lyon, 2007; Fox, Lyon, & Farce, 2007; Theobald et al., 2003). In a study examining cancer, it was reported that as many as 90% of cancer patients experience pain, 91% fatigue, and up to 25% depression (Fox & Lyon, 2006; Fox & Lyon, 2007). The symptoms experienced by patients with cancer may be due to the cancer itself and/or due to the treatments. Symptoms, particularly fatigue, may persist well into survivorship (Oh & Seo, 2011). A major role of the oncology nurse is to decrease the burden of symptoms.

Cytokines

Biobehavioral science is based in the assumption that the biology of a phenomenon is inextricably linked with behavior thereby making it necessary to examine them as two dimensions of the same whole. It is speculated that cytokines act neurologically to induce psychological and behavioral changes (Kelley, 2003). It is also speculated that the production

and release of certain cytokines can be effected by the cancer itself and these cytokines may mediate symptoms (Seruga, Zhang, Bernstein, & Tannock, 2008). A call by the National Cancer Institute (2006) to investigate strategies for the development and validation of biomarkers in cGVHD research could be beneficial in elucidating strategies to combat the devastating effects of cGVHD (Baird and Pavletic, 2006). The establishment of the relationship between symptoms and cytokines in this population may serve to determine the interplay of certain inflammatory cytokines and symptom severity which may in turn lead to advanced interventions to relieve bothersome symptoms for patients with cGVHD.

There is a growing body of evidence supporting the role of cytokines in symptom expression of patients with cancer and other chronic illnesses. This was first noted as observations of a flu-like syndrome of patients treated with immunological agents such as TNF and some interleukins (Myers, 2008). The cytokine interleukin 6 has been linked with the symptom of depression and cognitive impairment (Myers, 2008). Fatigue is the most common symptom among cancer patients and may persist well into survivorship. Interleukin 1 beta and Tumor Necrosis Factor have been associated with fatigue (Lee et al., 2004; Seurga et al., 2008). Other psychobehavioral symptoms of cancer such as pain and depression have been linked with cytokines interleukin 1, interleukin 6, Tumor Necrosis Factor, and interfeuron (Lee at al., 2004; Myers, 2008; Seruga et al., 2008). To develop targeted interventions for symptoms management in individuals with cGVHD, it is important to understand the relationship between cytokines and symptoms.

Quality of Life

Quality of life is a multi-dimensional concept encompassing several domains including physical, emotional, social, and functional (Pidala et al., 2011). It also includes the subjective

measure of an individual's evaluation of his well-being and functionality (Pidala et al., 2011). Quality of life in patients with cancer is altered due to many factors among which one is the symptoms that are experienced (Monga et al., 2007). . In patients surviving hematopoietic stem cell transplantation, quality of life returned to pre transplant levels within one to two years except for patients experiencing cGVHD (Baker and Fraser, 2008). Previous focus on patients with hematologic cancers undergoing bone marrow transplant has been survivorship. With the increase in survivorship, focus has turned toward managing the consequences of complications such as cGVHD. Symptom management and quality of life improvement is moving to the forefront of cGVHD management (Flowers et al., 2008; Lee et al., 2002; Lee et al., 2003).

Method

Articles were retrieved utilizing PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), and Cochrane Database of Systematic Reviews databases. Searches in PubMed and CINAHL were conducted to produce an exhaustive list of literature surrounding the concepts of symptoms, cytokines and quality of life in conjunction with cGVHD. The full description of the search terms used to capture the literature is presented in the appendix. The Cochrane Review Database was searched using the search term "chronic graft-versus-host disease". Articles were restricted, using search filters, to those adults greater than 18 years of age, published in English, and human studies. Inclusion criteria were: 1) the concept under investigation (symptoms, cytokines, or quality of life) must be described in relation to patients with cGVHD and must yield specific information about the concept, 2) any research method, and 3) any research design.

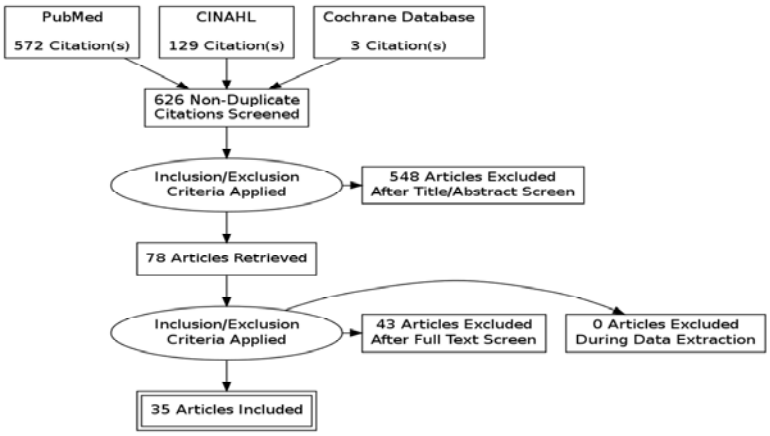
Exclusion criteria for this review were: 1) articles that only use broad terms (such as "symptoms") or do not provide any explicit information regarding the concepts under investigation (symptoms, cytokines, or quality of life).

Results

A total of 704 articles were returned. The flow diagram (Figure 1) describes the process by which articles were selected for this review. After excluding duplicate articles, applying inclusion and exclusion criteria, review of titles, review of abstracts, and finally full text screening, 35 articles were used for this literature review.

Figure 1

Chronic Graft-versus-Host Disease Articles Flow Diagram



Symptoms

There were a total of 11 symptoms articles included in this analysis. The literature regarding symptoms of patients with cGVDH is varied. Sample sizes ranged considerably, with a sample population as few as n=3 to as many as n=427 (Allen, Greenberg, and Amato, 2009; Pidala et al., 2012). One study was conducted at multiple sites (Pidala et al., 2012). Table 1 provides a description of the symptom literature.

Study design. A variety of descriptive designs were used to examine symptoms in cGVHD. There were no qualitative studies. There were three case studies (Allen et al., 2009; Elad et al., 2003; Takahide et al., 2007), two retrospective studies (Andree et al., 2008; de la Parra-Colin et al., 2011) and six prospective, cross-sectional studies (Akpek et al., 2003; Fall-Dickson et al., 2010; Mitchell et al., 2010; Pidala et al., 2012; Stratton et al., 2007; Treister et al., 2008).

Measurement approach. Researchers relied on a variety of instruments to assess patients' symptoms. Most (n=6) included information about symptoms that came from provider observance or by patient verbal description of symptom presentation (Akpek et al., 2003; Allen et al., 2009; de la Parra-Colin et al., 2011; Elad et al., 2003; Stratton et al., 2007; Treister et al., 2008). Information provided by patients described the presence of symptoms only. The visual analog scale, used to measure pain severity, was used in three studies (Elad et al., 2003; Fall-Dickson et al., 2010; Treister et al., 2008). In studies that examined ocular cGVHD, one used the ocular surface index and the other used the Schirmer test to measure symptoms (de la Parra-Colin et al., 2011; Takahide et al., 2007). The ocular surface index assesses the presence and interference of dry eyes and the Schirmer test assesses the presence of dry eyes. Two studies did not examine site specific cGVHD and used the Lee cGVHD scale (Mitchell et al., 2010; Pidala et

al., 2012). This is a scale that assesses the dimension of symptom bother. One study did not report how symptoms were assessed (Allen et al., 2009).

Context. The context in which symptoms were assessed varied. Some researchers assessed symptoms by specific site of disease and some assessed symptoms across sites of disease. Site specific studies include oral (Elad et al., 2003; Fall-Dickson et al., 2010; Treister et al., 2008), ocular (de la Parra-Colin et al., 2011; Takahide et al., 2007), gastrointestinal (Akpek et al., 2003; Andree et al., 2008), dermatomysitis (inflammation of the skin and muscles) (Allen et al., 2008), and genital, specifically vaginal cGVHD (Stratton et al., 2007). Two studies examined symptoms of patients with cGVHD of any site (Mitchell et al., 2010; Pidala et al., 2012).

The symptom most frequently examined was pain (Akpek et al., 2003; Elad et al., 2003; Fall-Dickson et al., 2010; Stratton et al., 2007; Takahide et al., 2007; Treister et al., 2008). The study conducted by Elad et al. (2003) reported severe oral pain whereas the study conducted by Fall-Dickson et al. (2010) reported mild oral pain. Other symptoms reported in the presence of oral cGVHD included odynophagia (pain when swallowing), avoiding certain foods and tightness in the mouth (Treister et al. 2008). Ocular cGVHD studies examined dry eyes, photophobia, and foreign body perception (de la Parra-Colin et al., 2011; Takahide et al., 2007). The feeling of having a foreign body in the eyes has been described as a "gritty" feeling like sand constantly abrading the cornea (Choi, Levine and Ferrara, 2010; Joseph, Couriel, and Komanduri, 2008; Vogelsang, 1996). Both studies that examining ocular cGVHD reported patients complained of photophobia (de la Parra-Colin et al., 2011; Takahide et al., 2007). Gastrointestinal cGVHD examined nausea, dysphagia, feeling full, heartburn, diarrhea and weight loss (Akpek et al., 2003; Andree et al., 2008). Abdominal pain was the most commonly

reported symptom in one study (Akpek et al., 2003) and nausea in another (Andree et al., 2008). The case study reported by Allen et al. (2009) found muscle weakness (fatigue) and myalgia to be the patients' complaints. Painful intercourse and pain due to strictures were present in all patients (n=33) with vaginal cGVHD (Stratton et al., 2007). Symptom bother was assessed in the two studies that examined symptoms in any site (Mitchell et al., 2010; Pidala et al; 2012). The scores were 28.4 and 20.7 respectively, out of a possible 100, with a higher score indicating greater symptom bother (Mitchell et al., 2010; Pidala et al., 2012). Specific symptoms were not reported in either of these studies.

Cytokines

Cytokines are small proteins that act to regulate the intensity and duration of immune response and mediate cell-to-cell communication. Elevated levels of cytokines are associated with autoimmune or chronic inflammatory diseases that are comparable to cGVHD (Baird & Montine, 2008; Bazzichi et al., 2007; Klimiuk et al., 2003). A total of 14 cytokine articles were included in this analysis. Sample sized ranged from n=3 to n=229 and from a one group design to a three group design (Cullup et al., 2003; Kaminska, et al., 2007). Table 2 provides a description of cytokine literature examined in the presence of cGVHD.

Study design. All reviews articles selected used a descriptive design to examine levels of cytokines; however, there was variability in the number of groups and the temporality among studies. Four studies used a single group (Craciun et al., 2002; D'Elios et al., 1997; Gorgun, Miller, & Foss, 2002; Poloni et al., 2011). One study included a donor group (Cullup, Dickson, Cavet, Jackson, & Middleton, 2003). All other studies used two groups (case group and control group) (Aractingi, Gluckman, Le Goue, Dubertret, & Carosella, 1996; Bladon & Taylor, 2006; Darvay, Salooja, & Russell, 2004; Fall-Dickson et al., 2010; Hettinga, Verdonck, Fijnheer,

Rijkers, & Rothova, 2007; Kaminska et al., 2010; Nakamura et al., 2005; Ricci et al., 2006; Tauchmanova et al., 2004). There were two case studies used in this analysis (Hettinga et al., 2007; Kaminska et al., 2010). Eight studies were longitudinal (Bladon & Taylor, 2006; Craciun et al., 2002; Darvay et al., 2004; Gorgun et al., 2002; Nakamura et al., 2005; Poloni et al., 2011; Ricci et al., 2006; Tauchmanova et al., 2004). Four studies were cross-sectional (Aractingi, et al., 1996; Cullup et al., 2003; D'Elios et al., 1997; Fall-Dickson et al., 2010). .

Measurement methodology. Cytokines can be measured through many vectors and by a variety of instruments. There was heterogeneity in methods used by the researchers across studies. The most common (n=10) vector for assessing cytokines was blood (Bladon & Taylor, 2006; Craciun et al., 2002; Cullup, 2003; D'Elios et al., 1997; Darvay et al., 2004; Gorgun et al., 2002; Nakamura et al., 2005; Poloni et al., 2011; Ricci et al., 2006; Tauchmanova et al., 2004). Other vectors included tissue (n=4), saliva (n=1), and ocular fluid (n=1) (Aractingi et al., 1996; D'Elios et al., 1997; Fall-Dickson et al., 2010; Hettinga et al., 2007, Kaminska et al., 2010; Poloni et al., 2011). The method for assessing the measurement of cytokines was inconsistent across studies. The two most often used were flow cytometry and enzyme-linked immunosorbent assay. Flow cytometry was used for cytokine analysis in six studies (Bladon & Taylor, 2006; Darvay et al., 2004; Gorgun et al., 2002; Hettinga et al., 2007; Ricci et al., 2006; Tauchmanova et al., 2004). Enzyme-linked immunosorbent assay was used for cytokine analysis in three studies (D'Elios et al., 1997; Fall-Dickson et al., 2010; Nakamura et al., 2005).

Context. The circumstances in which cytokines were measured include inteventional and non-interventional studies, site specific and non-site specific studies, and all families of cytokines. Interventional studies explored cytokine levels of patients before and after receiving extracorporeal photopheresis (Aractingi et al., 1996; Bladon & Taylor, 2006; Craciun et al.,

2002; Darvay et al., 2004; Gorgun et al., 2002). Pre-treatment levels of cytokines are reported to ascertain presence and levels of cytokines found in patients with cGVHD unmitigated by the effects of treatment. Other studies did not include an intervention. There were both site specific and non-site specific articles reviewed. Site specific articles included cutaneous (n=1), oral cGVHD (n=1), ocular (n=1) and renal (Aractingi et al., 1996; Fall-Dickson et al., 2010; Hettinga et al., 2007; Kaminska. et al, 2010). The remainder of the reviewed studies are not site specific.

There are three families of cytokines, hematopoietins (interleukins), interfeurons, and tumor necrosis factors. All studies measured levels of interleukines (IL). The IL most often examined (n=7) was IL-10 (Craciun et al., 2002; Gorgun et al., 2002; Hettinga et al., 2007; Kaminska. et al, 2010; Nakamura et al., 2005; Ricci et al., 2006; Tauchmanova et al., 2004). Interfeuron gamma was the only interfeuron examined and was the cytokine most often measured (n=9) (D'Elios et al., 1997; Darvay et al., 2004; Gorgun et al., 2002; Hettinga et al., 2007; Kaminska et al., 2010; Nakamura et al., 2005; Poloni et al., 2011; Ricci et al., 2006; Tauchmanova et al., 2004). Tumor necrosis factor was examined in seven studies (Aractingi et al., 1996; Bladon & Taylor, 2006; Craciun et al., 2002; Kaminska. et al, 2010; Nakamura et al., 2005; Ricci et al., 2006; Tauchmanova et al., 2004). The least examined cytokine was IL-12 (Poloni et al., 2011).

Numerous cytokines were measured across studies. There were consistencies across studies with regard to levels of some cytokines while levels of other cytokines across studies yielded varied results. Six studies examined cytokines from the IL-1 family. Three examined IL-1 alpha (α) (Bladon & Taylor, 2006; Cullup et al., 2003; Fall-Dickson et al, 2010) and three examined IL-1 beta (β) (Bladon & Taylor, 2006; Craciun et al., 2002; Poloni et al., 2011). Among patients with cGVHD, levels of IL-1α and IL-1β were higher in patients with cGVHD

across studies than in patients without cGVHD. There were four studies that assessed cytokine IL-2 (Darvay et al., 2004; Kaminska et al., 2010; Ricci et al., 2006; Tauchmanova et al., 2004). Results were inconsistent across studies. Two studies demonstrated elevated levels in patient with cGVHD, one demonstrated lower levels of IL-2 among patients with cGVHD and one demonstrated no difference between patients with and without cGVHD. There was inconsistency among studies (n=6) that measured levels of IL-4. Four found there to be no difference between patients with and without cGVHD and two found levels of IL-4 to be elevated among patients with cGVHD when compared to patients without cGVHD (D'Elios et al., 1997; Darvay et al., 2004; Gorgun et al., 2002; Nakamura et al., 2005; Ricci et al., 2006; Tauchmanova et al., 2004). Two articles examined IL-5. One article described no difference in IL-5 levels between patients with and without cGVHD and one article described elevated levels of IL-5 in patients with cGVHD compared with patients that were not diagnosed with cGVHD (Ricci et al., 2006; Tauchmanova et al., 2004). Studies examining IL-6 (n=4) found patients with cGVHD to have higher levels of IL-6 than patients without cGVHD (Bladon and Taylor, 2006; Fall-Dickson et al., 2010; Hettinga et al., 2007; Kaminska et al., 2010). In the study conducted by Aractingi et al. (1996), there was no difference in the expression of IL-8 between patients with cGVHD and patients without cGVHD. Bladon and Taylor (2006) and Poloni et al. (2011) found elevated levels of IL-8 among patients with cGVHD when compared with patients withoug cGVHD. Studies examining IL-10 yield varying results. Five of the seven studies yielded elevated evels of IL-10 (Craciun et al., 2002; Gorgun et al., 2002; Hettinga et al., 2007; Kaminskaet al., 2010; Tauchmanova et al., 2004). The remaining two found no difference in circulating levels of IL-10 between patients with and without cGVHD (Nakamura et al., 2005; Ricci et al., 2006).

Studies examining TNF-α (n=7) and IFN-γ (n=9) also yielded varying results. Three studies examining TNFα found elevated levels between patients with cGVHD and patients without cGVHD (Bladon & Taylor, 2006; Kaminska et al., 2010; Tauchmanova et al., 2004). Three found no difference in levels of TNFα between patients with cGVHD and patients without cGVHD. Aractingi et al. (1996) reports TNF α is expressed in patients with cGVHD.

The majority (n=6) of studies examining IFNγ in patients with cGVHD report elevated levels among patients with cGVHD (Darvay et al., 2004; Gorgun et al., 2002; Kaminska et al., 2010; Poloni et al., 2011; Ricci et al., 2006; Tauchmanova et al., 2004). Hettinga et al. (2007) and Nakamura et al. (2005) report no difference between cGVHD cases and non cGVHD controls. D'Elois et al. (1997) reports IFNγ is expressed in patients with cGVHD.

Quality of Life

A total of 10 quality of life articles were included in this analysis. Sample size ranged from n=37 to n=427 (Kim et al., 2010; Pidala et al., 2011). Table 3 provides a description of quality of life literature examined in the presence of cGVHD.

Study design. All quality of life research articles examined for this review used a descriptive study design. Aspects such as the use of a control group and sample size were varied. The majority of studies (n=6) used a cross-sectional study design to evaluate the effect of cGVHD on QoL (Fall-Dickson et al., 2010; Harris et al., 2010; Imanguli et al., 2010., Pallua et al., 2010; Pidala et al., 2011a; Pidala et al., 2011c). The remainder of the studies used a longitudinal study design (Herzberg et al., 2010; Kim et al., 2010; Lee et al., 2006; Pidala et al., 2011b). Two studies included a control group (Herzberg et al., 2010; Pallua et al., 2010). The remainder of the literature reviewed had a one group design. Eight studies used standardized scores to indicate level of quality of life and Two studies used "population norms" for

comparison of quality of life scores (Fall-Dickson et al., 2010; Pidalla et al., 2011b). Five studies included a sample size over one hundred (Herzberg et al., 2010; Imanguli et al., 2010; Pidala et al.,2011; Pidala et al., 2011; Pidala et al., 2012).

Measurement methodology. The tools to capture quality of life of patients with cGVHD are well documented in the literature as being reliable and valid instruments. The functional assessment of cancer therapy general was used in three studies (Fall-Dickson et al., 2010; Harris et al., 2010; Imanguli et al., 2010). The same measure with an the addition of a bone marrow transplant subscale was used in five studies (Herzberg et al., 2010; Lee et al., 2006; Pidala et al., 2011a; Pidala et al., 2011b; Pidala et al., 2011c). Pidala et al. (2011a,b,c) and Kim et al. (2010) used the short form- 36 to assess quality of life in addition to the functional assessment of cancer therapy. The human activity profile scale was also used in the study by Pidala et al. (2011c).

Context. Quality of life in patients with cGVHD is explored in site specific populations and non-specific site populations and there are a variety of factors associated with quality of life. Eight of the ten studies included all patients with cGVHD and did not examine specific sites (Harris et al., 2010; Herzberg et al., 2010; Kim et al., 2010; Lee et al., 2006; Pallua et al., 2010; Pidala et al., 2011a; Pidala et al., 2011b; Pidala et al., 2011c). Two studies evaluated quality of life of patients with oral cGVHD (Fall-Dickson et al., 2010; Imanguli et al., 2010). Factors associated with quality of life include severity of cGVHD (Fall-Dickson et al., 2010, Paulla et al., 2010), spirituality (Harris et al., 2010), physical functioning (Herzberg et al., 2010), and salivary gland dysfunction (Imanguli et al., 2010). Having cGVHD showed to decrease quality of life across studies. The study by Pidala et al. (2011c) did not find a difference in quality of life scoes for patients exhitbiting characteristics of both acute GVHD and cGVHD.

Discussion

This review sought to examine the current literature to find out what is known about symptoms, cytokines and quality of life of patients with cGVHD. The goal is to identify areas for future research leading to the development and testing of interventions to mitigate distressing symptoms of patients with cGVHD thereby improving quality of life. A total of 36 articles were extracted and reviewed. Each variable was examinied for information regarding study design, measurement and methodology, and context. All of the literature reviewed used a descriptive study design. The methods for measuring the concepts are varied as are the results. Thus it is difficult to draw conclusions. There is evidence that patients with cGVHD are experiencing distressing symptoms and cytokine dysregulation. Quality of life appears to be affected by many factors associated with cGVHD.

Symptoms

Symptoms are a departure from normal function or feeling noticed by an individual and may be indicative of presence of disease or abnormality and are a major source of distress and discomfort for patients with cancer (Theobald, Kirsh, Holtsclaw, Donaghy, & Passik, 2003). The National Institutes of Health (2002) reported that the most commonly experienced symptoms among patients with cancer are pain, depression, and fatigue. Insomnia is also frequently reported as a symptom associated with cancer (Fox & Lyon, 2007; Fox, Lyon, & Farce, 2007; Theobald et al., 2003). In a study examining cancer, it was reported that as many as 90% of cancer patients experience pain, 91% fatigue, and up to 25% depression (Fox & Lyon, 2006; Fox & Lyon, 2007). The symptoms experienced by patients with cancer may be due to the cancer itself and/or due to the treatments. Symptoms, particularly fatigue, may persist well into survivorship (Oh & Seo, 2011). A major role of the oncology nurse is to decrease the burden of

symptoms. Patients with cGVHD may experience similar symptoms; however due to the lack of literature aimed at helping patients with cGVHD manage their symptoms, adequate management of symptoms is a major barrier to caring for these patients (Williams et al., 2007). The literature is lacking in symptom management and little is known about which symptoms patients experience and to what extent. Distressing symptoms are the primary reason people seek medical attention, yet for patients with cGVHD, the symptoms experienced are not well elucidated. Most articles examined for this review imply symptoms are a source of distress; however, few sought to present a symptom profile using a multi-symptom measure that quantifies symptom frequency, severity, and interference with daily life. The literature examined for this review regarding the symptom experience is limited. Few studies examined symptoms of cGVHD using validated measures.

Another gap in the literature regarding symptoms in the presence of cGVHD is there are many systems affected by cGVHD that were not identified. There were no reviewed published studies that examined symptoms for pulmonary or hepatic involvement. Other sites affected by cGVHD, such as the skin, which is the most commonly affected organ, were lacking in the literature. Implementing studies to include larger sample size with the use of validated measures would add to the existing body of knowledge about which symptoms patients with cGVHD are experiencing and the frequency, severity and distress of symptoms for better symptom management.

Cytokines

Biobehavioral science is based in the assumption that the biology of a phenomenon is inextricably linked with behavior thereby making it necessary to examine them as two dimensions of the same whole. It is speculated that cytokines act neurologically to induce

psychological and behavioral changes (Kelley, 2003). It is also speculated that the production and release of certain cytokines can be effected by the cancer itself and these cytokines may mediate symptoms (Seruga, Zhang, Bernstein, & Tannock, 2008). A call by the National Cancer Institute (2006) to investigate strategies for the development and validation of biomarkers in cGVHD research could be beneficial in elucidating strategies to combat the devastating effects of cGVHD (Baird and Pavletic, 2006). The establishment of the relationship between symptoms and cytokines in this population may serve to determine the interplay of certain inflammatory cytokines and symptom severity which may in turn lead to advanced interventions to relieve bothersome symptoms for patients with cGVHD.

The complexity in the micro-environment of cGVHD is evident in the literature. There are numerous speculations as to the role that cytokines play in the presentation of this complication of allogeneic hematopoietic stem cell transplantation. Continued research is necessary to draw conclusion about the levels and patterns of cytokines present in patients with cGVHD and to establish relationship between cytokine levels and the occurrence and severity of cGVHD. Future research examining cytokines is essential for better understanding the relationship of cytokine-mediated immune dysfunction and the development of cGVHD in patients receiving an allogeneic hematopoietic stem cell transplant. Also, inflammatory markers associated with symptom presentation are necessary to gain understanding of the interplay of the biology and behavioral responses of patients with cGVHD.

Quality of Life

Quality of life in patients with cancer is altered due to many factors among which one is the symptoms that are experienced (Monga et al., 2007). Previous focus on patients with hematologic cancers undergoing bone marrow transplant has been survivorship. With the

increase in survivorship, focus has turned toward managing the consequences of complications such as cGVHD. Symptom management and quality of life improvement is moving to the forefront of cGVHD management (Flowers et al., 2008; Lee et al., 2002; Lee et al., 2003).

Quality of life is a major concern for patients with cGVHD. Symptoms that cause patients distress may be a contributing factor that impacts overall perception of quality of life; however, there is a gap in the literature to substantiate this hypothesis. One study examined in this review sought to elucidate the impact symptoms have on quality of life for patients with cGVHD and this study is site-specific. The majority of articles examining quality of life for this review used a cross-sectional design and did not include healthy controls. Many of the patient samples in the quality of life literature are over 100 participants and describe patient characteristics; however, there is a lack of description as to cGVHD classification in accordance with NIH guidelines. There is a gap in the literature of sample homogeneity as to which characteristics of cGVHD were examined in relation to quality of life thus definitive associations between cGVHD and quality of life are not established.

Conclusion

It does appear from the literature reviewed that patients with cGVHD are experiencing a myriad of distressing symptoms. The establishment of the impact that distressing symptoms have on patients' quality of life has yet to be well characterized. The literature also provides evidence that inflammatory markers may indicate the severity and possibly the persistence of cGVHD. Correlative studies have demonstrated an association among symptoms, cytokines and quality of life and have also demonstrated length of time since diagnosis and the severity of cGVHD also effect patient perception of quality of life. An initial step to the development and research of novel interventions to ameliorate distressing symptoms and increasing quality of life

for patients with cGVHD is to examine and describe, in depth and breadth, the symptoms patients are experiencing and how these symptoms are related to biological mechanisms such as inflammatory cytokines. Also, how these factors together influence the quality of life for patients with cGVHD. There is a need for further research examining these aspects of cGVHD using reliable and valid instruments as well as instruments that are comparable to draw conclusion across studies. This would allow the science for the development of interventions to mitigate distressing symptoms of patients with cGVHD forward to improve quality of life.

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Table 1.

Studies Examining Symptoms of Chronic Graft-Versus-Host Disease

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
Akpek, G., Chinratanalab, W., Lee, L., Torbenson, M., Hallick, J., Anders, V., & Vogelsang, G. (2003). Gastrointestinal involvement in chronic graft-versus-host disease: A clinicopathologic study. *Biology of Blood and Marrow Transplantation, 9,* 46-51. doi: 10.1053/bbmt.2003.49999	Prospective, descriptive, cross-sectional/ n= 40	To describe clinical findings in a group of patients with cGVHD whose gastrointestinal symptoms required endoscopic evaluation	Patient self-report and clinical assessment	74% complained of diarrhea; 45% complained of abdominal pain; 33% complained of nausea; 19% complained of weight loss; 12% complained of GI bleeding; 12% complained of dysphagia; 12% complained of "feeling full"; 5% complained of heartburn. No information was reported on the frequency or severity for the

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
				symptoms. No validated tools were used to measure the symptom experience and no definitions to quantify symptoms were described.
Allen, J.A., Greenberg, S.A, & Amato, A.A. (2009). Dermatomysitis-like muscle pathology in patients with chronic graft-versus-host disease. *Muscle and Nerve, 40,* 643-647. doi: 10.1002/mus.21353	Case Study/ n=3	To describe three patients with cGVHD who developed clinical and pathologic findings typically observed in dermatomysitis	Not reported	Patients complained of muscle weakness (fatigue) and myalgia. How these symptoms were measured is not disclosed. No information was reported as to the frequency or severity of the symptoms.
Andree, H., Hilgendorf, I., Leithaeuser, M., Junghanss, C., Holzhueter, S.,	Retrospectiv e, descriptive/ n=13	To retrospectively evaluate the efficacy of	Not reported	Thirteen patients were evaluated

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
Loddenkemper, C., . . . Wolff, D. (2008). Enteral budesonide in treatment for mild and moderate gastrointestinal chronic GVHD. *Bone Marrow Transplantation, 42,* 541-546. doi: 10.1038/bmt.2008.209		budesonide for the treatment of mild to moderate gastrointestinal cGVHD		and the description of symptoms was reported in a table describing each patient. Ten patients reported nausea; seven patients reported weight loss; six patients complained of mild to moderate diarrhea; eight patients had multi-organ involvement. No description of the frequency or interference and limited information about severity was reported. Measurement tools were not described.
de la Parra-Colin, P.,	Retrospectiv	To describe the	Patient	29% of

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
Agahan, A., Perez-Simon, J., Lopez, A., Caballero, D., Hernandez, E., Barrientos-Gutierrez, T., & Calonge, M. (2011). Dry eye disease in chronic graft-versus-host disease: Results from a Spanish retrospective cohort study	e, cohort, cross-sectional, descriptive/ n= 57	incidence, risk factors and outcome of dry eye disease associated with cGVHD at a single center over a five year period.	reported symptom measure not reported. Dry eye measured by Schirmer's test for dry eye disease	patients developed dry eye disease; 59% complained of photophobia ; 23% complained of irritation; 18% complained of feeling as though there was a foreign body in the eyes. No evaluation of frequency, severity, or interference of symptoms was reported.
Elad, S., Or, R., Shapira, M.Y., Haviv, A., Galili, D., Garfunkel, A.A., Bitan, M., & Kaufman, E. (2003). CO_2 laser in oral graft-versus-host disease: A pilot study	Case Study/ n=4	To evaluate the efficacy of the CO_2 laser to relieve severe pain caused by oral cGVHD	Visual analog scale and clinical evaluation	Prior to laser treatments, 2 patients rated their pain a 10/10; one rated his pain an 8/10; and one rated his pain a

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
				7/10. No evaluation of pain frequency or interference was reported.
Fall-Dickson, J.M., Mitchell, S.A., Marden, S., Ramsay, E. S., Guadagnini, J.P/. Wu, T., . . . Pavletic, S.Z. (2010). Oral symptom intensity, health-related quality of life, and correlative salivary cytokines in adult survivors of hematopoietic stem cell transplantation with oral chronic graft-versus-host disease. *Biology of Blood and Morrow Transplantation, 16,* 948-956. doi: 10.1016.j.bbmt.2010.01.017	Prospective, cross-sectional, descriptive/ n= 42	To examine the oral symptoms experience, health-related quality of life, and salivary proinflammatory cytokines in a sequentially accrued cohort of patients with oral cGVDH	Visual Analog Scale (0-10) for pain intensity; a 10cm Numeric rating Scale (0-10) for oral dryness; Functional Assessment of Cancer Therapy-General; Enzyme-linked Immunosorbent Assay	The mean oral pain score was 0.13 with a median of 0 and a range of 0-2; the mean oral dryness score was 2.56 with a median of 0 and a range of 0-10. More severe oral cGVHD was associated with a lower social/family well-being. Overall quality of life scores were lower in patients with cGVHD than the average score for the

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
				US population norm. Inflammatory cytokine Interleukin-6 was associated with oral cGVHD severity and Interleukin 1α was positively associated with oral dryness.
Mitchell, S.A., Leidy, N.K., Mooney, K.H., Dudkey, W.N., Beck, S.L., LaStayo, P.C., . . . Pavletic, S.Z. (2010). Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). *Bone Marrow Transplantation, 45,* 762-769. doi: 10.1038/bmt.2009.238	Prospective, cross-sectional/ n= 100	To determine the factors that account for variability in functional performance in long term allogeneic hematopoietic stem cell transplant survivors with cGVHD	Lee cGVHD symptom scale	The mean symptom score was 28.4 and the scores ranged from 0.7-68.6. Symptom bother was a significant independent predictor of functional performance. Depression was considered a co-morbid condition and was prevalent in 43% of the participants.

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
Pidala, J., Vogelsang, G., Martin, P., Chai, X., Storer, B., Pavletic, S., . . . Lee, S. (2012). Overlap subtype of chronic graft-versus-host disease is associated with an adverse prognosis, functional impairment, and inferior patient-reported outcomes: A Chronic Graft-versus-Host Disease Consortium study. *Haematologica, 97,* 451-458. doi: 10.3324/haematol.2011.055186	Prospective, multi-site, cross-sectional/ n= 427	To examine whether the sub-type of graft-versus-host disease was associated with a different prognosis, functional limitations, or patient-reported outcomes compared to "classic" chronic graft-versus-host disease without any acute features	Lee cGVHD symptom scale; Functional assessment of cancer therapy- Bone marrow transplantation; The human activity profile; The short form-36	Patients with overlap sub-type cGVHD had a median of 20.7 with a range of 0-65.3 and patients with classic cGVDH had a median of 18.1 with a range of 4.1-56.6. There was not a significant difference between the groups for symptom summary scores; however patients with overlap sub-type cGVHD had significantly higher scores for skin and nutrition symptom bother.
Stratton, P., Turner, M.L., Childs, R., Barrett, J., Bishop, M., Wayne, A.S., & Pavletic, S.	Prospective, observational, cross-sectional/ n=	To describe the diagnosis and management of female genital	Patient self-report	Vulvar pain, burning and dyspareunia. No

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
(2007). Vulvovaginal chronic graft-versus-host disease with allogeneic hematopoietic stem cell transplantation. *Obstetrics and Gynecology, 110,* 1041-1049.	33	cGVHD		symptom severity or frequency was reported. 21 participants who were sexually active prior to enrollment were no longer due to pain completely interfering with sexual activity.
Takahide, K., Parker, P.M., Wu, M., Hwang, W.Y., Carpenter, P.A., Moravec, C., . . . Flowers, M.E. (2007). Use of fluid-ventilated, gas permeable sclera lens for management of severe Keratoconjuntivitis Sicca secondary to chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation, 13,* 1016-1021. doi:10.1016/j.bbmt.2007.05.006	Case-Study/ n=9	To report outcomes of nine patients referred for sclera lens fitting as treatment for cGVHD related Keratoconjuntivit is Sicca refractory to standard therapies	Ocular surface disease index questionnaire	The mean score for the Ocular surface disease index was 81; symptoms reported were photophobia and pain.
Treister, N.S., Cook, E.F., Antin, F., Lee, S.J., Soiffer, R., & Woo,	Prospective, descriptive/ n=27	To characterize the distribution, type and extent	Patient questionnaire answering	Participants reported mouth pain

Citation	Design/n	Purpose	Patient Reported Symptom Measures/ Other Measures	Result
S.B. (2008). Clinical evaluation of oral chronic graft-versus-host disease. *Biology of Blood and Marrow Transplantation, 14*, 110-115. doi: 10.1016/j.bbmt.2007.06.017		of lesions and their correlation with patient-reported symptoms such as pain and discomfort	"yes" or "no"; Visual analog scale	(41% of the visits), avoiding certain foods (79% of the visits), mouth tightness (23% of the visits), and odynophagia (20% of the visits); 95% of the pain scores were ≤ 5 out of 10 (0=no pain and 10=worst pain); there were no pain scores > 7.

Key: cGVHD= chronic graft-versu- host disease, GI= gastrointestinal

Table 2.

Studies Examining Cytokines of Chronic Graft-Versus-Host Disease

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
Aractingi, S., Gluckman, E., Le Goue, C., Dubertret, L., & Carosella, E.D. (1996). Lymphocytes, cytokines and adhesion molecules in chronic graft-versus-host disease. *Journal of Clinical and Molecular Pathology, 49,* 225-231.	Descriptive, Case-Control/18 case, 8 control	To determine inflammatory and immune pathways responsible for the development and presentation of cGVHD	IL-1, IL-8, TNFα	Tissue	Immuno histo-chemical	IL-1 and TNFα were expressed in "diseased" epidermis versus "normal" epidermis of patients with cGVHD. IL-8 was expressed in all keratinocytes in all samples. IL-1 was significantly expressed in "normal" skin in patients with lichen planus-like cGVHD.
Bladon, J., & Taylor, P.C. (2006). The down-regulation of IL-1α and IL-6, in monocytes exposed to extracorporeal photopheresis (ECP)- treated lymphocytes, is not dependent on lymphocyte	Descriptive, Longitudinal/ n=12, n=9 cGVHD	To determine if monocyte immune-suppression related to ECP is related to phosphate-dylserine	TNFα, IL-1α, IL-1β, IL-6, IL-8	Blood	Flow cytometr y	All cytokine levels were elevated in patients with cGVHD prior to ECP.

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
phosphatidylserine externalization. *Transplant International, 19,* 319-324. doi: 10.1111/j.1432-2277.2006.00278.x						
Craciun, L. I., Stordeur, P., Schandene, L., Duvillier, H., Bron, D., Lambermont, M., . . . Dupont, E. (2002). Increased production of interleukin-10 and interleukin-1 receptor antagonist after extracorporeal photochemotherapy in chronic graft-versus-host disease. *Transplantation, 74,* 995-1000. doi: 10.1097/01.TP.0000031933.82269.AC	Descriptive, Longitudinal/ n=6	To examine production of IL-10 and IL-1RA after ECP treatment for cGVHD	IL-10, IL-1RA, TNFα, IL-1β, IL-12p40	Blood	Flow cytometry	No significant changes in TNFα, IL-1β, or IL-12p40; ECP enhanced the production of IL-10 and IL-1RA.

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
Cullup, H., Dickson, A.M., Cavet, J., Jackson, G.H., Middleton, P.G. (2003). Polymorphisms of interleukin-1α constitute independent risk factors for chronic graft-versus-host disease after allogeneic bone marrow transplant. *British Journal of Haematology, 122,* 778-787.	Descriptive, Case-Control/ n=98 patients, n=94 donors (case), n=229 control	To compare clinical outcomes (GVHD and survival) of allo-HSCT recipients with their genotype for two poly-morphisms present in the IL-1α gene	IL-1 α (two poly-morphisms: IL-1α-889 and IL-1α VNTR	Blood	Polymerase Chain Reaction	Allele 2 in the IL-1α-889 was significantly more prevalent in patients with cGVHD than in those without cGVHD; allele 2 in the IL-1α VNTR was not significantly different between the cGVHD group and the control group.
D'Elios, M.M., Romagnani, P., Scaletti, C., Annunziato, F., Manghetti, M., Mavilia, C., . . . Romagnani, S. (1997). In vivo CD30 expression in human diseases with predominant activation of Th2-like T cells	Descriptive/ 152 total participants; n= 22 with cGVHD	To provide evidence that CD30 expression is associated with Th2 dominated disorders	IFNγ, IL-4	Tissue and Blood	Immunohisto-chemical; ELISA	IFNγ expression noted in cGVHD tissue; IL-4 was not; IL-4 expression was noted in cGVHD blood samples. Serum CD30 levels were increased in all cGVHD samples
Darvay, A., Salooja, N., & Russell-Jones, R. (2004). The effect of extracorporeal photopheresis on intracellular cytokine	Descriptive, Longitudinal, Case-Control/n=9 case, n=x	To assess the effects of ECP on cytokine profiles of peripheral blood lymphocytes from patients with cGVHD	IL-2, IFNγ, IL-4	Blood	Flow cytometry	IL-2 was lower in patients with cGVHD than normal controls in both CD4 and CD8 T-cells; IFNγ was greater in

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
expression in chronic cutaneous graft-versus-host disease. European *Journal of Dermatology and Venerology, 18,* 279-284. doi: 10.111/j.1468-3083.2004.00814.x						patients with cGVHD than normal controls in both CD4 and CD8 T-cells at baseline; IL-4 greater in patients with cGVHD than normal controls at baseline in CD4 T-cells.
Fall-Dickson, J.M., Mitchell, S.A., Marden, S., Ramsay, E.S., Guaddgnini, J.P., Wu, T., . . . Pavletic, S.Z. (2010). Oral symptom intensity, health related quality of life, and correlative salivary cytokines in adult survivors of hematopoietic stem cell transplantation with oral chronic graft-versus-host disease. *Biology of Blood Marrow Transplant, 16,* 948-956. doi: 10.1016/jbbmt.2010.01.017	Cross-sectional, Descriptive, Case-Control/n=42 case, 23 control	To describe relationships among clinical characteristic of oral cGVHD and related pain, dryness, selected salivary pro-inflammatory cytokines and health related quality of life	IL-6, IL1α	Saliva	ELISA	31 subjects for analysis; there was a significant difference between the patient group and the control group for both IL-6 and IL-1α.

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
Gorgun, G., Miller, K., & Foss, F., (2002). Immunologic mechanisms of extracorporeal photochemotherapy in chronic graft-versus-host disease. *Blood, 100,* 941-947. doi: 10.1182/blood-2002-01-0068	Descriptive, Longitudinal/ 10	To examine the functional effects of ECP on alloantigen presentation and cytokine production	IFNγ, IL-4, IL-10	Blood	Flow cytometry	Patients receiving ECP had a decrease in IFNγ and an increase in IL-4 and IL-10.
Hettinga, Y.M., Verdonck, L.F., Fijnheer, R., Rijkers, G.T., & Rothova, A. (2007). Anterior uveitis: A manifestation of graft-versus-host disease. *Journal of Ophthalmology, 114,* 794-797.	Retrospective small case study/ 3 case, 4 control	To describe the occurrence of anterior uveitis after allo-HSCT	IL-6, IL-10, TNF-α, IFN-γ, sVCAM-1, RANTES	Ocular Fluid	Multiplex Immunoassay	IL-6, IL-10, RANTES, and sVCAM highly elevated in two cGVHD patients as compared with control patients.
Kaminska, D., Bernat, B., Vakulenko, O., Kuzniar, J., Tyran, B., Suchnicki, K., . . . Klinger, M. (2010). Glomerular lesion and increased cytokine gene	Case Study/ 2 cases, 1 control	To describe cytokine expression in two patients with glomerulopathies following allo-HSCT with chronic graft versus host disease	TNFα, TGFβ, IFNγ, IL-2, IL-6, IL-10	Renal Tissue	Digoxigenin mixture	Levels of TNFα, TGFβ, IFNγ, IL-2, IL-6 and IL-10 were at least five times greater in cases than levels in the control sample.

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
expression in renal tissue in patients with decompensated nephritic syndrome due to chronic graft versus host disease. *Renal Failure, 32,* 510-514. doi: 10.3109/08860221003664256						
Nakamura, K., Amakawa, R., Takebayashi, M., Son, Y., Miyaji, M., Tajima, K., . . . Fukuhara, S. (2005). IL-4 producing CD8+ T cells may be an immunological hallmark of chronic GVHD. *Bone Marrow Transplantation, 36,* 639-647. 48	Prospective, Longitudinal, Descriptive, n=19case, 10 controls; of the case group, 10 developed cGVHD	To examine cytokine expression in patients who underwent allo-HSCT with and without cGVHD	IL-4, IL-10, IFNγ	Blood	ELISA	IL-4 producing CD 8+ cells were significantly increased in the cGVHD group; IFN γ producing CD 8+ cells were significantly increased in the cGVHD group; there was no significant difference between groups for IL-4 or IFN γ producing CD 4+ cells; IL-10 was not significantly different between groups.
Poloni, A., Sartini, D., Emanuelli, M., Trappolini, S., Mancini, S., Pozzi, V., . . .	Prospective, Longitudinal, Descriptive study/14	To examine the role of inflammatory cytokines in recipients of	IL-8, IL-1β, IL-12A, IFNγ, TNFSF2,	Blood, Tissue samples	Microray analysis	CD4+ cells, TNFSF12 and PDGFβ were significantly elevated in

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
Leoni, P. (2011). Gene expression profile of cytokines in patients with chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation with reduced conditioning. *Cytokine, 53,* 376-383. doi: 10.1016/j.cyto.2010.12.008		allo-HSCT with reduced intensity conditioning on cGVHD	TNFSF3, TNFSF10, TNFSF12, TNFSF13 B, PDGFβ			patients with cGVDG; CD8+ cells, IFNγ was significantly decreased and TNFSF10 was significantly increased; CD 14+ cells, TNFSF3 and TNFSF10 were significantly decreased.
Ricci, P., Tauchmanova, L., Ristano, A., Carella, C., Mazziotti, G., Lombardi, G., . . . Serelli, C. (2006). Imbalance of the osteoprotegerin /RANKL ratio in bone marrow microenvironment after allogeneic hematopoietic stem cell transplantation. *Transplantation, 82,* 1449-1456. doi: 10.1097/01.tp.0000244588.42519.72	Longitudinal, Descriptive, Case-Control/ 36 case, 36 control; n= 36 cGVHD	To investigate OPG and RANKL in plasma of transplanted patients	IL-2, IL-4, IL-5, IL-10, IFNγ, TNFα	Blood	Multiplex	There was no significant difference found in any of the IL cytokines or TNFα between groups; patients who had received an allogeneic hematopoietic stem cell transplant had significantly higher levels of IFN γ than normal controls.
Tauchmanova, L.,	Longitudinal	To better	IL-2, IL-4,	Blood	Multiplex	All evaluated

Citation	Design/n	Purpose	Cytokine	Vector	Tool	Result
Matarese, G., Carella, C., DeRosa, G., Serio, B., Ricci, P., . . . Serelli, C. (2004). High serum leptin in patients with chronic graft-versus-host disease after hematopoietic stem cell transplantation. *Transplantation, 78,* 1376-1383. doi: 10.1097/01.TP.0000140485.20848.B7	Case-Control/60 cases, 60 controls; n=36 allo transplant, 21 with cGVHD	understand leptin production in patients with stem cell transplant	IL-5, IL-10, TNFα, IFNγ			cytokine levels were greater in the group of patients with cGVHD.

Key: alloHSCT= allogeneic hematopoietic stem cell transplantation, cGVHD= chronic graft-versus-host disease, ECP= extracorporeal photopheresis. ELISA = enzyme linked immunosorbent assay, IFN= interfeuron, IL = interleukin, PDGF= platelet- derived growth factor, SF= superfamily, sVCAM= soluble vascular cell adhesion molecule, TGF= transforming growth factor, TNF= tumor necrosis factor, OM= oral mucositis, OPG= Osteoprotegerin, *RA= receptor agonist, RANKL=* receptor activator of nuclear factor-kappaB ligand, *RANTES= regulated on activation, normal t cell expressed and secreted, VNTR= variable number tandem repeat,*

Table 3.

Studies Examining Quality of Life of Patients with Chronic Graft-Versus-Host Disease

Citation	Design/n	Purpose	Tool	Result
Fall-Dickson, J.M., Mitchell, S.A., Marden, S., Ramsay, E.S., Guadagnini, J.P., Wu, T., . . . Pavletic, S.Z. (2010). Oral symptom intensity, health related quality of life, and correlative salivary cytokines in adult survivors of hematopoietic stem cell transplantation with oral chronic graft-versus-host disease. *Journal of Biology of Blood and Marrow Transplantation, 16,* 948-956. doi:10.1016/jbbmt.2010.01.017	Descriptive, Cross-sectional n=42	To elucidate the relationships among clinical characteristics of oral cGVHD and related oral complications, proinflammatory salivary cytokines and health related quality of life	Functional assessment of cancer therapy-general/ Oral mucositis rating scale, ELISA	There was a significant negative relationship between oral cGVHD severity and the social well- being subscale of quality of life; there was a significant negative relationship between oral dryness and quality of life; total quality of life scores were lower in patients with cGVHD than U.S. population normative scores.
Harris, B., Berger, A.M., Mitchell, S.A., Steinberg, S. M., Baker, K. L., Handel, D.L., . . . Pavletic, S.Z. (2010). Spiritual	Prospective, Cross-sectional, Observational n= 52 patients with cGVHD	To describe the spiritual well-being of patients with cGVHD; to explore	Functional assessment of cancer therapy-general/ Functional	Spiritual well-being was significantly, positively

Citation	Design/n	Purpose	Tool	Result
well-being in long-term survivors with chronic graft-versus-host disease after hematopoietic stem cell transplantation. *Journal of Supportive Oncology, 8,* 119-125.		clinical and demographic factors associated with spiritual well-being of patients with cGVHD; to examine the association between spiritual well-being and cGVHD of patients with cGVHD	assessment of chronic illness Therapy-Spiritual;	correlated with all domains of quality of life (physical, social, emotional and functional)
Herzberg, P.Y., Heussner, P., Mumm, F.H.A., Horak, M., Hilgendorf, I., vonHarsdorf, S., . . . Wolff, D. (2010). Validation of the Human Activity Profile Questionnaire in patients after allogeneic hematopoietic stem cell transplant. *Journal of Biology of Blood and Marrow Transplantation, 16,* 1707-1717. doi:10.1016/jbbmt.2010.05.018	Prospective, Longitudinal, Cohort, Correlational n=176 (117 patients with cGVDH; 59 patients without cGVHD)	Validation of the Human Activity Profile in recipients of alloHSCT with and without cGVHD	Functional assessment of cancer therapy-Bone marrow transplantation/ Human activity profile, Lee cGVDH symptom scale, Short form-36, Berlin social support scale, Hospital anxiety and depression scale, NCCN-distress thermometer	117 patients had classic cGVHD (mild=33; moderate=50; severe=34); 24 patients had progressive onset cGVHD. Physical functioning has an overall effect on quality of life for patient with cGVHD; decreased physical function was associated

Citation	Design/n	Purpose	Tool	Result
				with a decreased quality of life and was noted with an increase in the severity of cGVHD.
Imanguli, M.M., Atkinson, J.C., Mitchell, S.A., Avila, D.N., Bishop, R.J., Cowen, E.W., . . . Pavletic, S.Z. (2010). Salivary gland involvement in chronic graft-versus-host disease: Prevalence, clinical significance, and recommendations for evaluation. *Journal of Biology of Blood and Marrow Transplantation, 16,* 1362-1369. doi:10.1016/j.bbmt.2010.03.023	Cross-sectional n=101	To systematically examine the characteristics and correlates of salivary gland function in cGVHD	Oral health impact profile; Functional assessment of cancer therapy-general	Oral quality of life scores were significantly higher (indicating greater impairment) in patients with salivary gland dysfunction; quality of life was significantly positively correlated with the degree of patient perceived oral discomfort; there was not a significant correlation between actual clinical oral

Citation	Design/n	Purpose	Tool	Result
				severity scores and patient perceived quality of life; there was no significant correlation between salivary dysfunction and quality of life.
Kim, S.J., Lee, J.W., Jung, C.W., Min, C.K., Cho, B., Shin, H. J., . . . Won, J.H. (2010). Weekly rituximab followed by monthly rituximab treatment for steroid refractory chronic graft-versus-host disease: Results from a prospective, multicenter, phase II study. *Haematologica, 95,* 1935-1942. doi:10.3324/haematol.2010.026104	Open-label, Multicenter, Prospective, Phase II study n= 37	To evaluate treatment response to rituximab, to evaluate changes in patient reported quality of life, to evaluate effectiveness to treatment for discontinuation of steroid use	Short from-36	All baseline scores for all quality of life domains below normal in patients diagnosed with cGVHD.
Lee, S.J., Kim, H.T., Ho, V.T., Cutler, C., Alyea, E.P., Soiffer, R.J., 7 Antin, J.H. (2006). Quality of life associated with acute and chronic graft-versus-host disease. *Bone Marrow Transplantation, 38,* 305-310. doi:10.1038/sjbmt.17	Prospective, Longitudinal n= 96 (group 1: no acute GVHD and no cGVHD; group 2: no acute GVHD and yes cGVHD; group 3: yes acute GVHD and yes cGVHD)	To measure the impact of acute and chronic graft-versus-host disease on quality of life and functional status prior to transplant, at six months and twelve	Functional assessment of cancer therapy-Bone marrow transplant/ Medical outcomes study-Short form 12	Baseline quality of life scores were not different among among patients; scores did not differ for mental functioning or

Citation	Design/n	Purpose	Tool	Result
05434		months post-transplant		physical functioning overtime for any group; the trial outcome index score for quality of life was significantly lower at 6 months for patients in group 3 and at 12 months for patients in group 2.
Pallua, S., Giesinger, J., Oberguggenberger, A., Kemmler, G., Nachbaur, D., Clausen, J., . . . Holzner, B. (2010). Impact of GvHD on quality of life in long-term survivors of haematopoietic transplantation. *Bone Marrow Transplantation, 45,* 1534-1539.	Case-Control Cross-sectional n= 100 Retrospective/Prospective Longitudinal n= 33	To investigate the impact of GvHD on the quality of life in survivors of bone marrow transplantation and peripheral blood stem cell transplantation; to investigate change in quality of life over time; Compare quality of life outcomes in hematopoietic stem cell transplant	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire	There were significant impairments in quality of life for patients with cGVHD when compared to patients without cGVHD or previous cGVHD in areas of role functioning and global quality of life.

Citation	Design/n	Purpose	Tool	Result
		survivors to healthy controls		
Pidala, J., Kurland, B., Chai, X., Majhail, N., Weisdorf, D.J., Pavletic, S., . . . Lee, S.J. (2011). Patient-reported quality of life is associated with severity of chronic graft-versus-host disease as measured by NIH criteria: Report on baseline data from the Chronic GVHD Consortium. *Blood, 117,* 4651-4657. doi:10.1182/blood-2010-11-319509	Prospective, Observational, Cross-sectional, Cohort enrolled across five centers n=298	To describe the relationship between cGVHD severity and quality of life; to compare quality of life in patients with cGVHD to norm population data; to compare quality of life in patients with cGVHD to patients with other chronic health conditions; to determine the ability of quality of life measures to discriminate cGVHD severity	Short form-36; functional assessment of cancer therapy-bone marrow transplant	Only 10% of patients had mild severity of cGVHD; All domains of both quality of life measures were significantly different between patients with mild cGVHD and severe cGVHD; All domains of both quality of life measures except the mental component score from the short form-36 were significantly different between patients with moderate cGVHD and severe cGVHD.

Citation	Design/n	Purpose	Tool	Result
Pidala, J., Kurland, B.F., Chai, X., Vogelsang, G., Weisdorf, D.J., Pavletic, S., . . . Lee, S.J. (2011). Sensitivity of changes in chronic graft-versus-host disease activity to changes in patient reported quality of life: Results from the Chronic Graft-Versus-Host Disease Consortium. *Haematologica, 96,* 1528-1535. doi:10.3324/haematol.2011.046367	Prospective, Longitudinal Observational, Cohort enrolled across six centers n= 336	To assess the association between changes in quality of life and cGVHD severity	functional assessment of cancer therapy-Bone marrow transplant and Short form-36	Most common cGVHD sites were skin, mouth, eye, and lung; At baseline, patients with cGVHD had lower than average (50) scores on the short form 36 with the lowest score reported for physical role; The patient's perception of severity negatively impacted quality of life scores.
Pidala, J., Vogelsang, G., Martin, P., Chai, X., Storer, B., Pavletic, S., . . . Lee, S.J. (2011). Overlap subtype of chronic graft-versus-host disease is associated with an adverse prognosis, functional impairment, and inferior patient reported outcomes:	Prospective, Observational, Cross-sectional, Cohort enrolled across nine centers n= 427	To identify differences in overlap subtype of cGVHD in an effort to distinguish it from late acute graft-versus-host disease and classic cGVHD	Functional assessment of cancer therapy-Bone marrow transplant/ Lee cGVHD symptom scale; Human activity profile;	352 of the patients had overlap syndrome and only 75 had classic cGVHD. Neither the cGVHD severity scores nor

Citation	Design/n	Purpose	Tool	Result
A Chronic Graft-Versus-Host Disease Consortium study. *Haematologica, 97,* 451-458.			Short form-36;	the quality of life scores differed significantly between the two groups.

Key: cGVHD= chronic graft-versus-host disease, ELISA= enzyme linked immunosorbent assay, NCCN= National Comprehensive Cancer Network

Chapter 3

IRB Proposal: Research Plan

VCU RESEARCH PLAN TEMPLATE

Use of this template is required to provide your VCU Research Plan to the IRB. Your responses should be written in terms for the non-scientist to understand. If a detailed research protocol (e.g., sponsor's protocol) exists, you may reference specific sections of that protocol. NOTE: **If that protocol does not address all of the issues outlined in each Section Heading, you must address the remaining issues in this Plan**. **It is NOT acceptable to reference a research funding proposal**.

ALL Sections of the Human Subjects Instructions must be completed with the exception of the Section entitled "Special Consent Provisions." Complete that Section if applicable. When other Sections are not applicable, list the Section Heading and indicate "N/A."

NOTE: The Research Plan is required with ALL Expedited and Full review submissions and MUST follow the template, and include version number or date, and page numbers.

DO NOT DELETE SECTION HEADINGS OR THE INSTRUCTIONS.

I. TITLE

Symptoms, Cytokines, and Quality of Life Profiles of Patients with Chronic Graft-Versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

II. RESEARCH PERSONNEL

A. PRINCIPAL INVESTIGATOR

List the name of the VCU Principal Investigator

DEBRA E. LYON

B. STUDY PERSONNEL

NOTE:

1. **Information pertaining to each project personnel, including their role, responsibilities, and qualifications, is to be submitted utilizing a *VCU IRB Study Personnel Information and Changes Form.* This form is available at http://www.research.vcu.edu/forms/vcuirb.htm.**
2. **A roster containing a list of project personnel is to be maintained as a separate study document which is retained with the Research Plan, and is to be updated as applicable. The roster is to include all VCU project personnel (including the principal investigator) who are *engaged* in this research protocol, as well as non-VCU personnel who are also *engaged* but do not have local IRB approval for this protocol from their own institution,. This template document, entitled *VCU IRB Study Personnel Roster*, is available at**

http://www.research.vcu.edu/forms/vcuirb.htm.

C. Describe the process that you will use to ensure that all persons assisting with the research are adequately informed about the protocol and their research-related duties and functions.

Dr. Lyon will work closely with the doctoral student, Debra Lynch Kelly, finalizing the procedures for participant screening, recruitment, data collecting, documentation, and manuscript preparation. The physicians and nurses of the Bone Marrow Transplant Center at the Massey Cancer Center will provide a clinical link for the recruitment of participants for this study. In the first month of the study, Debra Lynch Kelly will conduct a training session for staff in the Bone Marrow Transplantation Clinic. All personnel will be familiar with the proposal and measurement tools. A resource manual will be maintained on site from where participants will be recruited. The manual will contain the mission of the project, detail of operations, including the protocol, forms, IRB materials, the monthly enrollment form, elevated HAD-S scores and proper questionnaire completion. The principal investigator and the doctoral student have been trained extensively in research procedures and in issues regarding the protection of research subjects' rights and privacy. All study personnel have completed HIPAA training. Follow-up meetings by telephone calls, faxes, e-mail and face-to –face will be used for ongoing communication among the research team and the clinic.

III. CONFLICT OF INTEREST

Describe how the principal investigator and sub/co-investigators might benefit from the subject's participation in this project or completion of the project in general. Do not describe (1) academic recognition such as publications or (2) grant or contract based support of VCU salary commensurate with the professional effort required for the conduct of the project

No member of the research team, or of their immediate families, has a financial interest in any external entity related to the work to be conducted under the project or interested in the results of the project. To the best of our knowledge, no VCU employee has a financial interest, ownership, or equity interest in the funding source of this project.

IV. RESOURCES

Briefly describe the resources committed to this project including: (1) time available to conduct and complete the research, (2) facilities where you will conduct the research, (3) availability of medical or psychological resources that participants might require as a consequence of the research (if applicable), and (4) financial support.

1) The doctoral student, Debra Lynch Kelly, under the supervision of her advisor, Dr. Debra E. Lyon, will focus full-time on the completion of the study. The projected completion date is November, 2013. The doctoral student will attend bi-weekly multi-disciplinary meetings in the Bone Marrow Transplant Center. Data collection will commence in month two of the study and will continue through month seven. Final data analysis will be conducted throughout month ten of the year. Debra Kelly will work with the Clinical Coordinator, Valerie Charron, to arrange study visits.
2) The facility to be used for recruitment will be the Bone Marrow Transplant Clinic of the Massey Cancer Center at Virginia Commonwealth University Health System

3) Dr. McCarty, medical director of the bone marrow transplant program, will serve as medical resource for the study. Participants with elevated levels of depression (a score of >16 on the depressive sub-scale of the HAD-S (HADS-D), indicating severe depressive symptoms, will be referred to the clinical social worker in accord with the current system in place in the bone marrow transplant clinic for evaluation of acute psychiatric symptoms.
4) There is no financial support for this project. Gift cards will be provided to the study from the doctoral advisor's indirect account fund.

V. HYPOTHESIS

Briefly state the problem, background, importance of the research, and goals of the proposed project.

Chronic graft-versus-host disease is the perhaps the most detrimental and the most common late term complication following allogeneic hematopoietic stem cell transplant. Up to 90% of patients undergoing allogeneic hematopoietic stem cell transplantation will be diagnosed with this complication (Lee, Cook, Soiffer, & Antin, 2002; Lee, Vogelsang, & Flowers, 2003). Manifestations of chronic graft-versus host-disease can be mild to severe and can occur in any of the body systems with the integumentary system being the most common site. The literature regarding this phenomenon is predominantly that of a biomedical focus. Few studies have focused on distressing features of chronic graft versus host disease such as symptom frequency and severity and decreased quality of life. With increased survivorship of patients with cGVHD, improvement in the quality of life for patients with cGVHD is of growing importance (Flowers et al., 2011; Lee et al., 2002; Lee et al, 2003).

Symptom management is a major issue for patients experiencing cGVHD (Lee et al, 2002; Perez-Simon, Sanchez-Abarca, Diez-Campelo, Caballero, & San Miguel, 2006). There is a gap in the literature establishing the relationship between symptoms experienced in this vulnerable population and quality of life. The relationship between biological markers and behavioral responses may also impact the frequency and severity of symptoms experienced in patients with chronic graft-versus-host disease. As chronic graft-versus-host disease is speculated to be an allo-reactive complication, examining patterns and levels of inflammatory markers are of importance.

These features of chronic graft-versus-host disease make examining this phenomenon from a biobehavioral nursing perspective critical for caring for these patients. This study will elucidate features associated with chronic graft-versus-host disease from a biobehavioral nursing perspective. By understanding which symptoms are present and how inflammation presents for these patients, interventions to ameliorate symptom severity and frequency using multiple modalities may be tested and may be implemented to positively impact patients' quality of life.

VI. SPECIFIC AIMS

Therefore, the specific aims of this study are:
1) To describe symptoms, inflammatory markers, and quality of life of patients with cGVHD
2) To examine the associations among selected symptoms (pain, depression, and fatigue) of patients with cGVHD
3) To examine the associations among selected cytokines (IL-1β, IL-6, IL-10, TNF-α, and IFN-γ) of patients with cGVHD
4) To examine the associations among selected symptoms (pain, depression, and fatigue), cytokines (IL-1β, IL-6, IL-10, TNF-α, and IFN-γ) and quality of life of patients with cGVHD
5) To examine the associations among the top three severe and bothersome symptoms determined from the Memorial Symptoms Assessment Scale, selected cytokines, and quality of life.

VII. BACKGROUND AND SIGNIFICANCE

Include information regarding pre-clinical and early human studies. Attach appropriate citations.

Hematopoietic stem cell transplantation has become the standard treatment for many hematologic cancers including acute leukemia, chronic myelogenous leukemia, and multiple myeloma. Patients receiving an allogeneic

hematopoietic stem cell transplant (alloHSCT) are at risk for developing a serious, potentially life-threatening complication known as chronic graft-versus-host disease (cGVHD). This is a complex, multisystem issue involving immune dysregulation and immunodeficiency, impaired organ function, and decreased survival (Baird and Pavletic, 2006).

This phenomenon occurs in as many as 90% of all alloHSCT recipients who survive greater than 100 days post-transplant (Lee, Cook, Soiffer, & Antin, 2002; Lee, Vogelsang, & Flowers, 2003).Any of the body systems can be affected by cGVHD. Cutaneous and ocular cGVDH are the most commonly affected sites while pulmonary and hepatic cGVHD have the highest mortality. In addition to being the most serious complication of alloHSCT, cGVHD is also the most common (Pidala et al., 2011; Vogelsang, 2011). Debilitating consequences of cGVHD include loss of sight, pulmonary disease, and joint contractures as well as death resulting from chronic immune suppression (Filipovich et al., 2005).

The development of cGVHD is thought to be linked to alloreactivity and the processes are delayed or their effects are exerted slowly (Lee, 2005). The pathophysiology, however, is still poorly understood (Lee, 2005; Vogelsang, 2001). As cGVHD is speculated to be an inflammatory process, several cytokines such as interleukin-6 (IL-6), interferon-gamma (IFN-γ), interleukin-10 (IL-10), interleukin-10 (IL-10) as well as tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) from damaged cells may contribute to cGVHD development (Aracting, Gluckman, LeGoue, Dubertret, & Carosella, 1996; Craciun, 2002; Lee, 2005;).

Until recently, patients experiencing graft versus host disease were diagnosed with acute graft-versus-host disease (aGVHD) if presentations occurred prior to 100 days post-transplant and cGVHD was diagnosed if presentations occurred 100 days or more post transplant. In 2005, a series of papers produced by the National Institutes of Health consortium on cGVHD, established guidelines for new diagnostic and classification criteria for cGVHD (Filipovich et al., 2005). The recommendations for diagnosing and scoring cGVDH are as follows 1) distinguishing aGVHD from cGVHD, 2) presence of at least one diagnostic clinical sign of cGVHD or at least one distinctive manifestation confirmed by biopsy or other testing, and 3) exclusion of other diagnoses (Filipovich et al., 2005). In addition to diagnosing cGVHD, scoring cGVHD allows identification of disease severity. A 0-3 scoring system is recommended for evaluation of organ involvement and number of sites involved. A global assessment score (mild, moderate or severe) is ascertained by combining the organ and site specific scores (Filipovich et al., 2005). Classic and overlap syndrome are the two main designations for cGVHD type. Clasic cGVHD is absent of any aGVHD features and overlap cGVHD in which diagnostic or distinctive features of both aGVHD and cGVHD are present concurrently (Filipovich et al., 2005). The sequence of the development of cGVHD can be categorized as: 1) de novo (onset of cGVHD without prior diagnosis of aGVHD), 2) progressive (onset of cGVHD is an extension of aGVHD) and 3) quiescent (onset of cGVHD after resolution of aGVHD). Progressive cGVHD onset is the most common and is associated with the worst prognosis (Galbizo & Williams, 2006; Lee, Vogelsang, & Flowers, 2003).

Due to increased survivorship of patients with cGVHD, improving quality of life is of growing importance (Flowers et al., 2011; Lee et al., 2002; Lee et al., 2003). Symptom management is also a major issue for patients experiencing cGVHD (Lee et al., 2002; Perez-Simon, Sanchez-Abarca, Diez-Campelo, Caballero, & San Miguel, 2006). From December, 2005 through May, 2006, the National Cancer Institute published a series of papers in the areas of diagnosing and staging, histopathology, strategies for the development and validation of biomarkers, response criteria, ancillary therapy and supportive care, and the design of clinical trials for cGVDH (Baird and Pavletic, 2006). The development and validation of biomarkers includes examining both biological and behavioral (patient-reported) measures objectively with quality of life as a possible endpoint to measure success of research testing novel interventions for supportive care (Filipovich et al., 2005).

Theory

The proposed study adopts the Theory of Unpleasant Symptoms (Figure 1) to provide the theoretical perspective for this research to explore the relationships among symptoms commonly associated with cancer (pain, depression, and fatigue) and quality of life in patients diagnosed with cGVHD. The theory will be modified to include the biological markers (cytokines) and the relationships between and among symptoms, cytokines, and quality of life.

The Theory of Unpleasant Symptoms (TOUS) was developed by nurses who were researching symptoms in various clinical settings and realized that there were certain commonalities among symptoms while simultaneously

exhibiting uniqueness (Lenz, Suppe, Gift, Pugh, & Milligan, 1995). Further research led them to conclude that symptoms rarely occur in isolation but usually more than one at a time and that the relationships among the influencing factors (physiologic, psychological, and situational), the symptoms experienced and the outcome (performance) were not linear but interactive (Lenz, Pugh, Mulligan, Gift, & Suppe, 1997). The TOUS has been used as the framework for many studies in the examination of symptom clusters across many patient populations and has been used in many cancer related studies as well (Chen & Tseng, 2005; Farrell & Savage, 2010; Fox & Lyon, 2007; Fox, Lyon, & Farace, 2007; Jurgens et al., 2009). However, in the literature reviewed, the TOUS has not been tested in the cGVHD population.

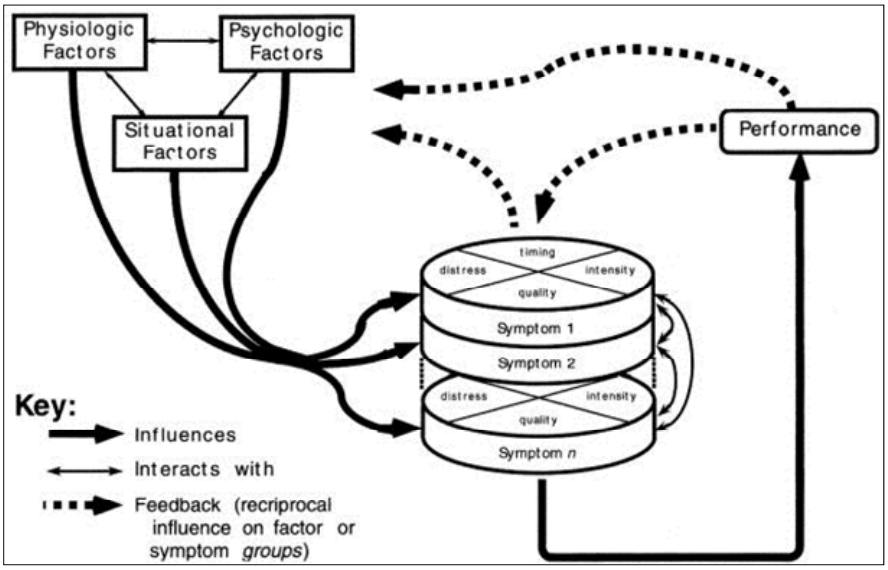

Figure 1. Updated version of the middle-range theory of unpleasant symptoms

Symptoms

Symptoms are a major source of distress and discomfort for patients with cancer (Theobald, 2006). The National Institutes of Health (2002) reported that the most commonly experienced symptoms among patients with cancer are pain, depression, and fatigue. Insomnia is also frequently reported as a symptom associated with cancer (Fox & Lyon, 2007; Fox, Lyon, & Farce, 2007; Theobald, 2006). In a study examining cancer, it was reported that as many as 90% of cancer patients experience pain, 91% fatigue, and up to 25% depression (Fox & Lyon, 2007). The symptoms experienced by patients with cancer may be due to the cancer itself and/or due to the treatments. Symptoms, particularly fatigue, may persist well into survivorship (Oh & Seo, 2011). A major role of the oncology nurse is to decrease the burden of symptoms. Patients with cGVHD may experience similar symptoms; however due to the lack of literature aimed at helping patients with cGVHD manage their symptoms, adequate management of symptoms is a major barrier to caring for these patients (Williams et al., 2007). The literature is lacking in symptom management and little is known about which symptoms patients experience and to what extent.

Pain

Pain is defined as an unpleasant sensory or emotional sensation causing distress and is the number one reason why people seek medical attention (Cheng, Foster, & Huang, 2003). Patients with cancer may not only be experiencing pain directly related to the cancer process but may experience pain caused by the treatments for cancer (Miaskowski et al., 2006). Pain results from diagnostic procedures, treatment, and psychological suffering (Kreitler & Merimski, 2007). Interventions to ameliorate pain in this population, is a challenge for health care providers, family, care-givers and the patient (Caraceni, 2001). The percentage of uncontrolled chronic cancer pain

has been shown to be as high as 96% and is reported by patients with cancer to be a major cause of distress (Caraceni, 2001; Stenseth, 2007). Patients with cGVHD experience many different types of pain; however, it is the severity of the pain that is found to be most distressing followed by the impact on quality of life (Perez-Simon, et al., 2006). In order to develop interventions to adequately manage pain in this patient population, there must be an adequate assessment of the pain (Theobald, 2004).

Depression

Depression is feeling "sad" or "blue" for an extended period of time and these feeling interfere with normal activities (National Institute of Mental Health [NIMH], 2010). Symptoms may include feeling sad or empty, hopeless, helpless. One may have a gloomy outlook on life and the inability to feel happiness towards to things which used to be enjoyable (NIMH, 2010). Depression and illness are often co-existing and one may be the cause, consequence or predisposition of the other (NIMH). Depression is present in up to 30% of all cancer patients and is a predictor of mortality (Kroenke et al., 2010). In a study with 215 randomly assigned patients with cancer, 68% had adjustment disorders with a depressed or anxious mood (Massie, 2004). Depression is reported as one of the symptoms most common in all types of cancer and negatively impacts quality of life (Fox et al., 2007; Miaskowski et al., 2004; Roeland, et al., 2010).

Fatigue

Fatigue is defined as weariness or tiredness or lack of energy (Mendoza et al., 1999). Fatigue experienced by the general population serves as a protective response to physical and psychological stress and is often relieved by rest; however, for patients with cancer fatigue is described as unrelieved by rest, chronic, unpleasant, distressing, and life altering (Servaes, Verhagen, & Bleijenberg, 2002). Fatigue is the most commonly reported symptom in patients with cancer and one of the main causes of emotional and physical distress. It is the symptom among cancer patients reported to cause the most interference with daily life (Lawrence et al., 2004; Lyon & Fox, 2007; Fox, Lyon, & Farace, 2007; Ross & Alexander, 2001). Cancer related fatigue can have devastating effects on the social and personal lives of patients experiencing such fatigue. Furthermore, this fatigue may last long after the completion of treatment (Prue, Rankin, Allen, Gracey, & Cramp, 2006). Fatigue is thought to be a side effect of treatment modalities and a consequence of the biologic effects of the cancer (Lawrence et al., 2004). A major disease and treatment burden for patients with cancer is fatigue (Mendoza et al., 1999). Patients experiencing cancer at different stages, throughout treatment and into survivorship experience fatigue (Seyidova-Khoshknabi, Davis, & Walsh, 2011).

Occurrence of reported fatigue has been shown to be as high as 99% in patients with cancer and 91% in patients with hematologic cancers requiring bone marrow transplantation (Lawrence et al., 2004; Seyidova-Khoshknabi et al., 2011). Management of symptoms associated with distress requires an assessment of the severity of the symptom and is essential for effective intervention and improved quality of life (Ross & Alexander, 2001).

Cytokines

Biobehavioral science is based in the assumption that the biology of a phenomenon is inextricably linked with behavior thereby making it necessary to examine them as two dimensions of the same whole. It is speculated that cytokines act neurologically to induce psychological and behavioral changes (Kelley, 2003). It is also speculated that the production and release of certain cytokines can be effected by the cancer itself and these cytokines may mediate symptoms (Seruga, Zhang, Bernstein, & Tannock, 2008). A call by the National Cancer Institute (2006) to investigate strategies for the development and validation of biomarkers in cGVHD research could be beneficial in elucidating strategies to combat the devastating effects of cGVHD (Baird and Pavletic, 2006). The establishment of the relationship between symptoms and cytokines in this population may serve to determine the interplay of certain inflammatory cytokines and symptom severity which may in turn lead to advanced interventions to relieve bothersome symptoms for patients with cGVHD. C-reactive protein (CRP) is an inflammatory marker regulated by pro-inflammatory cytokines. It is non-specific and is an acute phase marker. Several studies have shown a positive correlation between elevated CRP levels and increased depressive symptoms. Fewer studies have examined this phenomenon in patients with cancer.

Quality of Life

Quality of life in patients with cancer is altered due to many factors among which one is the symptoms that

are experienced (Monga et al., 2007). Previous focus on patients with hematologic cancers undergoing bone marrow transplant has been survivorship. With the increase in survivorship, focus has turned toward managing the consequences of complications such as cGVHD. Symptom management and quality of life improvement is moving to the forefront of cGVHD management (Flowers et al., 2011; Lee et al., 2002; Lee et al., 2003).

VIII. PRELIMINARY PROGRESS/DATA REPORT

If available.

N/A

IX. RESEARCH METHOD AND DESIGN

Include a brief description of the project design including the setting in which the research will be conducted and procedures. If applicable, include a description of procedures being performed already for diagnostic or treatment purposes.

This study will use a cross-sectional, correlative, descriptive design to address the following specific aims on patients with alloHSCT:

1) To describe symptoms, inflammatory markers, and quality of life of patients with cGVHD
2) To examine the associations among selected symptoms (pain, depression, and fatigue)
3) To examine the associations among selected cytokines (IL-1β, IL-6, IL-10, TNF-α, and IFN-γ)
4) To examine the association of selected symptoms and cytokines among each other and quality of life
5) To examine the associations among the top three severe and bothersome symptoms determined from the Memorial Symptoms Assessment Scale, selected cytokines, and quality of life.

Setting

Massey Cancer Center's Bone Marrow Transplant Center:

The Massey Cancer Center (MCC), which serves to coordinate clinical research on cancer at VCU, is among the nation's leading research and clinical institutions. One of only 60 National Cancer Institute (NCI) designated Centers in the United States and one of only two in Virginia, MCC is central Virginia's most important resource for cancer research, clinical trials, and treatment with an annual census of more than 1,400 patients. MCC is the focal point for basic and clinical research, education, and cancer health delivery activities. Located on the Medical Center Campus of VCU, MCC was designated as a clinical cancer center by the NCI in 1975 with the award of its first core grant; MCC has had continuous NCI center funding since that time.

There are 160 MCC member scientists (including Dr. Lyon) from 25 academic departments, of whom more than 90 are involved in collaborative research activities within the context of MCC programs. Research programs include developmental therapeutics, radiation biology and oncology, cancer cell biology, immune mechanisms, and cancer control. Post-doctoral training at MCC is supported by an NCI funded training grant. The Bone Marrow Transplant (BMT) Center has been continuously operating since 1988 and is the largest comprehensive BMT provider in the state. It is also an Anthem Blue Cross and Blue Shield Blue Distinction Center — one of just 70 nationwide.

Subject Recruitment, Enrollment, Tracking, and Retention

Participants will be recruited from Massey Cancer Center Bone Marrow Transplant Unit. The doctoral student will contact the potential participant after discussion with the transplant team. After obtaining informed consent, participants will complete questionnaires, and have a blood sample taken. A blood sample will be collected (less than one tablespoon) from an appropriate vein or venous access device.

The study visit, including the consent process, questionnaires and specimen collection, will take approximately one hour to complete. The study visit will be conducted during a routine clinic visit or another convenient time. After the participant has had all questions answered adequately and has signed the IRB approved Informed Consent Form, he will be assigned a patient identification number unique to the study to protect his identity. A tracking system, similar to that which is being used in Dr. Lyon's current studies will be used to enhance participant retention over the study period.

Prior to Initial Visit

Before the study visit, there will be demographic data collected on the patient such as age, sex, disease profile (type of cancer, HLA match, related versus unrelated donor), marital status, support system, past medical history, and socio-economic factors.

At Study Visit

At the study visit the patient will be asked to fill out symptom questionnaires (Pain-using the Brief Pain Inventory, Depressive Symptoms-using the Hospital Anxiety and Depression Scale, Fatigue-using the Brief Fatigue Inventory, Other Symptoms-using the Memorial Symptoms Assessment Scale and the Lee cGVHD Symptom Scale) and the Functional Assessment of Cancer Treatment- Bone Marrow Transplant quality of life questionnaire.

Participants will also fill out a questionnaire regarding lifestyle habits using the Lifestyle Profile. The Perceived Stress Scale will also be completed. Patients will have a blood specimen collected (less than a tablespoon). Blood samples will be collected in appropriate container and transported to the CBCR laboratory in the School of Nursing. Blood will be centrifuged in the CBCR. Samples will be stored at -20^0 C until further processing.

How Variables will be Measured

Variables examined in this study will be measured using the following instruments. All concepts and measures for domains of interest are presented in Table 1. The conceptual model (Figure 2) explains the concepts under investigation and their relationships.

Demographic, Individual, Disease, and Treatment Related Variables.

The medical record will be reviewed for information regarding transplant data such as patient and donor race, age, and gender; HLA and related versus unrelated donor; performance status, and type of cGVHD. It is important to collect information regarding patient related, disease related, and treatment related variables that may relate to the major study variables and are therefore possible significant covariates. The demographic and disease profile questionnaire will be completed by the doctoral student to ascertain the prescribed treatment plan and to capture specific details of the pre and post-transplant sequelae. In addition, participants will complete a lifestyle profile questionnaire (Walker, Fleschler, & Heaman, 1998) and a perceived stress scale (Cohen, 1988).

General Symptoms

Lee cGVHD Symptoms Scale

The Lee Symptom Bother Scale is a multi-symptom scale that measures the severity of symptoms as described as how much a symptom bothers the patient (Lee, Cook, Soiffer, & Antin, 2006). There are seven domains assessed: 1) skin, 2) eye, 3) mouth, 4) lung function, 5) nutrition, 6) psychosocial status, and 7) energy. All areas are rated using a 5 point Likert type scale where 0 indicates "Not at all" and 4 indicates "Extremely" bothered. A summary score is created by taking the mean of all items and linearly transforming that value to a 0-100 scale. The Chronbach's α is between .79 and .90. The test-retest reliability for all subscales is .74-.93 except psychosocial is .55 and lung is .28. The scale has good convergent validity (Lee et al., 2006).

Memorial Symptom Assessment Scale

To comprehensively explore which symptoms patients with cGVHD are experiencing, the Memorial Symptom Assessment Scale (MSAS-SF) will be used to obtain frequency, severity and distress of symptoms commonly reported by patients with cancer (Portney et al., 1994). This scale is a validated multidimensional symptom assessment instrument that assesses severity, frequency and distress of 32 prevalent symptoms (Chang, Hwang, Feuerman, Kasimis, & Thaler, 2000). This measure includes a physical symptom subscale, a psychologic subscale, and a global distress index. Tested with a sample of 299 cancer patients, the Cronbach alpha for the MSAS-SF subscales ranged from .76-.86 and the test-retest correlation coefficients ranged from .86-.94 at one day and one week respectively (Chang et al., 2000). Portenoy et al. (1994) tested the MSAS-SF with a group of 246 cancer patients and found a Cronbach's alpha of .88 for the physical subscale and .83 for the psychologic subscale. The total time to complete this form is approximately 10 minutes. In addition to the 32 prevalent symptoms, this form allows for patients to identify and quantify "other" symptoms. This scale has been validated in patients with cancer, congestive heart failure, auto-immune deficiency syndrome and in both in-patient and out-patient settings (Chang et al., 2000; Portenoy et al., 1994; Tranmer et al., 2003).

Selected Symptoms

Pain

Pain will be assessed using the **Brief Pain Inventory (BPI).** This instrument was chosen for its use in the oncology population, its validity and it feasibility (Cleeland, 2009). The BPI was originally created in 1989 by the Pain Research Group under the leadership of Dr. Charles S. Cleeland at the University of Wisconsin's School of Medicine in response to a need for patients with cancer to have adequate pain management (Cleeland, 2009). The utilization of the BPI for the measurement of pain is well established (Borden et al., 2006; Callstrom et al., 2002; Garbez, Chan, Neighbor, & Puntillo, 2006; Hadi et al., 2008; McMillan, Tofthagen, Tittle, & Laughlin, 2008). The BPI has been psychometrically validated in many languages including English, Arabic, Chinese, Filipino, French, German, Spanish, and Thai (Cleeland, 2009). The BPI was created to evaluate two dimensions of pain: 1) the

severity and 2) the interference.

Validity for this tool was established through a two-factor structure, internal stability, and test-retest reliability. Through factor analyses, pain severity and pain interference each had an eigenvalue greater than one (Cleeland, 2009). According to Kaiser (1960), there are as many reliable factors as there are eigenvalues greater than one. In a national study conducted by the Eastern Cooperative Oncology Group involving 1,261 participants with recurrent or metastatic cancer diagnoses from 80 centers this two-factor structure was confirmed (Cleeland, 2009). Internal stability was also assessed and the Cronbach's alpha was .80-.87 pain severity and .89-.92 for the interference items (Mendoza, Mayne, Rublee, & Cleeland, 2006). The test-retest reliability was established for one day to one week and was .93 for "worst" pain, and .78 for "usual" pain. The test-retest was lower (.59) for pain "now" (Cleeland, 2009). A German study involving 109 patients with cancer found similar results (Cleeland, 2009).

The BPI consists of a body diagram to indicate location of pain and a general question asking if pain is present. Four items assess pain intensity or severity using an eleven point scale where 0 indicates no pain and 10 indicates the worst pain imaginable. There is also a question regarding medications taken for pain relief and the efficacy of the medication taken. There are seven interference questions. The eleven point scale is used to assess how much pain interferes with daily living where 0 indicates that pain does not interfere at all with the activity, and 10 indicates pain completely interferes with that activity. The activities are further divided into affective dimensions (relations with others, enjoyment of life, and mood) and general dimensions (walking, general activity and work). The categorization of sleep was unclear (Cleeland, 2009). The developers of the BPI recommend calculating the severity score by adding the four items and dividing the score by four to find the mean severity score (Cleeland, 2009). The interference score is calculated the same way and can only be used if four or more of the seven items is completed (Cleeland, 2009). The developers of the instrument do not indicate scoring of the categorical question regarding the presence or absence of pain and as such was used as a characteristic description. There is also no recommendation for scoring the use of analgesics and the efficacy of the medications taken. This instrument takes less than ten minutes to complete. The questionnaire can be completed by the participant or by the investigator and is easy to translate for patients whose primary language is not English (Mendoza et al., 2006).

Depressive Symptoms

Depressive symptoms will be assessed using the subscale for depression from the **Hospital Anxiety and Depression Scale (HADS).** This scale was chosen for its use in the oncology population, its validity and it feasibility (Zigmond & Snaith, 1983). The measurement has been widely used in cancer settings as well as general medical settings and is reported to be the most often used scale to assess depressive symptoms in the palliative care setting (Mitchell, Meader, and Symonds, 2010). In a systematic review of the literature to evaluate the validity of the HADS, twenty four out of the fifty studies used the HADS in an oncology or palliative population (Mitchell et al., 2010).

The HADS was developed in 1983 by Zigmond and Snaith to provide clinicians with a reliable screening tool for psychiatric disorders. This tool was a modification from the General Health Questionnaire in an effort to make the questionnaire less time consuming and provide information regarding the "nature" of the condition (Zigmond & Snaith, 1983). It was the intention of the developers of this instrument to have separate scores for anxiety and depression (Zigmond & Snaith, 1983). For the purposes of this study, only the subscale of depression was analyzed.

This instrument is used to assess the presence and severity of anxiety and depressive symptoms over a seven day period. The depression subscale is comprised of seven items using a four point scale ranging from 0 (least severe) to 3 (most severe). These items were based on the anhedonic state (Zigmond & Snaith, 1983). A higher score indicates more depression and a score of greater than 16 is considered severe and may indicate a need for intervention.

Cronbach's alpha has been found to be high (.82-.90) for the HADS depression subscale (Mykletun, Stordal, & Dahl, 2001). In principal component analysis (of depression), a two-factor analysis yielded an eigenvalue of 3.6 (Mykletun et al., 2001). The depressive symptom questions loaded with depression (Mykletun et al., 2001). It is a brief self-report tool that takes less than five minutes to complete (Zigmond & Snaith, 1983).

Fatigue

Fatigue will be assessed using the **Brief Fatigue Inventory (BFI).** This instrument was chosen for its use in the oncology population, its validity and its feasibility (Mendoza et al., 1999). The BFI is a nine item, eleven point

scale that assesses physical, affective, cognitive and social domains in a two dimensions, pain intensity or severity (sensory) and interference (reactive) that can be described as the subjective report of fatigue severity (Mendoza et al., 1999; Seyidova-Khoshknabi, Davis, & Walsh, 2011). It can be administered as a self-report, interview with a research staff, or interactive voice response system (Mendoza et al., 1999). Severity scores are as follows: 1) mild (1-3), 2) moderate (4-6) and 3) severe (7-10). The wording of the tool was designed to be understandable by patients who are educationally disadvantaged and for ease of translation for non-English speaking patients. It is also able to be translated into many languages (Mendoza et al., 1999).

The BFI was developed by researchers from the M. D. Anderson Cancer Center in Houston, Texas for the purpose of assessing fatigue in patients with cancer or fatigue related to cancer treatment (including patients who have undergone bone marrow transplantation) (Mendoza et al., 1999). It was also developed to assess the severity of fatigue experienced and the impact of fatigue on daily functioning (Mendoza, et al., 1999). The BFI has been psychometrically validated in many languages including English, Chinese, Filipino, German, Greek, Japanese, Korean and Russian (Mendoza et al., 1999).

Validation for this instrument was established in through construct validity, concurrent validity, and discriminant validity. Construct validity was established through factor analysis which demonstrated high validity with a score of .81 for usual fatigue and .92 for activity related fatigue (Mendoza, et al., 1999). Concurrent validity was established through correlation of the BFI with The Profile of Mood States and the fatigue subscale of the Functional Assessment of Cancer Therapy. The BFI was significantly correlated to the fatigue subscales of both the Profile of Mood States ($r = .84$, $p < 0.001$) and the Functional Assessment of Cancer Therapy ($r = -.88$, $p < 0.001$) (Mendoza, et al., 1999). The Profile of Mood States and the Functional Assessment of Cancer Therapy are also significantly correlated ($r = -.92$, $p < 0.001$) (Mendoza et al., 1999). Discriminant validity was established through comparing BFI scores of patients expected to have fatigue based on performance status (Mendoza et al., 1999). The scores were significantly different ($p < 0.001$) (Mendoza et al., 1999). Also, a Cronbach's coefficient alpha was calculated for BFI. The Coefficient ranges from 0 to 1. Ascending values indicate less measurement error. The Cronbach's alpha ranged from .95-.96 for individual items and an internal consistency of .96 overall (Mendoza et al., 1999). The questionnaire takes approximately five minutes to complete and a global score can be ascertained by averaging the total score (Mendoza et al., 1999).

Cytokines

Cytokines will be analyzed using the Bio-Plex® (Bio-Rad) multiplex assay. Compared to the traditional enzyme-linked immunosorbant assays (ELISA), the Bio-Plex is comparable and more sensitive to lower concentration levels of cytokines than the ELISA. One laser identifies a specific bead and another laser identifies the reported antibody associated with the bead-bound cytokine. One hundred beads for each of the 17 cytokines in every sample are assayed and a mean cytokine binding for the sample is determined. The manufacturer reports that the assay accurately measures cytokine values in a range of 1-2500pg/ml. This is acceptable for this study. Also the measure is precise showing less than 1% cross reactivity among other cytokines or with other molecules. All samples will be retained for the data set by log transforming below-detection levels of cytokines by assigning a value below the previously detected value from previous measure. Serum CRP will be measured using the ALPCO's (American Laboratory Products Company) high-sensitivity CRP assay which uses latex particle enhanced immunoturbidimetry for quantitative CRP determination.

Quality of Life

Quality of life will be assessed using the **Functional Assessment of Cancer Treatment- Bone Marrow Transplantation (FACT-BMT).** This instrument was chosen for its use in the bone marrow transplant population, its validity and its feasibility (McQuellon et al., 1997). This instrument was developed in 1997 by a group of oncology experts. The items chosen for this measure were generated from a list produced by oncology experts and patients to assess issues specific to the bone marrow transplant population. The FACT-BMT incorporates items from the Functional Assessment of Cancer Therapy General (FACT-G) scale with a bone marrow transplant subscale. The use of this instrument is well established (Kropp et al., 2000; Lau et al., 2002; Lee et al., 2006; Pidala et al., 2011).

The validity of the FACT-BMT is established through internal consistency and construct validity. Internal sistency was reported using the Cronbach's alpha. The Cronbach's alpha coefficients were .84 for physical well-

ng, .69 for social/family well-being, .67 for emotional well-being, and .78 for functional well-being. The Cronbach's ha was .88 for the FACT-G total and .89 for the FACT-BMT (Lau et al., 2002). When compared with the quality of life dy group of the European Organization for Research and Treatment of Cancer (EORTC QLQ-30), all like domains has gnificant positive relationship ranging from .30 to .77 (Kropp et al., 2000).

The FACT-BMT is a self-administered questionnaire developed to measure multiple dimensions of quality of life in the bone marrow transplant population. It consists of the 27-item FACT –G and a 23-item bone marrow transplant subscale. The FACT-G assesses physical well-being (7-items), social/family well-being (6-items), emotional well-being (6-items), and functional well-being (7-items) and uses a five point Likert-type scale to score the responses. A value of 0 represents the statement has been "not at all" true for the individual at all over the last seven days and a 4 represents the statement has been "very much" true for the individual over the last seven days (Lau et al., 2002). This quality of life measurement has been translated and validated into over 20 languages (Lau et al., 2002).

Table 1. Data Collection and Major Variables

Domain	Concept	Operational Measure
Physiologic	Demographic	Medical Record Data Demographic Profile Questionnaire
	Lifestyle	Lifestyle Profile Questionnaire
	Performance Status	Eastern Cooperative Oncology Group
Donor/Situational	Disease/ Treatment	Medical Record Disease Profile Questionnaire
Psychologic	Perceived Stress	Perceived Stress Scale
Behavioral Manifestations	Pain	Brief Pain Inventory
	Depression	Hospital Anxiety and Depression-Scale
	Fatigue	Brief Fatigue Inventory,
	General Symptoms	Memorial Symptom Assessment Scale
		Lee Chronic Graft-versus-Host Disease Scale
Biological Factors	Immunology/Inflammation	Cytokines (IL-1β, IL-6, IL-10, TNF-α, and IFN-γ) CRP
Outcome	Quality of Life	Functional Assessment of Cancer Treatment-Bone Marrow Transplant

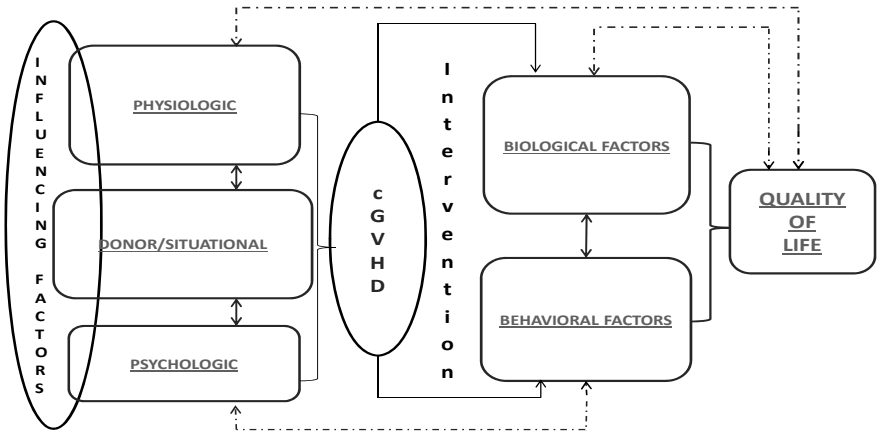

Figure 2. Conceptual Model

X. PLAN FOR CONTROL OF INVESTIGATIONAL DRUGS, BIOLOGICS, AND DEVICES.

Investigational drugs and biologics: IF Investigational Drug Pharmacy Service (IDS) is not being used, attach the IDS confirmation of receipt of the management plan.

Investigational and humanitarian use devices (HUDs): Describe your plans for the control of investigational devices and HUDs including:
(1) how you will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s);
(2) plan for storing the investigational product(s)/ HUD as specified by the sponsor (if any) and in accordance with applicable regulatory requirements;
(3) plan for ensuring that the investigational product(s)/HUDs are used only in accordance with the approved protocol; and
(4) how you will ensure that each subject understands the correct use of the investigational product(s)/HUDs (if applicable) and check that each subject is following the instructions properly (on an ongoing basis).

N/A

XI. DATA ANALYSIS PLAN

For investigator–initiated studies.

Descriptive statistics will be used to characterize the sample in terms of demographic variables (gender, race/ethnicity, stage of disease, and treatment modalities). Estimated correlations for all pairwise combinations among selected symptoms, cytokines and quality of life will be calculated. All statistical analyses will be done utilizing JMP software. Dr. Ronald K Elswick in the School of Nursing holds a PhD in Biostatistics and is a faculty member in the School of Nursing. Dr. Elswick serves on the doctoral student's dissertation committee.

XII. DATA AND SAFETY MONITORING

- **If the research involves greater than minimal risk and there is no provision made for data and safety monitoring by any sponsor, include a data and safety-monitoring plan that is suitable for the level of risk to be faced by subjects and the nature of the research involved.**

- **If the research involves greater than minimal risk, and there is a provision made for data and safety monitoring by any sponsor, describe the sponsor's plan.**
- **If you are serving as a Sponsor-Investigator, identify the Contract Research Organization (CRO) that you will be using and describe the provisions made for data and safety monitoring by the CRO. Guidance on additional requirements for Sponsor-Investigators is available at http://www.research.vcu.edu/irb/wpp/flash/X-2.htm**

This study is a descriptive study with minimal risks and therefore no adverse events (AE) are expected. However, if any event occurs and is possibly related to the study, the doctoral student, with PI supervision, will assume responsibility for reporting the even to the health care provider and any referral for recommended treatment. She will also notify the Virginia Commonwealth University Institutional Review Board (VCU IRB). AE reporting forms are available online at the VCU website.

The data from the proposed study will come from three sources: questionnaires collected by the doctoral student in a secure location to maintain privacy, cytokine data, from the School of Nursing lab, and patient information from medical records data to be collected by the doctoral student. All information will be maintained in locked filing cabinets within a locked office in a secured building. Only the PI and the doctoral student will have access to the information.

XIII. MULTI-CENTER STUDIES

If VCU is the lead site in a multi-center project or the VCU PI is the lead investigator in a multi-center project, describe the plan for management of information that may be relevant to the protection of subjects, such as reporting of unexpected problems, project modifications, and interim results.

Chapter 4

Symptoms, Cytokines and Quality of Life of Patients with Chronic Graft-versus-Host Disease following Allogeneic Hematopoietic Stem Cell Transplantation: A Cross-sectional, Correlational Study

Chronic graft-versus-host disease (cGVHD) is a serious complication following allogeneic hematopoietic stem cell transplantation (HSCT) marked by immune dysregulation and debilitating clinical sequelae (Perez-Simon, Sanchez-Abarca, Diez-Campelo, Caballero, & San Miguel, 2006). Allogeneic transplant refers to HSCT using donor stem cells versus autologous HSCT which is the use of previously harvested stem cells from the patient who then receives his own cells back during the transplant. Donor cells for allogeneic HSCT are matched according to human leukocyte antigens (HLA), proteins that make up a person's tissue type and play an important role in immune response (National Cancer Institute). As cGVHD is a complication of donor immune cells' ability to assimilate in the host environment, donor cells mount an over-exaggerated immune response (Bishop & Pavletic, 2008; Choi, Levine, & Ferrara, 2010). This is called an allo-reaction and is characterized by inflammatory responses that may have deleterious effects; therefore examining patterns and levels of inflammation are of importance (Vose, 2011). Manifestations of cGVHD usually appear several months after transplantation and the

pathophysiology of cGVHD remains vexing (Ratanatharathorn, Ayash, Lazarus, Fu, & Uberti, 2001).

Reports have demonstrated that as many as 80% of patients undergoing allogeneic HSCT develop cGVHD (Lee, Cook, Soiffer, & Antin, 2002; Lee, Vogelsang, & Flowers, 2003). Complications include scleroderma, destruction of saliva and tear ducts, and liver and pulmonary dysfunction (Filipovich et al., 2005). With an increase in number of allogeneic transplants and a decrease in mortality due to earlier transplantation, better HLA matching between donor and recipient and improvements in transplant conditioning, there is a resultant shift of focus to survivorship issues (Flowers et al., 2008). Important survivorship issues include symptom management, enhancing quality of life (QoL) and improving functional status for survivors of allogeneic HSCT (Flowers et al., 2008; Lee et al., 2002; Lee et al., 2003; Schlomchik, Lee, Couriel, & Pavletic, 2007). Progress toward achieving these outcomes includes adequate assessment and targeted therapeutic interventions to mitigate distressing symptoms and long-term complications (Perez-Simon et al., 2006).

Symptom management is a major issue for patients experiencing cGVHD (Lee et al, 2002; Perez-Simon et al., 2006). Yet, there remains a gap in the literature establishing the relationship between symptoms in this population and QoL (Lynch-Kelly, 2014). Further, there has been little study of the relationship of symptoms and biological markers of cGVHD although the interplay between biological markers and symptoms may impact the frequency and severity of symptoms experienced by patients with cGVHD (Lynch-Kelly, 2014).

Understanding symptoms of cGVHD, inclusive of the biological underpinnings of symptoms, is a fundamental step toward managing symptoms effectively. Knowing the relationships among symptoms and QoL gives insight into the impact symptoms may have on

QoL for patients with cGVHD. Thus, the aims of this study were to 1) examine *the levels of symptoms* (cGVHD specific, general symptoms, and cluster symptoms [pain, depression and fatigue]), *inflammation* (cytokines [Interleukin {IL}-1β, IL-6, IL-10, TNF, and INF-γ] and C-reactive protein [CRP]) and *QoL* in patients diagnosed with cGVHD and 2) examine the relationships between and among symptoms, inflammation and QoL in individuals with cGVHD. Knowledge about symptoms and biological mechanisms (e.g. increased systemic inflammation expression) involved in symptom manifestation is important for the development and testing of novel interventions to successfully manage symptoms and improve QoL for patients with cGVHD.

Background and Significance

HSCT has become the standard treatment for many hematologic cancers including acute leukemias, chronic leukemias, multiple myeloma, and myelodysplastic syndrome (Pidala, 2011). Before HSCT, patients receive conditioning therapy of chemotherapy, radiation, or both to destroy the cancer cells after which donor cells are infused through a central venous catheter similarly to a blood transfusion (Alyea et al., 2006; Gupta, Lazarus, & Keating, 2003; Toze et al., 2005). There has been a 165% increase in the number of allogeneic HSCT from 1994-2005 and survival rates post 100 days HSCT increased nearly 86% (Hahn et al., 2013). This increase in HSCT is partially due to advances in conditioning known as a mini transplant involving lower doses of chemotherapy and radiation thus allowing HSCT for individuals who may have once been ineligible (Hahn et al., 2013).

One of the complications of HSCT is GVHD. There are two types of GVHD, acute and chronic. Acute GVHD usually appears within the first 100 days post-transplant and involves different immune cell subsets and different cytokine profiles than cGVHD (Ratanatharathorn et

al., 2001). Acute GVHD is speculated to involve alloreactive memory T cells existent in donor cells. Usually, cGVHD presents post 100 days and the pathobiology cGVHD is not well elucidated (Pidala, 2011). The focus of this study is on cGVHD.

The exact cause of cGVHD is unknown; but is speculated to involve mechanisms associated with proliferation and exaggeration of inflammation as with other autoimmune disorders (Baird & Montaine, 2008; Bazzichi et al., 2008; Klimiuk, Sierakowski, Domyslawska, & Chweicko, 2011). Diagnosis and staging of cGVHD is relatively recent. In 2005, the National Institutes of Health (NIH) cGVHD consortium developed criteria for distinguishing cGVHD by type of onset, severity of presentation, and number of organs involved (Filipovich et al., 2005). Acute GVHD is a primary risk factor for the development of cGVHD. Other factors such as gender match, transplant conditioning, and diagnosis have been identified as risk factors of cGVHD as well (Flowers et al., 2011; Remberger et al., 2002). Any of the body systems can be affected by cGVHD. Skin (cutaneous) and eye (ocular) cGVDH are the most frequently occurring while those with lung (pulmonary) and/or liver (hepatic) cGVHD have the highest mortality (Pidala et al., 2012; Vogelsang, 2001). In addition to being perhaps the most serious complication following allogeneic HSCT, cGVHD is also the most common (Pidala et al., 2011; Vogelsang, 2001).

Due to increased survivorship of patients with cGVHD, improving QoL is of growing importance (Flowers et al., 2011; Lee et al., 2002; Lee et al., 2003). From December, 2005 through May, 2006, the National Cancer Institute (NCI) published a series of papers in the areas of diagnosing and staging, histopathology, strategies for the development and validation of biomarkers, response criteria, ancillary therapy and supportive care, and the design of clinical trials for cGVDH (Baird & Pavletic, 2006). The validation of biomarkers includes examining

both biological and behavioral (patient-reported) measures with QoL as a possible endpoint to measure success of research testing novel interventions for supportive care (Filipovich et al., 2005).

Theory

This study adapted the Theory of Unpleasant Symptoms (TOUS) (Lenz, Suppe, Gift, Pugh, & Milligan, 1995) to provide the theoretical perspective to explore the relationships among symptoms commonly associated with cancer (pain, depression, and fatigue) and QoL in patients diagnosed with cGVHD. The TOUS was developed after observation of symptoms in various clinical settings demonstrated there were certain commonalities among symptoms while simultaneously exhibiting uniqueness (Lenz et al., 1995). Symptoms are a multidimensional concept including: 1)temporality, 2) quality, 3) intensity, and 4) distress (Lenz et al., 1995). Further research led to the conclusion that symptoms rarely occur in isolation but usually more than one at a time and that the relationships among the influencing factors, the symptoms experienced and the outcome are not linear but interactive (Lenz, Pugh, Milligan, Gift, & Suppe, 1997). The TOUS has been used as the framework for many studies in the examination of symptoms across many patient populations including cancer symptom research (Chen & Tseng, 2007; Farrell & Savage, 2010; Fox & Lyon, 2007; Fox, Lyon, & Farace, 2007; Jurgens et al., 2009).

The TOUS was modified (Figure 1) to portray the biobehavioral perspective used to examine the specific aims of this study. Biobehavioral research assumes that biology and behavior are inextricably linked, thus necessitates examining biological correlates with behavioral manifestations. The model depicts the relationships among concepts examined in this study. It assumes: 1) multiple symptoms occur simultaneously, 2) relationships exist between

and among symptoms, 3) inflammation is present and is related to symptoms, and 4) relationship exist among symptoms, inflammation, and QoL.

Symptoms

Symptoms are a major source of distress and discomfort for patients with cancer (Lee et al., 2002; Perez-Simon et al., 2006; Theobald, Kirsh, Holtsclaw, Donaghy, & Passik, 2006). Patients with cGVHD may experience multiple symptoms but little is known about which symptoms and to what extent, as such adequate management of symptoms is a major barrier to caring for these patients (Williams et al., 2007).

cGVHD specific symptoms. Symptoms of cGVHD have been predominantly explored in studies focusing on a single organ system affected by cGVHD such as skin, mouth, or eyes with symptom description related to the specific body system (Lynch-Kelly, 2014). For example, studies examining oral cGVHD have focused on dry mouth and oral pain (de la Parra-Colin, et al., 2011; Fall-Dickson, 2010; Hettinga, Verdonck, Fijnheer, Rijkers, & Rothova, 2007). Studies examining gastro-intestinal cGVHD, have focused on distressing symptoms of bloating and nausea (Akpek et al., 2003). As cGVHD can affect multiple body systems concurrently, having a detailed description of symptoms by body system is important for supportive treatment. Findings from cGVHD studies have noted symptoms similar to those of other cancers and include pain, nausea, bloating, weight loss, depressive symptoms, and sexual dysfunction (Akpek et al., 2003; Andree, 2008; Mitchell et al., 2010; Stratton et al., 2007; Wong et al., 2013).

General symptoms. Patients with cancer report the presence of many symptoms such as pain, numbness in hands and feet, bowel disturbances, and vomiting (American Cancer Societym n.d.). Insomnia is also frequently reported as a symptom associated with cancer (Fox & Lyon, 2007; Fox et al., 2007; Theobald et al., 2006). These symptoms may be due to the cancer itself or

treatments and have been shown to persist after treatment cessation. The percentage of uncontrolled chronic cancer pain has been shown to exceed 75% in some instances and is reported to be a major cause of distress (Caraceni et al., 2001; Stenseth, Bjornnes, Kaasa, & Klepstad, 2007). Approximately 30% of cancer patients report depression (Oh & Seo, 2011). Depression may persist well into survivorship and is a predictor of both fatigue and mortality (Kroenke et al., 2010; Oh & Seo, 2011).

Cluster symptoms. Common symptoms across cancer populations reported by the National Institute of Nursing Research (NINR) (2011) are pain, depression, and fatigue. In a studies examining lung, breast and ovarian cancer, it was reported that as many as 90% of cancer patients experience pain, 91% fatigue, and up to 25% depression (Chen & Tseng, 2007; Fox & Lyon, 2007). The symptom triad of pain, depression and fatigue often co-occur in patients with cancer and are also described in the cGVHD literature but not as concurrent, correlating symptoms examined with in-depth measures of pain, depression and fatigue. Management of symptoms requires adequate symptom assessment and is essential for improving QoL (Ross & Alexander, 2001).

Pain. Pain is the unpleasant sensory or emotional sensation causing distress and is the number one reason why people seek medical attention (Cheng, Foster, & Huang, 2003). Patients with cancer may not only be experiencing pain directly related to the cancer process but may experience pain caused by treatments. Pain can cause both physical and psychological suffering (Kreitler & Merimski, 2007; Miaskowski et al., 2006). It has been estimated that 40% to 80% of cancer patients experience pain (Porteny & Lesage, 1999). In order to develop interventions to adequately manage pain in this patient population, there must be an adequate assessment of the pain (Theobald et al., 2006).

Depression. Depression is feeling "sad" or "blue" for an extended period of time and these feelings interfere with normal activities (National Institute of Mental Health [NIMH], 2010). Symptoms may include feeling sad or empty, hopeless, helpless. One may have a gloomy outlook on life and the inability to feel happiness towards things which used to be enjoyable (NIMH, 2010). Depression and illness often co-exist; one may be the cause, consequence or predisposition of the other (NIMH, 2010). In a study with 215 randomly assigned patients with cancer, 68% had a depressed or anxious mood (Massie, 2004). Depression is reported as one of the most common symptoms in all types of cancer and negatively impacts QoL (Fox et al., 2007; Miaskowski et al., 2004).

Fatigue. Fatigue is weariness or tiredness or lack of energy (Mendoza et al., 1999). Fatigue experienced by the general population serves as a protective response to physical and psychological stress and is often relieved by rest. However, for patients with cancer, fatigue is described as distressing, life altering, unrelieved by rest, and chronic (Servaes, Verhagen, & Bleijenberg, 2002). Fatigue is the most commonly reported symptom in patients with cancer. It is also highly reported by patients after bone marrow transplantation. Fatigue is thought to be a side effect of treatment modalities and a consequence of biologic effects (Lawrence, Kupelnick, Miller, Devine, & Lau, 2004; Seyidova-Khoshknabi, Davis, & Walsh, 2011). Fatigue has been described as the symptom that most interferes with daily life. It has been reported by patients as a symptom that begins before diagnosis and persists after treatment completion (Lawrence et al., 2004; Lyon & Fox, 2007; Fox et al., 2007; Mendoza et al., 1999; Prue, Rankin, Allen, Gracey, & Cramp, 2006; Ross & Alexander, 2001; Seyidova-Khoshknabi et al., 2011).

Inflammation

Cytokines and CRP. Cytokines are non-antibody proteins that act as mediators among cells to induce or prohibit inflammatory responses in the body. It is speculated that cytokines act neurologically to induce psychological and behavioral changes (Kelley, 2003). It is also speculated that the production and release of certain cytokines can be effected by the cancer itself and these cytokines may mediate symptoms (Seruga, Zhang, Bernstein, & Tannock, 2008). A call by the NCI (2006) to investigate strategies for the development and validation of biomarkers in cGVHD research could be beneficial in elucidating strategies to combat the devastating effects of cGVHD (Baird & Pavletic, 2006). The establishment of the relationship between symptoms and cytokines may serve to determine the interplay of certain inflammatory cytokines and symptom severity which may in turn lead to advanced interventions to relieve bothersome symptoms for patients with cGVHD.

An acute phase reactant, CRP, was once thought to be produced only by hepatic cells (Yeh, 2005). Studies have now demonstrated both epithelial cells and respiratory cells produce CRP. Furthermore, CRP has a direct effect on epithelial cells to stimulate production of cytokines (Gould & Wiser, 2001; Jabs et al., 2004). Levels of CRP rise in response to inflammation and are used in current practice to monitor progression or remission of certain conditions and treatment efficacy for some auto-immune conditions such as rheumatoid arthritis and systemic lupus erythematous. These conditions appear to have similar clinical presentations as cGVHD (Baird & Montine, 2008; Bazzichi et al., 2007; Klimiuk et al., 2003; Seruga, Zhang, Bernstein, &Tannock, 2008).

QoL

The World Health Organization (WHO) broadly defines QoL as the perception an individual has of their life situation with regards to goals, expectations, standards and concerns (1997). QoL is affected by many aspects of an individual's health and encompasses many domains such as physical, social, emotional and functional well-being (Cella et al., 1997). The presence of distressing symptoms is one factor that contributes to decreased QoL among cancer survivors (Monga et al., 2007). The evaluation of treatment efficacy once focused on survival time (quantity) with little regard for QoL. Currently, one of the considerations for treatment efficacy is the impact treatment will have on QoL. Preservation of as high a QoL as possible is now evaluated as a part of treatment decisions.

Materials and Methods

Design, Sample, and Setting

This study used a prospective, descriptive, cross-sectional design. Participants were recruited from a convenience sample of patients diagnosed with cGVHD receiving post allogeneic HSCT care at an urban health care facility. Patients were eligible for participation if they were at least 18 years of age, had a diagnosis of cGVHD, and could speak English. Patients were ineligible for participation if they had begun taking antidepressants within a month, were pregnant, or incarcerated. Prior to the conduct of the study, a power analysis calculated using nQueary Advisor ® v.7.0 determined that a 0.05 two-sided Fisher's z test of the null hypothesis that the Pearson correlation coefficient p=0, has 80% power to detect a ρ as small as 0.43 when the sample size is 40. However due to recruitment issues, a sample of N=24 was recruited for this study.

Procedure

This study was approved by the Massey Cancer Center's Protocol Review Monitoring Committee and the health care system's Institutional Review Board. Patients were referred to the study by the transplant center's medical director in consultation with the attending physician and the clinical coordinators. Written consent was obtained from all participants. Individual and disease factors were collected from both the medical record and self-report by participants. Severity of cGVHD was obtained using standard criteria based on evaluation of organ systems in accordance with the NIH global rating scale (Filipovich et al., 2005). Symptom and QOL data were collected by patient self-report. A blood draw for measures of inflammatory cytokines and CRP was collected by the clinic nurse via venipuncture or a venous access device at a regularly scheduled clinic visit. Study visits took approximately one hour to complete. Participants received a $25.00 visa card after completing the study.

Measures

Individual and disease factors. All individual factors and disease factors were collected by either chart review or patient report. Information collected included demographic information on age, race, ethnicity, and marital status. Other individual factors collected included type of cancer, donor characteristics and functional status were also collected. Disease factors were related to cGVHD onset, NIH global rating, blood platelet count and immunosuppressive therapy.

Symptoms.

cGVHD Specific Symptoms.

Lee cGVHD Symptom Scale. The Lee cGVHD Symptom Scale was used to assess symptom bother by body system (Lee et al., 2006). There are seven subscales, each based on the

body system that may be affected by cGVHD: 1) skin, 2) eye and mouth, 3) breathing, 4) eating and digestion, 5) muscles and joints, 6) energy, and 7) mental and emotional. Items are rated using a 5-point Likert-type scale where 0 indicates "*Not at all*" and 4 indicates "*Extremely*" bothered over the past month. A summary score is created by linearly transforming the mean of all items to a 0-100 scale. This measures has demonstrated adequate internal consistency reliability with Cronbach's alphas ranging from .79 to .90 and good convergent validity (Lee et al, 2006). The Cronbach's alpha for this study was .79.

General Symptoms.

Memorial Symptom Assessment Scale. The Memorial Symptom Assessment Scale (MSAS) was used to assess dimensions of 32 prevalent cancer symptoms (Portenoy et al., 1994). The MSAS consists of three subscales: 1) physical, 2) psychological, and 3) global distress. Each item is assessed for the presence or absence of a particular symptom. If the symptom is present, most items (24) are rated on a 4-point or 5-point Likert-type scale for: 1) frequency (where 1 indicates "*rarely*" and 4 indicates "*almost constant*"), 2) severity (where 1 indicates "*slight*" and 4 indicates "*very severe*") and 3) distress (where 0 indicates "*not at all*" and 4 indicates "*very much*") over the past week. The distress of a symptom is broadly defined as the extent to which a symptom impedes the ability to cope and how much the symptom is a bother (Cleeland, 2000; Lenz et al., 1995). Distress negatively impacts daily living and decreases QoL in patients with cancer (Cleeland, 2000). The remaining 8 items are rated on severity and distress only, not on frequency. A mean score is calculated for each item, each subscale, and the total measure. This instrument has been tested and validated in many patient populations (Chang, Hwang, Feuerman, Kasimis, & Thaler, 2000; Portenoy et al., 1994; Tranmer et al., 2003). This measure has

demonstrated adequate internal consistency reliability with Cronbach's alphas ranging from .76 to .88 (Chang et al., 2000; Portenoy et al., 1994). The Cronbach's alpha for this study was .89.

Cluster symptoms.

Pain. The Brief Pain Inventory (BPI) was used to assess dimensions of pain (Cleeland, 2009). The BPI consists of two subscales: 1) severity and 2) interference (Cleeland, 2009). Four items assess pain severity and seven items assess interference. Each item is rated on an 11-point Likert-type scale where 0 indicates "*no pain*" or "*no interference*" and 10 indicates "*the worst pain imaginable*" or "*complete interference*" over the past twenty-four hours. A mean score is calculated for each subscale and the total measure. Fifty percent of the questions must be answered to calculate a score. The measure has demonstrated adequate internal consistency reliability with Cronbach's alphas ranging from .80 to .87 for pain severity items and from .89 to 0.92 for interference items (Cleeland, 2009). The Cronbach's alpha for this study was .95.

Depression. The depression subscale of the Hospital Anxiety and Depression Scale (HADS) was used to assess symptoms of depression (Zigmond & Snaith, 1983). This instrument has been used widely in cancer settings as well as general medical settings (Mitchell, Meader, & Symonds, 2010). The depression subscale is comprised of seven items. Each item is rated on a 4-point Likert-type scale where 0 indicates "*least severe*" and 3 indicates "*most severe*" for how the participant is currently feeling. The score is the sum of all items for the subscale. The measure has demonstrated adequate internal consistency reliability with Cronbach's alphas ranging from .82 to .90 (Mykletun, Stordal, & Dahl, 2001). The Cronbach's alpha for this study was .77.

Fatigue. The Brief Fatigue Inventory (BFI) was used to assess dimensions of fatigue (Mendoza et al., 1999). The BFI consists of two subscales: 1) severity and 2) interference. Three

items assess fatigue severity and six items assess fatigue interference. Each item is rated on an 11-point Likert-type scale where 0 indicates "*no fatigue*" or "*no interference*" and 10 indicates "*worst fatigue imaginable*" or "*complete interference*" over the past twenty-four hours. A mean score is calculated for each subscale and the total measure (Mendoza et al., 1999; Seyidova-Khoshknabi et al., 2011). The measure has demonstrated adequate internal consistence reliability with Cronbach's alphas ranging from .95 to .96 (Mendoza et al., 1999, Mendoza, Mayne, Rublee, & Cleeland, 2006). The Cronbach's alpha for this study was .93.

I**nflammation.** Blood was collected in a 3ml Ethylenediamineteraacidic tube and transported (on ice) to the research lab. The blood was centrifuged at 1030 rpm for 10 minutes at 4°c. Plasma was aliquotted to 3 microfuge tubes (500µl each). Samples were stored in a -80°c freezer until processed for analysis.

Cytokines. Serum cytokine levels were analyzed using the BioPlex®(Bio-Rad) multiplex assay. Bioplex allows the simultaneous measurement of multiple cytokines in a single biological sample. Dual laser technology allows for the detection of multiple analytes across numerous fluorescent spectra; this provides accurate quantification of cytokines.

CRP. Serum CRP levels were measured using the ALPCO's (American Laboratory Products Company) high-sensitivity CRP enzyme-linked immunosorbant assay per manufacturer's protocol.

QoL. QoL was assessed using the Functional Assessment of Cancer Treatment- Bone Marrow Transplantation (FACT-BMT) (McQuellon et al., 1997). The FACT-BMT measures multiple dimensions of QoL. It consists of the 27-item FACT –General (G) and a 12-item BMT subscale. The FACT-G assesses physical well-being (PWB) (7-items), social/family well-being (SWB) (6-items), emotional well-being (EWB) (6-items), and functional well-being (FWB) (7-

items). The trial outcome index (TOI) is the sum of the PWB, FWB, and BMT subscales. Each item is rated on a 5-point Likert-type scale where 0 represents the statement has been "*not at all*" true for the individual and a 4 represents the statement has been "*very much*" true for the individual over the past week (Lau et al., 2002). To produce the subscale score, the sum of the item scores are multiplied by the number of items in the subscale then divided by the number of items answered. At least 50% of the items must be answered to score this measure. The total FACT-BMT score is the sum of all subscores. The measure has demonstrated adequate internal consistency reliability with Cronbach's alphas of .84 for physical well-being, .69 for social/family well-being, .67 for emotional well-being, and .78 for functional well-being. The Cronbach's alpha was .88 for the FACT-G total and .89 for the FACT-BMT (Kopp et al., 2000; Lau et al., 2002). The Cronbach's alpha for this study was .91.

Data Analysis

Descriptive statistics were used to characterize the individual and disease factors of the sample and to profile symptoms, cytokines and QoL. Frequencies and percentages were used to describe categorical variables. Means and standard deviations or median and ranges were used to describe continuous variables. Student's *t*-tests were performed to compare cytokine and CRP levels for each item on the MSAS between individuals who reported having the symptom and individuals who did not report having the symptom. Biologic variables were log transformed to meet the statistical assumption of normality. Specificity was evaluated by visually inspecting the dot plot for spectral overlap of biological data. To test associations among symptoms, cytokines, CRP, and QoL, Pearson product-moment correlation coefficient was used for all pairwise combinations of variables displaying normal distribution. Spearman's rank correlation coefficient was used to test associations for skewed data. All statistics were calculated using

statistical software package JMP 10.0. This was an exploratory analysis thus alpha was set at .05.

Results

Profiles of Symptoms, Cytokines and QoL

The first aim of this study was to examine *the levels of symptoms* (cGVHD specific, general symptoms, and cluster symptoms [pain, depression and fatigue]), *inflammation* (cytokines [Interleukin {IL}-1β, IL-6, IL-10, TNF, and INF-γ] and C-reactive protein [CRP]) and *QoL* in patients diagnosed with cGVHD. Individual and disease factors are profiled in Tables 1 and 2. In this sample (N=24), the majority of participants were female (58.3%), Caucasian (87.5%), and married (79.2%). Half of the participants were not employed. The median age of participants was 54 years and ranged from 28 to 73 years. The median time from transplant to cGVHD diagnosis was 191 days with a range of 123 to 702 days. The mean hemoglobin level was 12.5 (2.2). Most participants (29.2%) had a diagnosis of acute myelogenous leukemia. Most received stem cells from a relative (79.2%) and were gender matched (58.8%). Functional impairment was noted in 91.7% of participants.

Symptoms.

cGVHD specific symptoms. The Lee scale assessed the bother of a symptom for the past week. For the skin, the most frequently reported symptom was changes in skin color (50%). On the eyes and mouth subscale, dry eyes was the most reported symptom (83%). Nearly half of participants (49%) were either "quite a bit" or "extremely bothered" by dry eyes and 75% were bothered by having to use eye drops frequently. On the breathing subscale, shortness of breath was reported by 50% of participants. Two participants reported being "extremely" bothered by the need to use supplemental oxygen. On the eating and digestion subscale, all participants were

able to receive nutrition without any intravenous or feeding tube supplementation. On the muscles and joints subscale, being bothered by limited joint movement and "aches" was reported by 50% of participants. On the energy subscale, loss of energy was reported by 79% of participants and the need to sleep more was bothersome for 66.7% of participants. On the mental and emotional subscale, difficulty sleeping was the most reported symptoms (58.4%). The symptoms for the Lee cGVHD Scales are reported in Table 3 and Table 4.

General symptoms. The MSAS assessed the frequency, severity, and distress of symptoms for the past week. The most frequently reported symptom was lack of energy (83.3%) followed by dry mouth (66.7%). Among those experiencing the symptom, the most often reported symptoms were dry mouth, and lack of appetite. The most severe symptoms were pain and sexual dysfunction and the most distressing symptoms were sexual dysfunction and lack of energy. The mean scores for each subscale and overall score and description individual symptom items of the MSAS are reported in Table 4 and Table 5.

Cluster symptoms. Pain, depressive symptoms, and fatigue were examined using in-depth measures for each symptom. The majority of participants (54%) reported having pain and nearly half (46%) reported interference with activity because of pain. Pain severity scores for worst pain ranged from 1.0 to 10.0, for least pain 0.0 to 4.0, for average from 0.0 to 5.0. The overall median pain severity scores ranged from 0.0 to 5.8. Pain interference scores ranged from 0.0 to 8.8. The overall total pain scores ranged from 0.0 to 6.4. Nearly all (96%) participants reported having some depressive symptoms. Median scores for depressive symptoms ranged from 0.0 to 11.0. Fatigue severity scores for worst fatigue ranged from 0.0 to 10.0 and for usual fatigue ranged from 0.0 to 8.0. Fatigue interference scores ranged from 0.0 to 9.0. The overall

total fatigue scores ranged from 0.0 to 8.0 (see Table 6 for description of cluster symptom scores).

Inflammation. Blood samples were collected on all participants and the specificity was confirmed by visually inspecting the dot plot for spectral overlap of biological data. In a comparison between the serum levels of cytokines, CRP, and general symptoms, there were significant differences noted between cytokines and symptoms. Participants reporting lack of energy had significantly elevated (difference of 2.23, SE= .98, 95% CI = .19-4.27) serum levels of IL-6 compared to individuals who did not report lack of energy (df= 22, t= 2.07, p= .03). Participants reporting problems with urination had significantly higher (difference of 1.81, SE= .73, 95% CI= .30-3.31) serum levels of IL-1β compared to individuals who did not report problems with urination (df= 22, t= 2.07, p= .02). Participants reporting swelling of arms and legs had significantly lower (difference of 1.18, SE= .54, 95% CI= .06-2.3) of serum IL-10 compared to individuals who did not report swelling of arms and legs (df=22, t= 2.07, p=.04). Figures 4a-f present levels of inflammatory markers of patients with and without symptoms reported on the MSAS. Levels of serum cytokines and CRP are reported in Table 7.

QoL. The FACT-BMT scores (see Table 8) demonstrate impaired QoL for many participants. The FWB subscale had the lowest mean of all scales measured by the FACT-BMT followed by the PWB subscale. The TOI subscale score was about 72% of the total physical and functional well-being. The ranges for all scales were varied with some participants experiencing decreased QoL on all scales.

Associations among Symptoms, Cytokines and QoL

The second aim of this study was to examine the relationships between and among symptoms (top three general symptoms and cluster symptoms), inflammation and QoL in

individuals with cGVHD. There were six symptoms identified by the MSAS that were present in over 30% of participants with a total mean score greater than 2 out of 4:1) pain, 2) lack of energy, 3) dry mouth, 4) difficulty sleeping, 5) shortness of breath, and 6) sexual dysfunction. Significant correlations were noted among MSAS items pain, lack of energy, dry mouth and sexual dysfunction. The MSAS pain item significantly correlated with the BPI total pain score ($r = .78$; $p < .01$). The MSAS lack of energy item significantly correlated with other MSAS items dry mouth ($r = .48$; $p = .02$) and sexual dysfunction ($r = .53$; $p < .01$). The MSAS lack of energy item also showed significant correlations with cluster symptoms HADS-D ($r = .65$; $p < .01$), and the BFI total fatigue score ($r = .78$; $p < .01$). The MSAS sexual dysfunction item significantly correlated with the BFI severity subscale ($r = .43$, $p = .03$).

Dimensions of cluster symptoms demonstrated some significant correlations among each other. The BPI total score did not show significant correlations with the BFI total score. Figure 2 displays the correlations between the BPI and the BFI. The HADS_D demonstrated significant positive correlations with the BPI Interference subscale and all scales of the BFI shown in Figure 3.

Inflammation. Cytokines and CPR were found to have several significant correlations among each other, symptoms, and QoL. Cytokine IL-1β had significant positive correlations with TNF ($r = .78$; $p < .01$), IFN-γ (r= .97; p< .001), IL-6 ($r = .44$; $p = .031$), and IL-10 ($r = .79$; $p < .001$). Cytokine IL-6 showed significant correlations with IFN-γ (r= .58; p< .01), MSAS item lack of energy ($r = .42$; $p = .04$), MSAS item dry mouth ($r = .42$; $p = .04$), and near significance with the EWB subscale ($r = -.40$; $p = .05$). Cytokine IL-10 showed significant positive correlations with IFN-γ (r= .78; p< .01), TNF ($r = .82$; $p = <.01$), and MSAS item difficulty sleeping ($r = .43$; $p = .03$). TNF was significantly correlated with IFN-γ (r= .73; p=< .01). CRP was significantly

correlated with the SWB subscale (r= -.56; p< .01), and was nearing significance with MSAS item sexual dysfunction (r= .41; p= .05).

QoL. Many significant correlations were found among QoL and pain, depression and fatigue. The MSAS pain item significantly correlated with the PWB subscale (r= -.57, p< .01). The MSAS item lack of energy showed significant correlations with the PWB subscale (r= -.70, p< .01), the FWB subscale (r= -.53; p< .01), the BMT subscale (r= -.71; p< .01), the FACT-G subscale (r= -.64; p< .01), and the FACT_BMT (r= -.68, P< .01). The MSAS dry mouth item correlated to the BMT subscale (r= -.55, p< .01), the TOI subscale (r= -.41; p=.04), and the FACT-BMT (r= -.42, p= .04). The MSAS sexual dysfunction item correlated with the SWB subscale (r= -.44; p=.03) and the BMT subscale (r= -.44; p= .03). Cluster symptoms pain, depression, and fatigue showed significant correlations with the FACT-BMT and the subscales of the FACT-G, TOI, and BMTS. Correlations among cluster symptoms and QoL are noted in Table 9.

Discussion

This study described symptoms, inflammation, and QoL and examined associations among these variables in a sample of patients diagnosed with cGVHD following allogeneic HSCT. Markers of inflammation (cytokines IL-1β, IL-6, IL-10, TNF, and IFN-γ and CRP) have been noted in cGVHD literature and were selected to examine as biological correlates of cGVHD symptoms (Lynch-Kelly, 2012).

Reported symptoms and findings of existent relationships from this study highlight the symptom complexity of patients with cGVHD. Among the most pronounced symptoms captured by the MSAS were dry mouth, difficulty sleeping, shortness of breath, and sexual dysfunction.

Dry mouth was reported among participants with and without oral cGVHD. Certain medications and treatments can cause dry mouth. Dry mouth can cause serious health issues such as an increased number of dental carries and creates an environment for invasion of opportunistic microorganisms (Visvanathon & Nix, 2010). There was a positive association between dry mouth and inflammatory marker IL-6 which has been associated with Sjogren's syndrome, a complication of inflammatory cell infiltration of the lacrimal and salivary ducts manifesting as dryness of the eyes and mouth (Ratanatharathorn et al., 2001). Secondary Sjogren's syndrome may be a clinical sequela of cGVHD (Kawanami et al., 2012). This association supports findings by Fall-Dickson et al. (2010) as the potential for IL-6 as a candidate biomarker for oral cGVHD. The significant correlation between dry mouth and lack of energy as well as a negative trend between dry mouth and QoL warrant further exploration of these findings.

Sleeping difficulties have been cited as being among the most commonly experienced symptoms of patients with cancer and other chronic diseases and has a negative impact on physical functioning and poorer QoL (Basta, Chrousos, Velo-Bueno, & Vgontzas, 2007). A positive association between difficulty sleeping and IL-10 is consistent with literature which suggestive of dysregulation in the circadian release of IL-10 (Basta et al., 2007; Roque, Correia-Neves, Mesquita, Palha, & Sousa, 2009).

Shortness of breath was reported among all participants with pulmonary cGVHD regardless of cGVHD severity. Pulmonary cGVHD carries a higher rate of mortality than cGVHD of other body systems (Gazourian et al., 2014). Careful attention to the respiratory status, including assessment of shortness of breath, of patients is essential for early detection of pulmonary complications. Shortness of breath (dyspnea) occurring at rest is a late sign of

pulmonary complications so assessment of early signs of dyspnea is important. Dyspnea is subjective and is based on the individual's perception of feeling short of breath with varying degrees of activity. The Borg dyspnea scale is a widely used scale to assess perception of dyspnea (Borg, 1970). There are objective measures of lung function such as pulmonary function tests (PFT). Patients with cGVHD have PFTs performed at intervals post allogeneic HSCT; however, keeping a watchful eye between PFTs and monitoring respiratory status are necessary for early intervention. Strategies to alert providers to a decline in pulmonary function earlier than conventional practice could lead to earlier interventions that may result in sustaining acceptable pulmonary function (Stadler et al., 2009).

Sexual dysfunction among individuals with cGVHD is focused on women with vaginal cGVHD. There have been advancements in treatments and strategies to mitigate this symptom; however, it still remains an issue. In a study of 23 women diagnosed with genital cGVHD, 21 women were unable to remain sexually active due to complications such as pain, scaring and strictures (Stratton et al., 2007). This study demonstrated that sexual dysfunction was not limited to only women diagnosed with vaginal cGVHD. Seven females and four males reported having sexual dysfunction. Two had a diagnosis of vaginal cGVHD, thus this appears to be an issue to assess with all individuals with cGVHD (Wong et al., 2013). Sexual dysfunction had significant positive correlations with lack of energy, nearing significant positive correlation with inflammatory marker CRP, and a significant negative correlation with the SWB QoL subscale. Other than fatigue, sexual dysfunction was the only variable to significantly correlate with SWB.

Pain, depression, and fatigue are established in the literature as being among the most common symptoms of patients with cancer. Significant positive correlations were demonstrated among many dimensions of the cluster symptom measures. Although cGVHD is a complication

following treatment, this finding suggests a constellation of symptoms that may form a symptom cluster in this population. Each of the measures used in this study to explore symptoms included items for pain, depression and fatigue. Significant correlations were noted between similar items. Pain, depressive symptoms and fatigue all negatively correlated with QoL. Exploring these relationships over time with a larger sample is necessary for determination. The positive correlations among symptoms and cytokines IL-6, IL-10, and CRP merit examining these findings in a larger sample. A significant increase in serum IL-6 levels between patients with and without lack of energy was found; however, there was no difference noted in IL-6 levels of patients with mild, moderate, or severe cGVHD. A study conducted by Rohleder, Aringer, and Boenter (2012) found increased IL-6 levels in individuals with impaired sleep and fatigue. This finding brings into question the identification of IL-6 as a potential biological correlate of fatigue independent of cGVHD severity.

Cytokines play a major role in influencing and regulating inflammatory responses. Dysregulation of cytokines has been associated with auto-immune diseases such as rheumatoid arthritis and systemic lupus erythematosus (Kishimoto, 2010; Munroe et al., 2014). Significant correlations were found among cytokines IL-1β, IL-6, IL-10, and IFN-γ. Historically, cytokines have been described as pro-inflammatory or anti-inflammatory and instrumental in promoting acute responses from T-helper (T_H) 1 cells or mediating B-cell proliferation from T_H2 cells (Mossmann, Cherwinski, Bond, Giedlin, & Coffman, 1986). T_H lymphocytes are demarcated by the expression of cell surface molecule CD4 and are identified by the cytokines they produce. The discovery of the T_H1 and T_H2 model was a seminal breakthrough in the field of immunology. Further research into this delicate interplay has led to further delineation of inflammatory mediators; however, the use of the T_H1 and T_H2 archetype continues in use as a

way to gain insight about inflammation (Muller, 2002). The notion of T_H1 cells as strictly an anti-viral or anti-tumor reponse and T_H2 as solely involved with humoral immune response has been redefined to examine many disease states. T cell derived cytokines are being examined in disease states such as schizophrenia, depression, and chronic pain and cGVHD (Kim et al., 2004; Yoon, Kim, Lee, Kwon, & Kim, 2012). Typically, IL-10 (produced by T_H2 cells) acts to suppress secretion of IFN-y by T_H1 cells and shifts immune response to cell-mediated immunity and dampens the immune response (Plotnikoff, Faith, Murgo, & Good, 2007). IL-6 inhibits TNF and IL-1β, thus associations noted in this study are consistent with the cytokine pathways (Kishimoto, 2010). Cytokine IL-6 has been identified as a key cytokine in symptoms of depression and fatigue and has been noted as a mediator of oral inflammation (Fall-Dickson, et al., 2010). The positive association between lack of energy and IL-6 and the significant increase in serum levels, make IL-6 a candidate for a potential biomarker of fatigue in cGVHD.

The NINR recognizes the negative impact symptoms have on quality of life and supports research to improve understanding symptoms and the biological mechanisms underlying symptoms (NINR, 2011). The goal of which is to improve quality of life through better symptom management. In studies of patients who received HSCT, patients without cGVHD one to two years following HSCT did not report having impaired QoL whereas patients with cGVHD reported QoL scores, at the same time-point following HSCT, below that of both population norms and other cancer patients (Baker & Frasier, 2008; Fall-Dickson et al., 2010; Webster, Cella, & Yost, 2003). Some participants of this study had QoL scores that were below both general U.S. population and cancer population normative values. Though this study reports QoL mean scores similar to U.S. population normative values, significant negative correlations were noted among symptoms and QoL. Severity of cGVHD and symptoms have demonstrated a

negative correlation to QoL (Pidala et al., 2011; Pidala et al., 2012). Findings of the significant negative correlations among symptoms and QoL suggest symptoms may be a predictor of QoL outcomes however, need to be examined further.

There are some limitations of this study. Genrealizability of these results is limited due to the small sample size of this study and lack of control group. This study was conducted at a single site, limiting the number of participants eligible for this study. The study was conducted at a center's long term follow up clinic. As such, patients are monitored closely for any complications consistently and may receive intervention earlier more frequently than individuals seen in other institutions performing bone marrow transplantation without a long term follow up clinic. This may partially explain the low pain scores and/or higher mean QoL scores noted in this study. There was no eligibility criteria set for the length of time since diagnosis although this was captured as an individual and disease factor. This may have skewed important information about symptoms. Time from onset of cGVHD may effect associations and should be considered as part of the eligibility criteria in future studies. This study examined inflammatory markers, cytokines and CRP, but did not include the use of controls. The result is a profile of levels of cytokines and CRP for this sample and does provide information useful in assessing these levels for future studies. To compensate for the lack of a control group, inflammation was examined by symptom and individuals that did not have the symptom served as the control. A confounder of this method may be the possibility of an inflammatory response preceding the behavioral response of the symptom. This was a cross-sectional study thus a limitation is assessment of symptoms and biomarkers at a single time point. Results may differ at another time.

The findings of this study provide a profile of the symptoms, inflammation and QoL of patients diagnosed with cGVHD and associations among those variables. Noted were evidence of associations among symptoms and inflammation as were significant negative associations among symptoms and QoL. Further examination of these associations should be tested using a larger sample with a longitudinal design to better understand the effect of time on these relationships and the impact of the symptom trajectory on QoL. The presence of symptoms individuals with cGVHD experience emphasizes the significance for clinical evaluation of symptoms in this population and draws attention to existent relationships among symptoms, inflammation, and QoL. Further exploration of these relationships is pivotal in understanding the interplay among symptoms and inflammation and their impact on QoL and is essential towards developing targeted interventions aimed at mitigating symptoms of cGVHD.

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Table 1

Individual Factors (N=24)

Characteristic	n	%
Sex		
Female	14	58.3
Male	10	41.7
Race		
Caucasian	21	87.5
African American	3	12.5
Ethnicity		
Hispanic	2	8.3
Non-Hispanic	22	91.7
Married		
Yes	19	79.2
No	5	20.8
Employment		
Full Time	10	41.2
Part Time	2	8.3
Not Working	12	50.0
Diagnosis		
AML	7	29.2
CML	3	12.5
MDS	4	16.6
MM	3	12.5
Other	7	29.2
Conditioning		
Total Body Irradiation	11	45.8
Other	13	54.2
Gender Match		
Yes	14	58.8
No	10	41.2
Donor Type		
Related	19	79.2
Unrelated	5	20.8
ECOG		
0	2	8.3
1	17	70.8
2	5	20.8

Note: AML=acute myelogenous leukemia; CML= chronic myelogenous leukemia, MDS= myelodyplasic symdrome, MM= multiple myeloma; Diagnosis Other = non-Hodgkin's lymphoma, B-cell lymphoma, T-cell lymphoma, multiple myeloma; Conditioning Other = reduced intensity radiation and/or chemotherapy; ECOG= European Cooperative Oncology Group.

Table 2

Disease Factors (N=24)

Variable	n	%
cGVHD onset		
De Novo	17	70.8
Quiescent	4	16.7
Progressive	3	12.5
NIH cGVHD global rating		
Mild	4	16.7
Moderate	12	50.0
Severe	8	33.3
Number of organs involved		
1	4	16.7
2	8	33.3
$\geq$ 3	12	50.0
Platelet		
< 100,000	4	16.7
$\geq$ 100,000	20	83.3
Immunosuppressive Therapy		
Systemic	11	45.8
Topical	5	20.8
Both	6	25.0
None	2	8.4

Note: De Novo= never had acute chronic graft-versus-host disease (aGVHD); Quiescent= resolved aGVHD; Progressive= has signs of aGVHD but has progressed to cGVHD; platelet count is in microliters of whole blood.

Table 3

Frequency of Symptom Bother by Body System and Total Scores from the Lee cGVHD Symptom Scale (N=24)

Symptom	n (%) not at all bothered	n (%) slightly bothered	n (%) moderately bothered	n (%) quite a bit bothered	n (%) Extremely bothered
SKIN					
Abnormal skin color	12 (50.0)	3 (12.5)	4 (16.7)	3 (12.5)	2 (8.3)
Rashes	14 (58.4)	6 (25.0)	2 (8.3)	2 (8.3)	0
Thickened skin	20 (83.3)	0	1 (4.2)	0	3 (12.5)
Sores on skin	18 (75.0)	4 (16.7)	2 (8.3)	0	0
Itchy skin	13 (54.2)	2 (8.3)	5 (20.8)	3 (12.5)	1 (4.2)
EYES AND MOUTH					
Dry eyes	4 (16.7)	3 (12.5)	5 (20.8)	7 (29.2)	5 (20.8)
Need to use eye drops frequently	5 (20.8)	1 (4.2)	3 (12.5)	5 (20.8)	10 (41.7)
Difficulty seeing clearly	7 (29.2)	3 (12.5)	7 (29.2)	3 (12.5)	4 (16.7)
Need to avoid certain foods due to mouth pain	17 (70.8)	4 (16.7)	0	1 (4.2)	2 (8.3)
Ulcers in mouth	22 (91.7)	0	1 (4.2)	0	1 (4.2)
Receiving nutrition from an intravenous line or feeding tube	24 (100.0)	0	0	0	0
BREATHING					
Frequent cough	14 (58.3)	1 (4.2)	4 (16.7)	4 (16.7)	1 (4.2)
Colored sputum	18 (75.0)	3 (12.5)	2 (8.3)	0	1 (4.2)
Shortness of breath with exercise	6 (25.0)	6 (25.0)	4 (16.7)	5 (20.8)	3 (12.5)
Shortness of breath at rest	18 (75.0)	3 (12.5)	1 (4.2)	2 (8.3)	0
Need to use oxygen	22 (91.7)	0	0	0	2 (8.3)
EATING AND DIGESTION					
Difficulty swallowing solid foods	16 (16.7)	5 (20.8)	2 (8.3)	0	1 (4.2)
Difficulty swallowing liquids	23 (95.8)	0	0	1 (4.2)	0
Vomiting	21 (87.5)	1 (4.2)	2 (8.3)	0	0
Weight loss	21 (87.5)	0	3 (12.5)	0	0
MUSCLES AND JOINTS					
Joint and muscle aches	8 (33.3)	7 (29.2)	5 (20.8)	2 (8.3)	2 (8.3)

Symptom	n (%) not at all bothered	n (%) slightly bothered	n (%) moderately bothered	n (%) quite a bit bothered	n (%) Extremely bothered
Limited joint movement	13 (54.2)	4 (16.7)	3 (12.5)	3 (12.5)	1 (4.2)
Muscle cramps	12 (50.0)	6 (25.0)	2 (8.3)	1 (4.2)	3 (12.5)
ENERGY					
Loss of energy	5 (20.8)	6 (25.0)	7 (29.2)	4 (16.7)	2 (8.3)
Need to sleep more/take naps	8 (33.3)	5 (20.8)	7 (29.2)	2 (8.3)	2 (8.3)
Fevers	23 (95.8)	1 (4.2)	0	0	0
MENTAL AND EMOTIONAL					
Depression	17 (70.8)	3 (12.5)	4 (16.7)	0	0
Anxiety	12 (50.0)	8 (33.3)	4 (16.7)	0	0
Difficulty sleeping	10 (41.7)	4 (16.7)	5 (20.8)	1 (4.2)	4 (16.7)

Table 4

Total Scores for the Lee cGVHD Symptom Scale and the Memorial Symptom Assessment Scale (MSAS)

Variable	Subscale	Mean (SD)	Median	Range
Lee cGVHD Symptom Scale		21.80 (13.00)	-	4.1-45.5
	Skin	-	15.0	0.0-70.0
	Eyes and Mouth	31.10 (20.20)	-	0.0-83.3
	Breathing	-	17.5	0.0-65.0
	Eating and Digestion	-	6.3	0.0-43.8
	Muscles and Joints	-	21.9	0.0-93.8
	Energy	25.70 (18.60)	-	0.0-66.7
	Mental and Emotional	20.80 (16.50)	-	0.0-58.3
MSAS		00.65 (.43)	-	0.2-1.7
	Global Distress Index	00.91 (.64)	-	0.0-2.4
	Physical Symptoms	00.69 (.52)	-	0.0-1.8
	Psychological Symptoms	00.74 (.54)	-	0.0-2.0

Note: Scoring for the Lee cGVHD Symptoms Scale is 0-100 with higher scores indicating greater symptom bother; MSAS scores range from low (0) to high (4).

Table 5

Memorial Symptom Assessment Scale Results (N=24)

Symptom	Present n	Frequency Mean (SD)	Severity Mean (SD)	Distress/Bother Mean (SD)	Total Mean (SD)
Difficulty Concentrating	13	2.25 (0.87)	1.42 (0.67)	1.42 (1.31)	1.69 (0.86)
Pain	12	2.92 (1.00)	2.6 (1.00)	2.08 (1.16)	2.70 (0.82)
Lack of Energy	20	2.84 (0.90)	2.16 (0.90)	2.11 (1.41)	2.37 (0.90)
Cough	14	2.29 (0.91)	1.64 (0.63)	1.41 (1.23)	1.69 (0.78)
Feeling Nervous	8	1.88 (0.35)	1.14 (0.38)	0.86 (0.38)	1.29 (0.23)
Dry Mouth	16	3.50 (0.63)	2.31 (0.95)	2.06 (1.24)	2.63 (0.78)
Nausea	4	1.50 (0.58)	1.75 (0.50)	1.50 (1.00)	1.58 (0.57)
Feeling Drowsy	14	2.07 (0.62)	1.64 (0.63)	1.00 (0.88)	1.57 (0.48)
Numbness/Tingling in Hands and Feet	13	2.54 (1.05)	1.31 (0.48)	1.08 (0.95)	1.64 (0.66)
Difficulty Sleeping	12	2.76 (0.93)	2.00 (0.91)	1.46 (1.20)	2.06 (0.87)
Feeling Bloated	5	3.40 (0.55)	2.20 (1.10)	2.80 (1.10)	2.80 (0.84)
Problems with Urination	4	2.50 (0.58)	1.25 (0.50)	2.25 (1.50)	2.00 (0.61)
Vomiting	2	2.00 (0.00)	2.00 (1.41)	2.50 (2.12)	2.17 (1.18)
Shortness of Breath	13	2.53 (1.00)	1.92 (0.86)	1.85 (1.34)	2.10 (0.99)
Diarrhea	2	2.50 (0.71)	1.50 (0.71)	1.50 (0.71)	1.83 (0.71)
Feeling Sad	6	1.83 (0.41)	1.33 (0.52)	1.50 (0.55)	1.56 (0.34)
Sweats	6	2.67 (0.52)	1.67 (0.52)	1.83 (1.67)	2.06 (0.71)
Worrying	14	1.79 (0.58)	1.36 (0.50)	1.00 (0.56)	1.38 (0.45)
Sexual Dysfunction	11	2.73 (1.10)	2.55 (1.29)	2.82 (1.25)	2.47 (1.31)
Itching	8	2.38 (0.92)	1.50 (0.76)	1.38 (1.19)	1.75 (0.89)
Lack of Appetite	2	3.50 (0.71)	3.00 (1.41)	3.00 (1.41)	3.17 (1.18)
Dizziness	2	2.00 (0.00)	1.50 (0.71)	1.50 (0.71)	1.67 (0.47)
Difficulty Swallowing	7	2.14 (0.69)	1.86 (0.69)	2.14 (1.57)	2.05 (0.91)
Feeling Irritable	8	1.63 (0.74)	1.25 (0.46)	1.50 (1.41)	1.46 (0.69)
Mouth Sores*	3	N/A	1.33 (0.58)	1.33 (1.53)	1.33 (1.04)
Change in Taste*	3	N/A	1.00 (0.00)	2.00 (0.00)	1.50 (0.00)
Weight Loss*	2	N/A	1.50 (0.71)	1.50 (2.12)	1.50 (1.40)
Hair Loss*	5	N/A	2.40 (1.52)	2.00 (1.58)	2.20 (0.91)
Constipation*	3	N/A	3.00 (1.73)	2.33 (2.08)	2.67 (1.89)
Swelling Arms/Legs*	7	N/A	2.00 (0.58)	2.00 (1.50)	2.00 (0.71)
Don't Look Like Myself*	7	N/A	2.14 (1.07)	2.57 (.98)	2.36 (0.99)
Skin Changes*	8	N/A	2.25 (1.04)	2.34 (1.06)	2.31 (1.00)

*Note: *Only severity and distress are measured for these symptoms; SD=standard deviation; scores are based on a 4-point Likert-type scale where 4 indicate the highest symptom presentation.*

Table 6

Mean Scores of Cluster Symptoms

Measure	Mean (SD)	Median	Range
Brief Pain Inventory			
Total	-	0.3	0-6.4
Interference	-	0.0	0-8.3
Severity	-	0.8	0-5.8
Hospital Anxiety and Depression Subscale	4.1 (3.5)	-	0-11.0
Brief Fatigue Inventory			
Total	3.0 (2.4)	-	0-8.0
Interference	2.4 (2.6)	-	0-9.5
Severity	4.0 (2.5)	-	0-9.3

Table 7

Cytokine and C-reactive Protein (CRP) Distributions

Inflammatory Marker	Mean (SD)	Median	Range
Cytokines			
IL-1β	4.70(4.31)		0.03-14.93
IL-6	23.70 (20.20)		0.01-85.50
IL-10	-	16.00	0.50-109.08
TNF	27.05(25.17)		1.27-96.16
IFNy	126.56 (124.30)		2.03-508.17
CRP	-	6.42	0.53-90.00

Note: Cytokines are reported in picograms/milliliter; CRP=C-reactive protein; CRP is reported in milligrams/milliliter. SD= standard deviation; cytokine and CRP raw values.

Table 8

Quality of Life Scores from the FACT-BMT

Measure	Subscale	Mean (SD)	Range
FACT_BMT (0-148)		113.28 (20.90)	58-136
	FACT_G (0-108)	83.89 (16.15)	41-101
	BMTS (0-40)	29.38 (5.44)	17-38
	TOI (0-96)	69.08 (16.76)	30-88
	PWB (0-28)	20.66 (6.59)	6 to 27
	SWB (0-28)	23.99 (3.68)	12 to 28
	EWB (0-24)	20.21 (3.18)	10 to 24
	FWB (0-28)	19.04 (6.16)	5 to 28

Note: FACT= Functional Assessment of Cancer Therapy; G= General; BMT=Bone Marrow Transplant; S= subscale; PWB= Physical Well-being; SWB= Social Well-being; EWB= Emotional Well-being; FWB= Functional Well-being; TOI= Trial Outcome Index and is the sum of the PWB, FWB, and BMTS; SD= standard deviation

Table 9

Correlations among Cluster Symptoms and Quality of Life

	1	2	3	4
1-BPI	1.00	0.36	0.24	-0.51
2-HADS-D	0.36	1.00	0.82	-0.87
3-BFI	0.24	0.82	1.00	-0.80
4-FACT-BMT	-0.51	-0.87	-0.80	1.00

Note: A p value < .05 was considered statistically significant. Pain significantly correlated with quality of life; depression significantly correlated with fatigue and quality of life; fatigue significantly correlated with quality of life; BPI= Brief Pain Inventory; HADS-D= Hospital Anxiety and Depression subscale; BFI= Brief Fatigue Inventory; FACT-BMT= Functional Assessment of Cancer Therapy-Bone Marrow Transplant.

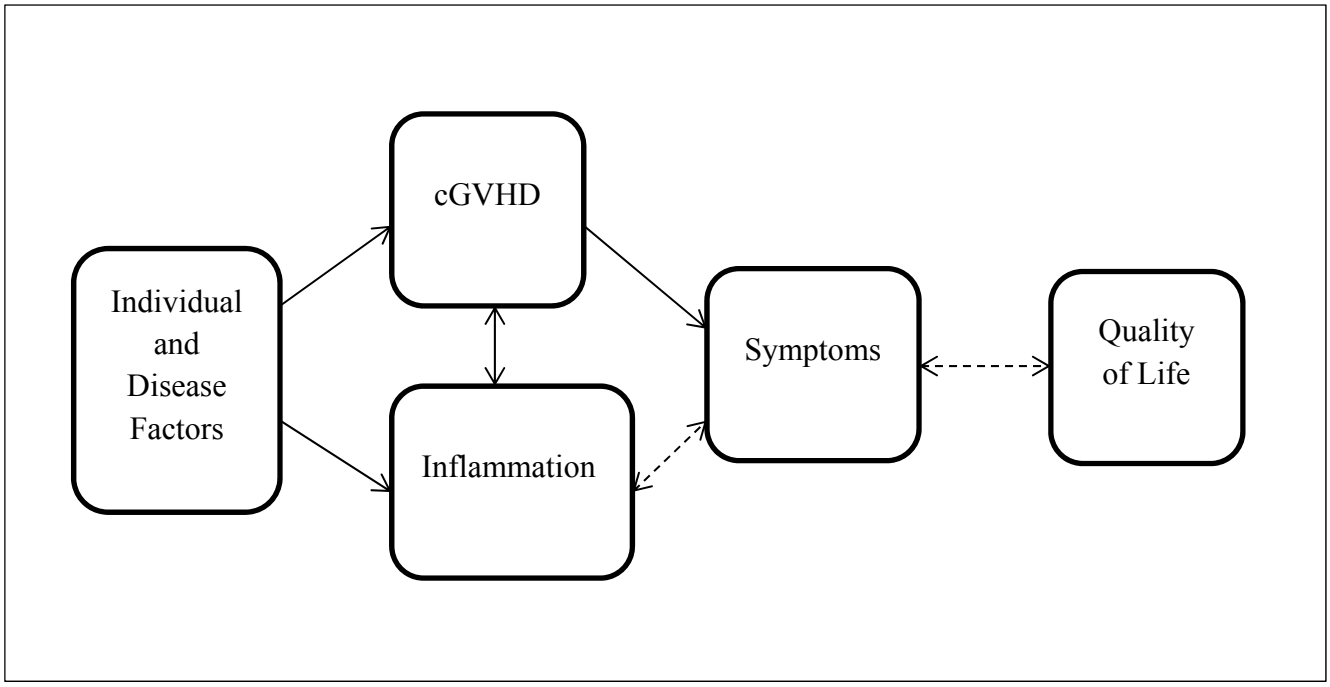

Figure1. Biobehavioral Conceptual Model to Examine Chronic Graft-Versus-Host-Disease. Chronic graft-versus-host disease (cGVHD) is influenced by individual and disease factors and influences symptoms. There is an interaction between cGVHD and inflammation. Inflammation and symptoms have a reciprocal relationship as do quality of life and symptoms.

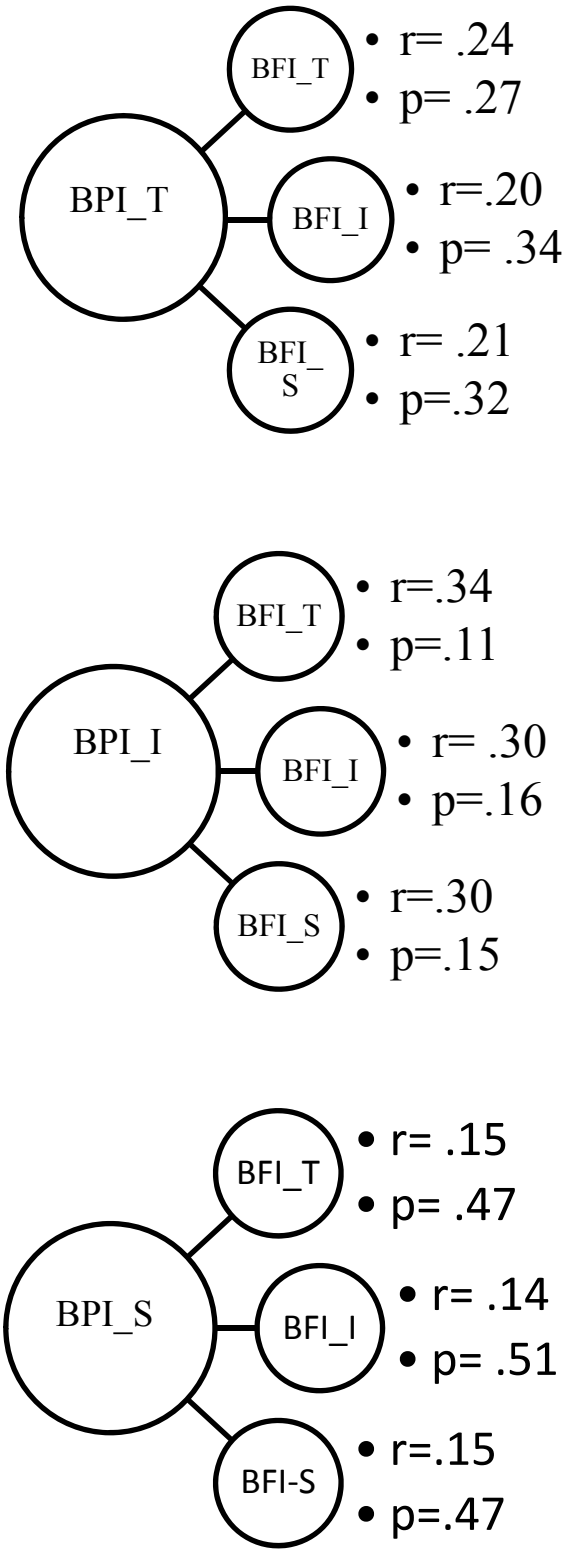

Figure 2. Correlations found in this study between the Brief Pain Inventory (BPI) total measure (T) and the subscales interference (I) and severity (S) and the Brief Fatigue Inventory (BFI) total measure (T) and the subscales interference (I) and severity (S). A p value less that .05 is considered significant.

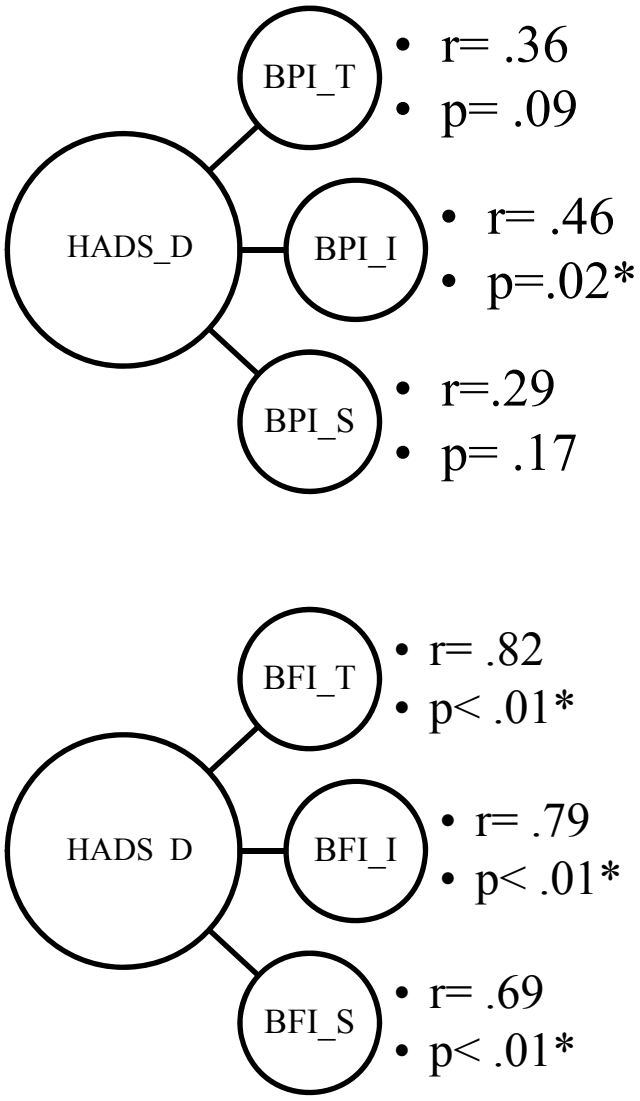

Figure 3. Correlations found in this study between the Hospital Anxiety and Depression Scale (HADS) depression subscale (D) and the Brief Pain Inventory (BPI) total measure (T) and the subscales interference (I) and severity (S). Correlations found in this study between the HADS-D and the Brief Fatigue Inventory (BFI) total measure (T) and the subscale interference (I) and severity (S). A p value less than .05 is considered significant. The symbol (*) marks significant correlations.

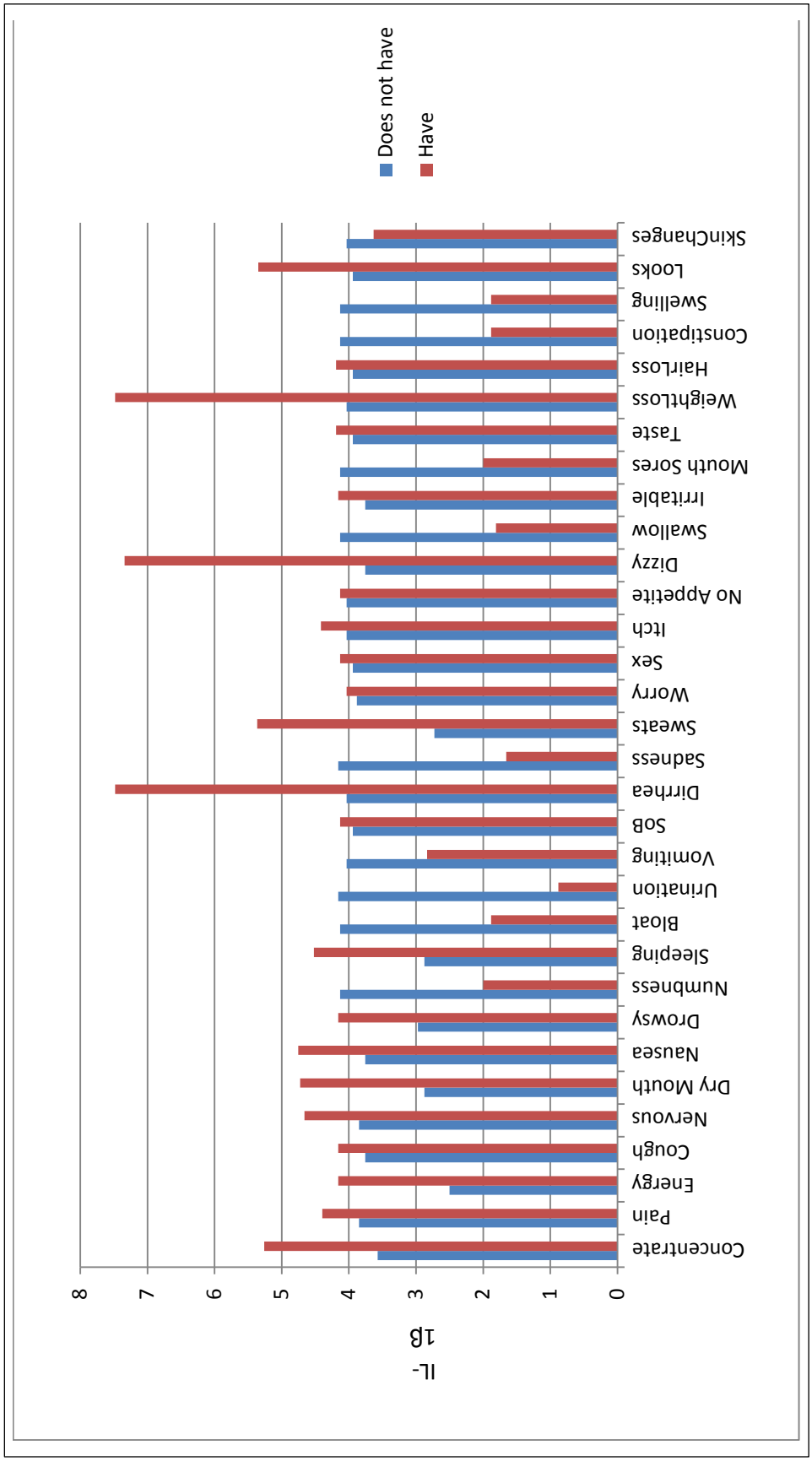

Figure 4. Difference in serum cytokine IL-1β levels between patients who had and did not have symptoms reported by the Memorial Symptom Assessment Scale.

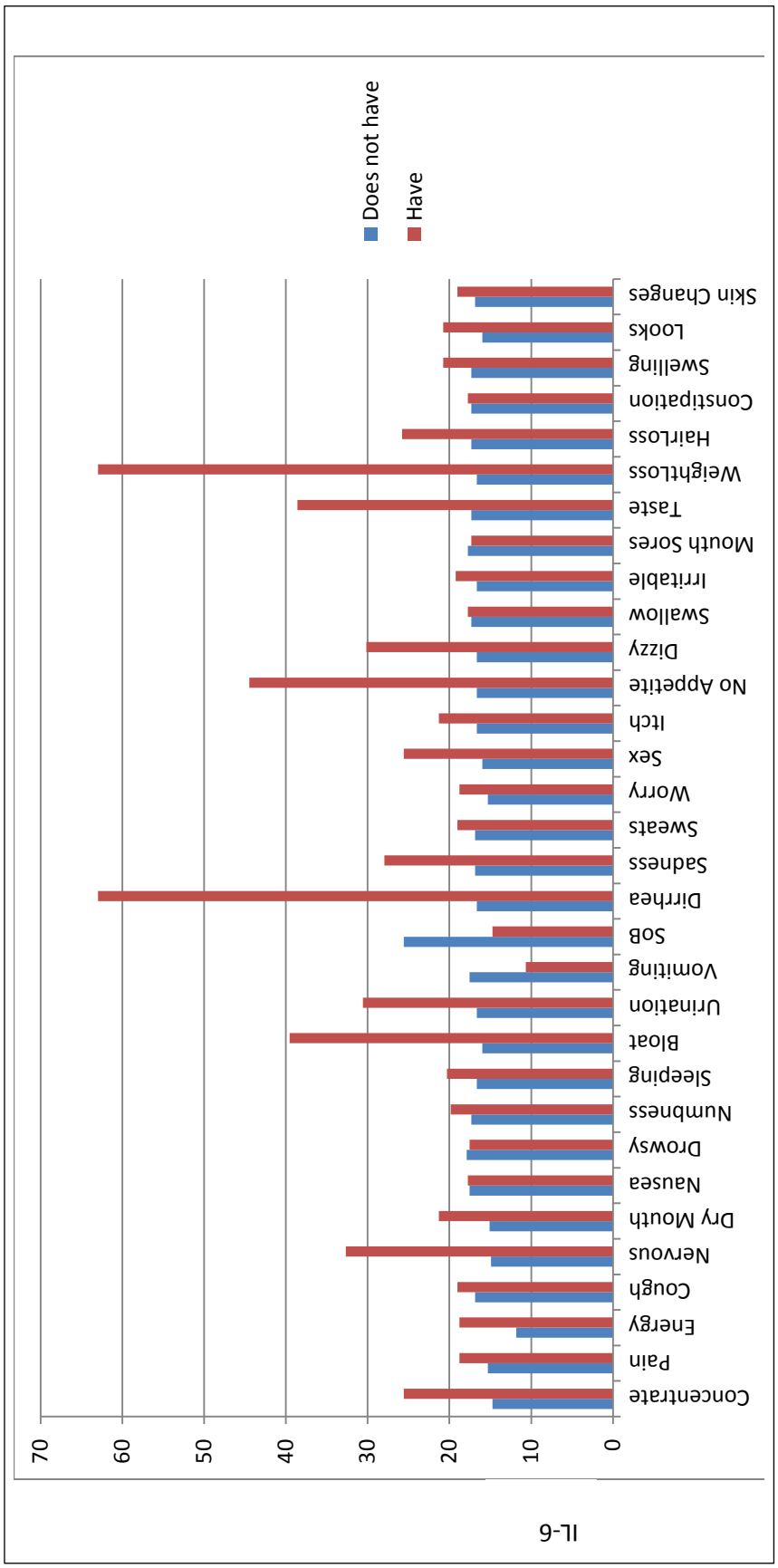

Figure 5. Difference in serum cytokine IL-6 levels between patients who had and did not have symptoms reported by the Memorial Symptom Assessment Scale.

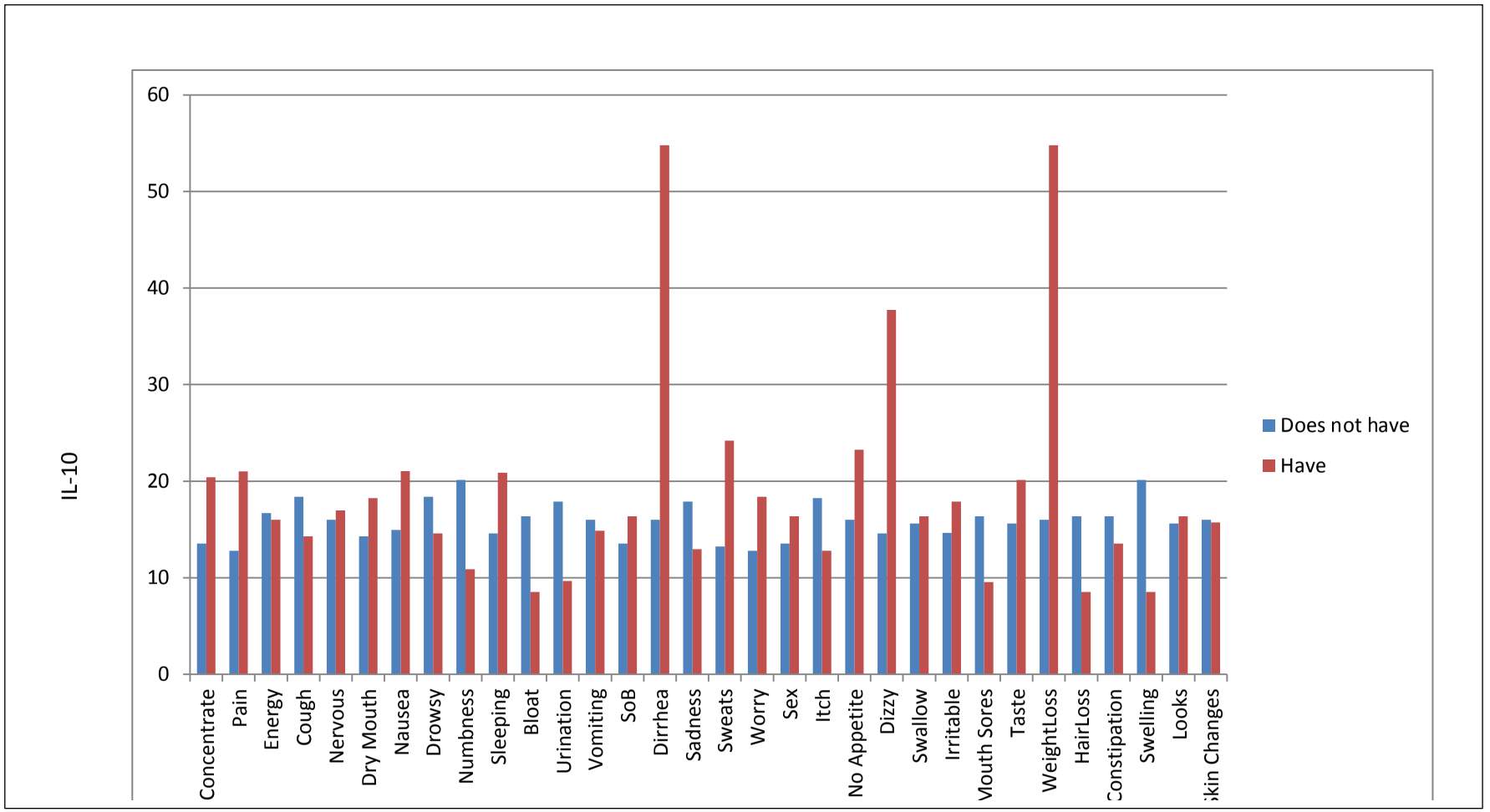

Figure 6. Difference in serum cytokine IL-10 levels between patients who had and did not have symptoms reported by the Memorial Symptom Assessment Scale.

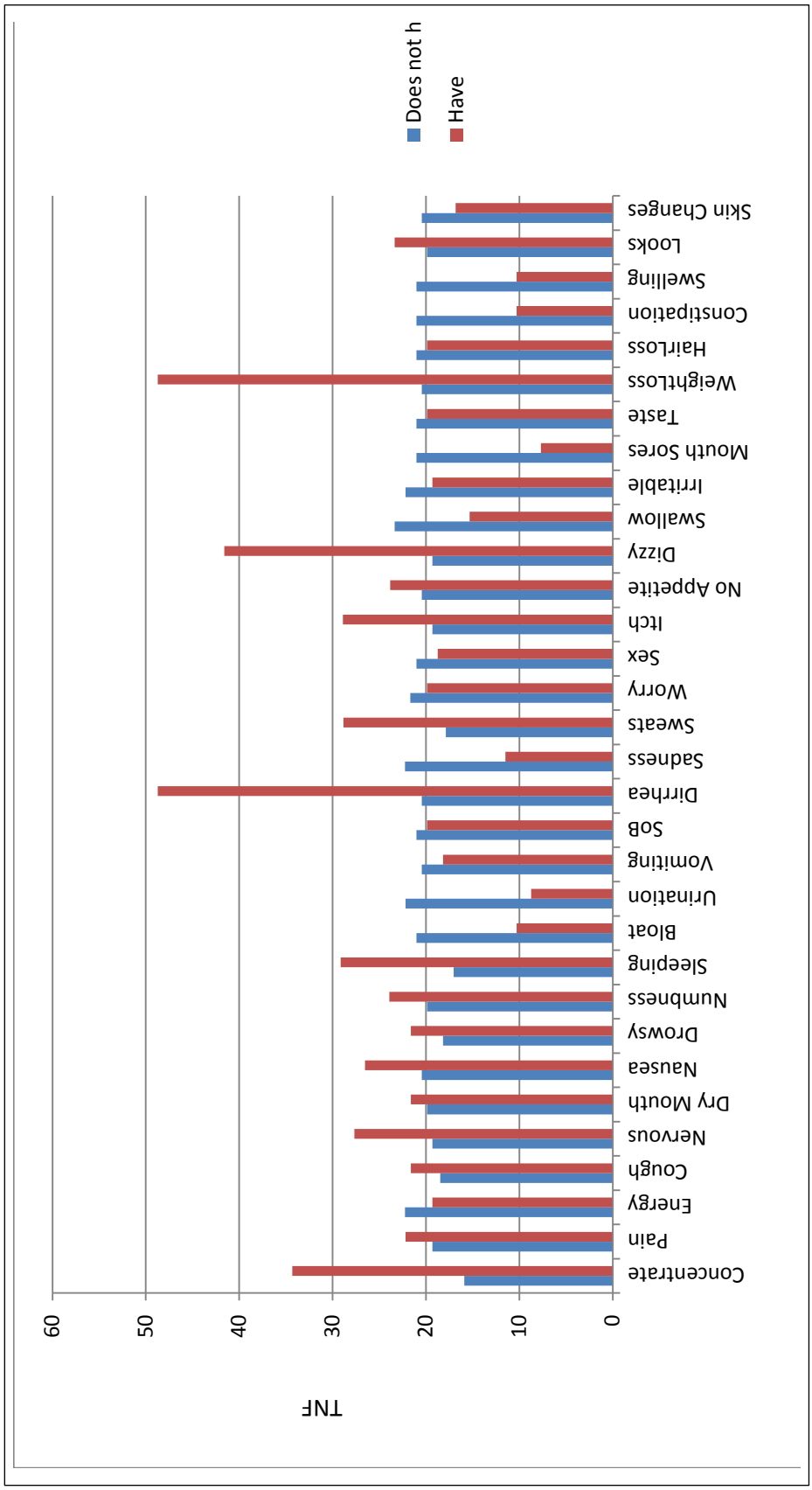

Figure 7. Difference in serum cytokine TNF levels between patients who had and did not have symptoms reported by the Memorial Symptom Assessment Scale.

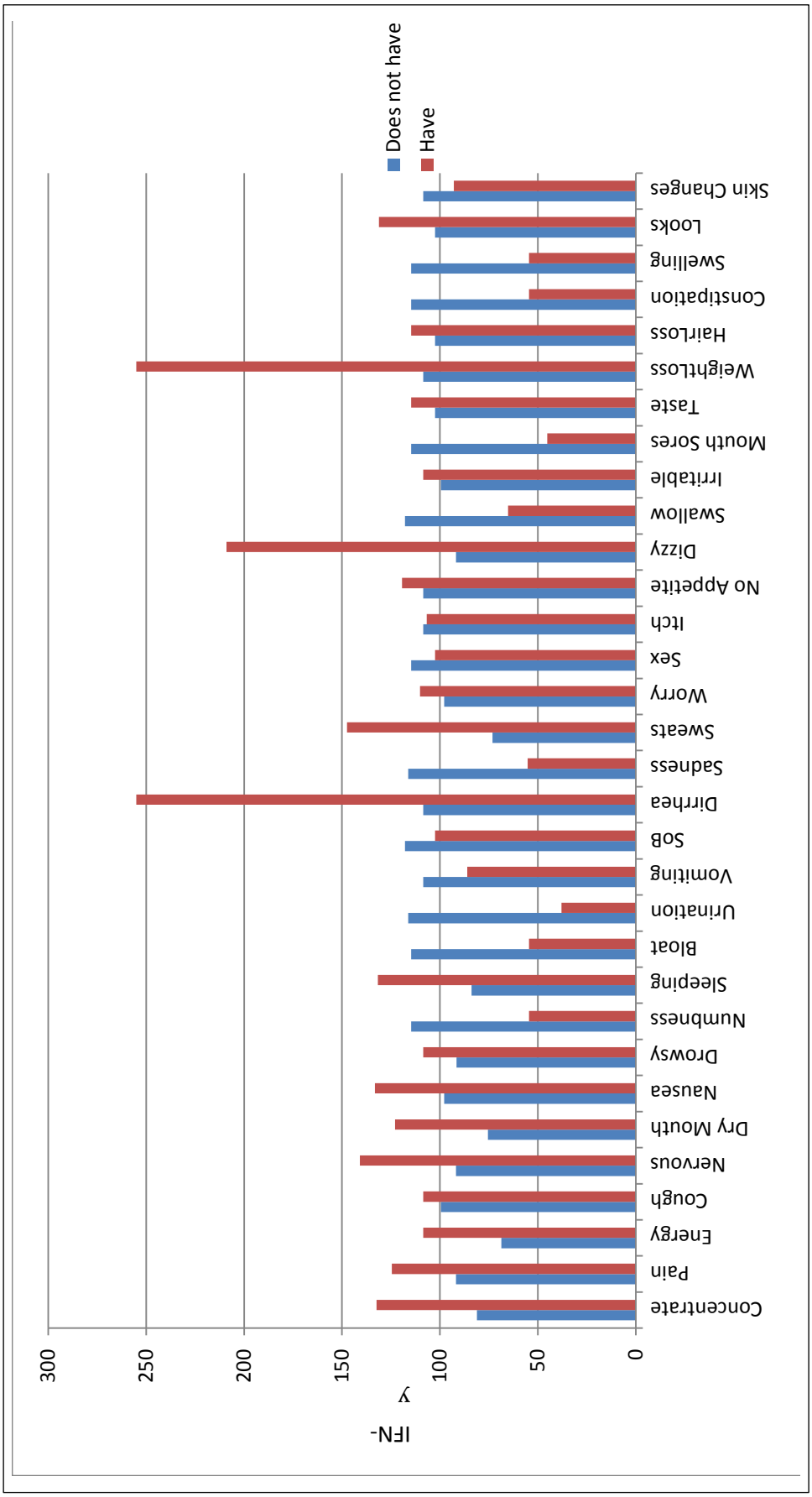

Figure 8. Difference in serum cytokine IFN-γ levels between patients who had and did not have symptoms reported by the Memorial Symptom Assessment Scale.

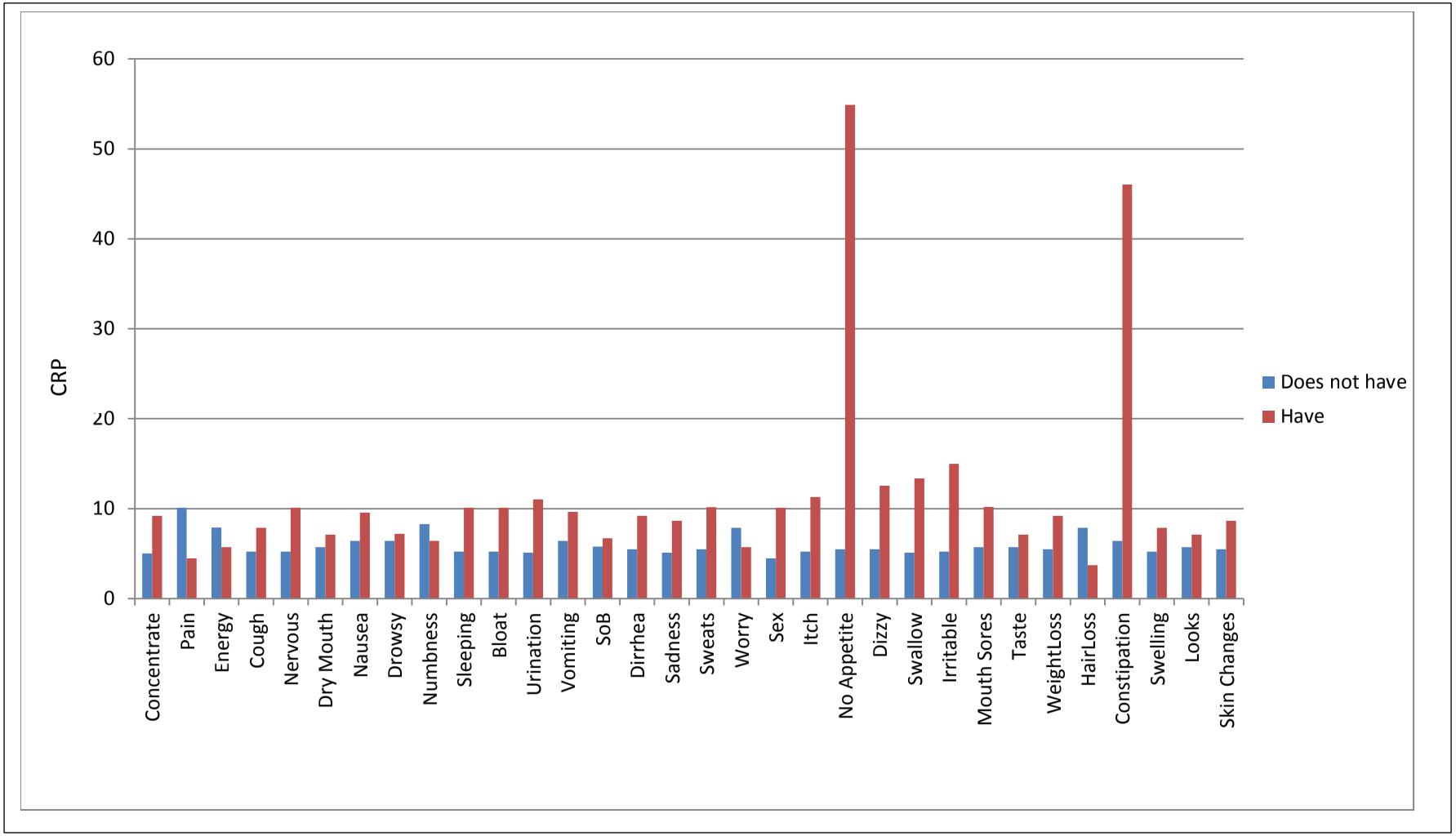

Figure 9. Difference in serum cytokine CRP levels between patients who had and did not have symptoms reported by the Memorial Symptom Assessment Scale.

Chapter 5

Summary

To better understand the symptomology of chronic graft-versus-host disease (cGVHD) inclusive of possible biological mechanisms of symptoms and how they may relate to quality of life (QoL), this dissertation study focused on elucidating a profile of symptoms, inflammation, and QoL in a sample of participants diagnosed with cGVHD. In addition, it was of interest to determine if there were relationships between and among these variables. As a certified oncology nurse working with bone marrow transplant recipients, this researcher witnessed the distress caused by cGVDH. Symptoms were particularly distressing for patients and were often difficult to manage, yet there was not much known about typical symptoms or if certain symptoms co-occurred. Secondly, as cGVHD is a complication individuals are living with, at times for many years, survivorship issues, such as QoL, are of interest in cGVHD research and have been suggested to be included in clinical trials as possible endpoints to determine intervention efficacy (Filipovich et al., 2005; Schulman, 2006).

Cytokines, a surrogate marker of inflammation, have been found to be associated with symptoms of cancer such as pain, depression and fatigue (Meyers, 2008; Seruga, 2008). Cytokines have also been examined in cGVHD and have been found to be associated with some auto-immune diseases that present similarly to cGVHD (Baird & Montaine, 2008; Klimiuk, Sierakowski, Domyslawska, & Chwiecko, 2011). Therefore, it was a logical for this researcher to explore cytokines previously examined in cGVHD, in symptoms individuals with cGVHD may

be experiencing. Of specific interest to this researcher was knowing which symptoms present with cGVHD and to what extent, through a biobehavioral lens, and how QoL is affected by cGVHD. The first step in this research inquiry was a review of the literature to determine what was already known and where there were gaps that needed to be addressed. Findings from this empirical review prompted the specific aims for this initial research into the symptomology of cGVHD.

Using the knowledge about the gaps in literature into the symptomology of cGVHD, a study was proposed to describe the symptoms, inflammation, and QoL in individuals diagnosed with cGVHD and examine the associations between and among symptoms (cGVHD specific, general [prevalent in other cancer populations], and cluster [pain, depression, and fatigue]), inflammatory markers (IL-1β, IL-6, IL-10, TNF and IFN-γ) and CRP, and QoL. To this researcher's knowledge, this is the first study using the general symptom measure (MSAS) and cluster symptom measures (BPI, HADS, and BFI) in this population.

There were several prominent symptoms noted across all symptom measures. Comparisons of pro-inflammatory cytokines and CRP levels were noted to show an observed pattern of elevation in individuals reporting the presence of specific general symptoms as opposed to individuals who did not report having the same symptom. Cytokine IL-6 had a significant increase between individuals reporting lack of energy and individuals without lack of energy. Pain, depressive symptoms, and fatigue were noted in many participants. There did not seem to be any decrease in QoL means for the FACT-BMT total; however, the PWB and the FWB subscales demonstrated the lowest scores. Several individuals had lower than average QoL scores. There were significant correlations between and among symptoms, inflammatory markers, and QoL. Significant correlations among domains of pain, depression and fatigue,

indicate the possibility of a symptom cluster. Inflammatory markers were consistent with cytokine pathways and appear to be over-expressed in this sample of individuals. There were many negative associations among symptoms and QoL indicating a possibility of symptom influence on QoL. This study provides preliminary information into the interplay between inflammation and symptom presentation and need to be examined further to make any conclusion. The initial plans for this program of research will be to replicate this study with the following: 1) a larger sample size, 2) use of a control group for cytokine comparison, and 3) use of in-depth measures of noted general symptoms such as sleeping difficulty.

One of the most significant findings in this study was the presence of symptoms that may be only suspect of a particular site of cGVHD such as dry mouth or sexual dysfunction. Thorough assessment of symptoms is necessary to most effectively manage symptoms. Evidence about how symptoms present and the frequency and severity of symptoms, provides information for use when assessing patients' symptoms.

Another key finding of this study was the potential influence inflammation may have on symptom presentation. Knowledge about symptoms and mechanisms affecting the frequency and severity of symptoms may enable practitioners to implement strategies for anticipatory guidance of cGVHD complications during pre and post transplant counseling.

Significant differences in cytokine levels Il-1β, Il-6, and IL-10 make these cytokines candidate markers for future investigation. The complication of cGVHD is complex and the etiology is poorly understood. Current research is focused on identification of target biomarkers for identification of possible disease initiation, progression, remission, and recurrence. It is of interest to know how cGVHD manifests. Knowing if symptoms and cytokines cluster by body system and if cGVHD clusters by body system is of interest. There may be different biological

and behavioral profiles depending on the affected site. Knowledge about how symptoms present and biological mechanisms, such as inflammation, is fundamental to the development and testing of novel interventions to mitigate symptoms and improve QoL for individuals with cGVHD.

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Appendix A

Search Terms for State of the Science Manuscript

The PubMed search terms to capture literature about symptoms and cGVHD were ((("Signs and Symptoms"[Mesh] OR Symptom*[Title/Abstract])) AND (("Graft vs Host Disease"[Majr] OR Chronic Graft-vs-Host Disease* OR Chronic Graft versus Host Disease*[Title/Abstract] OR cGVHD[Title/Abstract] NOT Acute Graft-vs-Host Disease*[Title/Abstract] OR Acute Graft versus Host Disease*[Title/Abstract] OR aGVHD[Title/Abstract] AND (English[lang])) AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang] AND adult[MeSH])). The PubMed search terms to capture literature about cytokines and cGVHD were (("Cytokines"[Mesh] OR cytokines[Title/Abstract] AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang] AND adult[MeSH]))) AND (("Graft vs Host Disease"[Majr] OR Chronic Graft-vs-Host Disease* OR Chronic Graft versus Host Disease*[Title/Abstract] OR cGVHD[Title/Abstract] NOT Acute Graft-vs-Host Disease*[Title/Abstract] OR Acute Graft versus Host Disease*[Title/Abstract] OR aGVHD[Title/Abstract] AND (English[lang])) AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang] AND adult[MeSH]). The PubMed search terms to capture literature about quality of life and cGVHD were (("Cytokines"[Mesh] OR cytokines[Title/Abstract] AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang]

AND adult[MeSH]))) AND (("Graft vs Host Disease"[Majr] OR Chronic Graft-vs-Host Disease* OR Chronic Graft versus Host Disease*[Title/Abstract] OR cGVHD[Title/Abstract] NOT Acute Graft-vs-Host Disease*[Title/Abstract] OR Acute Graft versus Host Disease*[Title/Abstract] OR aGVHD[Title/Abstract] AND (English[lang])) AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang] AND adult[MeSH])) AND ("last 10 years"[PDat] AND Humans[Mesh] AND English[lang] AND adult[MeSH]). The CINAHL search terms to capture literature about symptoms and cGVHD were ((MH "Graft Versus Host Disease") OR Chronic Graft-vs-Host Disease* OR Chronic Graft versus Host Disease* OR cGVHD) NOT (Acute Graft-vs-Host Disease* OR Acute Graft versus Host Disease* OR aGVH) AND ((MH "Signs and Symptoms (Non-Cinahl)") OR (MH "Symptoms") OR symptom*).

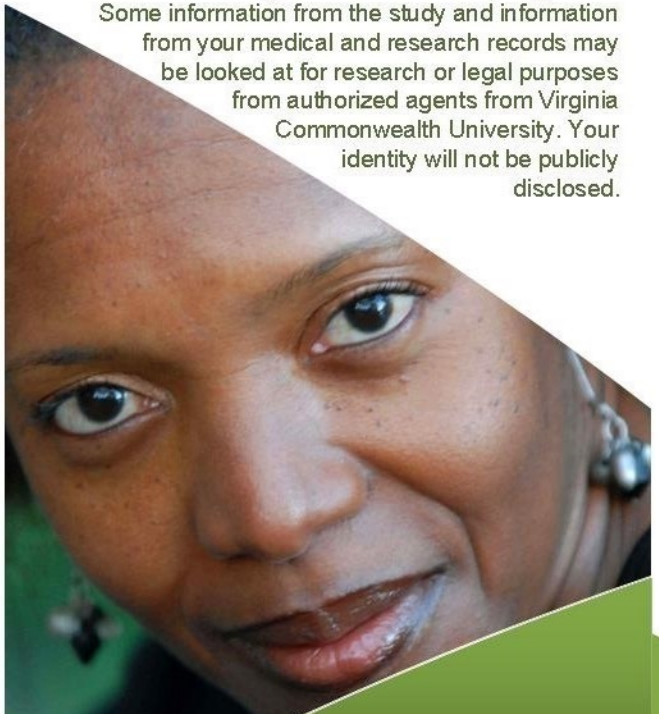
The CINAHL search terms to capture literature about cytokines and cGVHD were ((MH "Graft Versus Host Disease") OR Chronic Graft-vs-Host Disease* OR Chronic Graft versus Host Disease* OR cGVHD) NOT (Acute Graft-vs-Host Disease* OR Acute Graft versus Host Disease* OR aGVH) AND ((MH "Cytokines OR Chemokines (Non-Cinahl)") OR (MH "Cytokines OR Chemokines") OR cytokine OR chemokine*). The CINAHL search terms to capture literature about quality of life and cGVHD were ((MH "Graft Versus Host Disease") OR Chronic Graft-vs-Host Disease* OR Chronic Graft versus Host Disease* OR cGVHD) NOT (Acute Graft-vs-Host Disease* OR Acute Graft versus Host Disease* OR aGVH) AND ((MH "Quality of life (Non-Cinahl)") OR (MH "Quality of life") OR quality of life*)

ARE THERE COSTS?

There are no costs for participating in this study other than the time you will spend for data collection appointments. You will not be charged for any aspect of the study. You will receive a $25.00 gift For your participation in this study.

WHAT ABOUT CONFIDENTIALITY?

We will make all reasonable efforts to protect your privacy. We will not tell anyone the information you give us. Some information from the study and information from your medical and research records may be looked at for research or legal purposes from authorized agents from Virginia Commonwealth University. Your identity will not be publicly disclosed.



Symptoms, Cytokines, and Quality of Life Profiles of Patients with Chronic Graft-versus-Host Disease

WHO DO I CONTACT FOR MORE INFORMATION?

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Principal Investigator:

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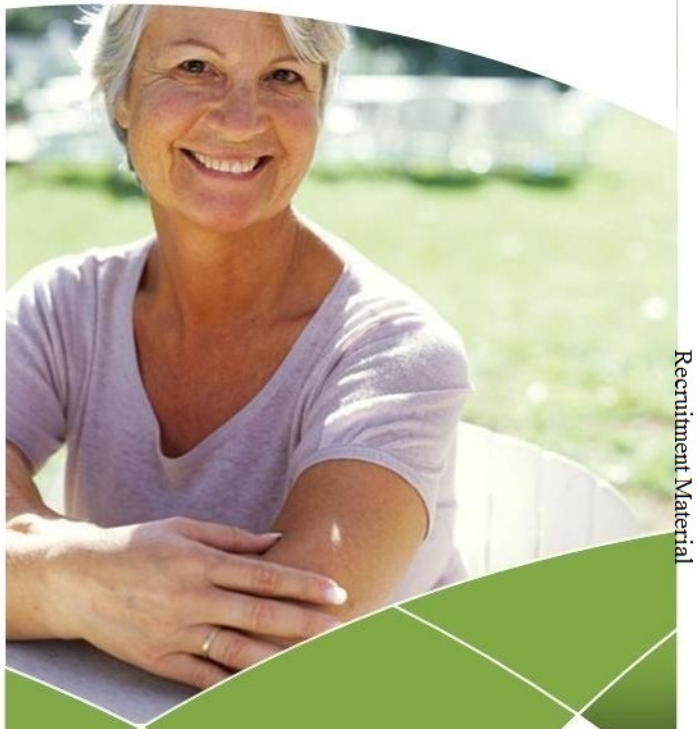
SYMPTOM RESEARCH:

FOR PATIENTS WITH CHRONIC GRAFT-VERSUS-HOST DISEASE



VCU MASSEY CANCER CENTER
Virginia Commonwealth University

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of the study is to examine the relationships among experienced symptoms in patients with chronic graft-versus-host disease and inflammatory markers. It is also to examine how these symptoms effect quality of life for patients with chronic graft-versus-host disease.

WHAT IS THE NAME OF THIS STUDY?

Symptoms, Cytokines, and Quality of Life Profiles of Patients with Chronic Graft-versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

WHO ARE THE INVESTIGATORS?

Debra Lynch Kelly, DCD, RN. OCN
Doctoral Student, School of Nursing,
Virginia Commonwealth University

Debra Lyon, PhD, RN, FNP-BC
Associate Professor, School of Nursing
Virginia Commonwealth University

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of the study is to examine the relationships among experienced symptoms in patients with chronic graft-versus-host disease and inflammatory markers. It is also to examine how these symptoms effect quality of life for patients with chronic graft-versus-host disease.

WHAT IS REQUIRED OF ME?

If you decide to participate in this research, you will be asked to sign a consent form after all of your questions have been answered and you understand what is being asked of you. There is one study visit which will take about one hour to complete. At your study visits, you will be asked to answer some questions about how you are doing by filling out some questionnaires. A blood sample will also be collected at your visit. We will try to combine this with your regularly scheduled blood tests.

AM I ELIGIBLE TO PARTICIPATE?

If you answer yes to all of the following questions, then you may be eligible.

- ⇒ Are you at least 18 years of age?
- ⇒ Are you a recipient of an allogeneic hematopoietic stem cell transplant?
- ⇒ Have you been diagnosed with Chronic Graft-versus-Host Disease?

Symptoms, Cytokines, and Quality of Life Profiles of Patients with Chronic Graft-Versus-Host Disease following Allogeneic Hematopoietic Stem Cell Transplantation




If you are a Bone Marrow recipient and have a diagnosis of

CHRONIC GRAFT-VERSUS-HOST DISEASE

Debra Lynch Kelly, DCD, RN, OCN at Virginia Commonwealth University is conducting a research study examining Symptoms, Inflammatory Markers and Quality of Life

You may be eligible for this study if you:

- ⇒ Are at least 18 years of age
- ⇒ Have received an allogeneic bone marrow transplant
- ⇒ Have a current diagnosis of chronic graft-versus-host disease

Volunteers will be compensated for participating

YOU WILL NOT BE TAKING A STUDY DRUG

Call 804-240-3803 for more information

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4/3/13 HV

Chronic Graft Versus Host Disease

Enrollment Documentation

Study ID: ___ ___ ___ ___

Date of Enrollment: _____

Please check all that apply:

_____The patient is at least 21 years of age

_____The patient has a diagnosis of cGVHD

_____The patient is able to understand and speak English

_____The patient does not have dementia

_____The patient does not have active psychosis

_____The patient has not started any anti-depressant medication within 30 days

_____The patient is not pregnant

_____The patient is not incarcerated

If any of the above is not verified, the patient should NOT be enrolled in the study.

The following has been discussed with the patient:

_____The informed consent in its entirety

_____The voluntary nature of the study

_____Alternatives to participation

_____Questions about the study

The following actions have been completed:

_____The patient has willingly agreed to participate in the study

_____The patient has verbalized understanding of the study and has signed the consent form

_____The patient has received a copy of the signed consent form

The patient is scheduled for a visit on

Date:

Location:

Time:

A trained staff member will meet the patient at scheduled visit to complete study session.

Other pertinent data: _____

_____

_____

_____

Study Nurse: _____ Date: _____

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RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Symptoms, Cytokines, and Quality Of Life Profiles of Patients with Chronic Graft-versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

VCU IRB NO.: Pending HM15063

If any information contained in this consent form is not clear, please ask the study staff to explain any information that you do not fully understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE STUDY

The purpose of this research study is to examine symptoms such as pain, depression, and fatigue that may be experienced by patients with chronic graft-versus-host disease and see if they are related to certain inflammatory markers. Also, the purpose of this study is to see if these factors are associated with quality of life of patients diagnosed with chronic graft-versus-host disease. You are being asked to participate in this study because you have been diagnosed with chronic graft-versus-host disease.

DESCRIPTION OF THE STUDY AND YOUR INVOLVEMENT

If you decide to be in this research study, you will be asked to sign this consent form after you have had all your questions answered and understand what will happen to you.

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The greatest risk to you is the release of information from your health records. We will do our best to make sure your personal information will be kept private. The likelihood that your information will be given to someone not authorized is very small. Results

Approved
4/13/13 HV / ER

from this study may be published but individual patients will not be identified in the publication.

USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Authority to Request Protected Health Information

The following people and/or groups may request my Protected Health Information:

- Principal Investigator and Research Staff
- Research Collaborators
- Data Safety Monitoring Boards
- Others as Required by Law
- Study Sponsor
- Institutional Review Boards
- Government/Health Agencies

Authority to Release Protected Health Information

The VCU Health System (VCUHS) may release the information identified in this authorization from my medical records and provide this information to:

- Health Care Providers at the VCUHS
- Study Sponsor
- Data Coordinators
- Data Safety Monitoring Boards
- Others as Required by Law
- Principal Investigator and Research Staff
- Research Collaborators
- Institutional Review Boards
- Government/Health Agencies

Once your health information has been disclosed to anyone outside of this study, the information may no longer be protected under this authorization.

Type of Information that may be Released

The following types of information may be used for the conduct of this research:

☐ Complete health record	☒ Diagnosis & treatment codes	☐ Discharge summary
☒ History and physical exam	☐ Consultation reports	☒ Progress notes
☒ Laboratory test results	☐ X-ray reports	☐ X-ray films / images
☐ Photographs, videotapes	☐ Complete billing record	☐ Itemized bill
☐ Information about drug or alcohol abuse		☐ Information about Hepatitis B or C tests
☐ Information about psychiatric care		☐ Information about sexually transmitted diseases

☐ Other (specify):

Right to Revoke Authorization and Re-disclosure

You may change your mind and revoke (take back) the right to use your protected health information at any time. Even if you revoke this Authorization, the researchers may still use or disclose health information they have already collected about you for this study. If you revoke this Authorization you may no longer be allowed to participate in the research study. To revoke this Authorization, you must write to the Principal Investigator.

BENEFITS TO YOU AND OTHERS

You may not get any direct benefit from this study, but the information we learn from people in this study may benefit other patients in the future. The results from this study

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4/3/13 HV / EP

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will not be provided to you. They will not be in your medical health record nor will participation in this study effect your treatment.

COSTS
There are no costs for participating in this study other than the time you will spend at your study visits. All costs of the study are covered. There are no charges for your study visit; however the study will not cover additional charges incurred while on the study.

PAYMENT FOR PARTICIPATION
You will receive a $25.00 gift card upon completion of this study. You will be asked to provide your social security number in order to receive payment for your participation. Your social security number is required by federal law. It will not be included in any information collected about you for this research. Your social security number will be kept confidential and will only be used in order to process payment.

ALTERNATIVES
The alternative to participating in this study is not to participate in this study.

CONFIDENTIALITY
Potentially identifiable information about you will consist of demographic data collected at the start of the study and data collected from the questionnaires. Data is being collected only for research purposes. Your data will be identified by ID numbers, not names and will be stored separately from medical records in a locked research area. All personal identifying information will be kept in password protected files and these files will be deleted when no longer needed for analyses. Other records including study questionnaires will be kept in a locked file cabinet for ten years after the study ends and will be destroyed at that time. Access to all data will be limited to study personnel. A data and safety monitoring plan is established.

We will not tell anyone the answers you give us; however, information from the study and information from your medical record and the consent form signed by you may be looked at or copied for research or legal purposes by Virginia Commonwealth University. Personal information about you might be shared with or copied by authorized officials of the Department of Health and Human Services.

What we find from this study may be presented at meetings or published in papers, but your name will not ever be used in these presentations or papers.

IF AN INJURY OR ILLNESS HAPPENS
The likelihood of an injury as a result of you participation in this study is very small; however, if you are injured by, or become ill, from participating in this study, please contact your study doctor immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

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Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study.

To help avoid research-related injury or illness it is very important to follow all study directions.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

You do not have to participate in this study. If you choose to participate, you may stop at any time without any penalty. You may also choose not to answer particular questions that are asked in the study.

Your participation in this study may be stopped at any time by the study staff without your consent. The reasons might include:

- the study staff thinks it necessary for your health or safety;
- you have not followed study instructions;

QUESTIONS

In the future, you may have questions about your participation in this study. If you have any questions, complaints, or concerns about the research, contact:

VCU Medical Center

Debra E. Lyon, RN, PhD, FNP, FAAN
Professor and Chair
VCU School of Nursing
Family and Community Health
PO Box 980567
Richmond, VA 23233
(804) 828-5635
delyon@vcu.edu

Debra Lynch Kelly, DCD, RN, OCN
Doctoral Student
VCU School of Nursing
PO Box 980567
Richmond, VA 23233
(804)828-3310
dkelly2@vcu.edu

If you have any general questions about your rights as a participant in this or any other research, you may contact:

Office of Research
Virginia Commonwealth University
800 East Leigh Street, Suite 3000
P.O. Box 980568
Richmond, VA 23298
Telephone: (804) 827-2157

Contact this number for general questions, concerns or complaints about research. You may also call this number if you cannot reach the research team or if you wish to talk with someone else. General information about participation in research studies can also be found at http://www.research.vcu.edu/irb/volunteers.htm.

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CONSENT

I have been given the chance to read this consent form. I understand the information about this study. Questions that I wanted to ask about the study have been answered. My signature says that I am willing to participate in this study. I will receive a copy of the consent form once I have agreed to participate.

Participant name printed	Participant signature	Date

Name of Person Conducting Informed Consent Discussion / Witness [3]
(Printed)

Signature of Person Conducting Informed Consent Discussion / Witness	Date

Principal Investigator Signature (if different from above)	Date [4]

Approved
4/3/13 HV / EP

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Template Rev Date: 5-15-12

OFFICE OF RESEARCH
Recd
FEB 20 2013
SUBJECT PROTECTION

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Symptoms, Cytokines, and Quality Of Life Profiles of Patients with Chronic Graft-versus-Host Disease Following Allogeneic Hematopoietic Stem Cell Transplantation

VCU IRB NO.: Pending HM15063

If any information contained in this consent form is not clear, please ask the study staff to explain any information that you do not fully understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

PURPOSE OF THE STUDY

The purpose of this research study is to examine symptoms such as pain, depression, and fatigue that may be experienced by patients with chronic graft-versus-host disease and see if they are related to certain inflammatory markers. Also, the purpose of this study is to see if these factors are associated with quality of life of patients diagnosed with chronic graft-versus-host disease. You are being asked to participate in this study because you have been diagnosed with chronic graft-versus-host disease.

DESCRIPTION OF THE STUDY AND YOUR INVOLVEMENT

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Approved
4/3/13/ HV / EC

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Approved
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(Printed)

Signature of Person Conducting Informed Consent Discussion / Witness _____ Date _____

Principal Investigator Signature (if different from above) _____ Date [4] _____

Approved
4/3/13 HV / EP

Verified by: _____ Date: _____

Sent to Data Entry Date: _____ Received from Data Entry Date: _____

cGVHD Study

Study ID _____

Date _____

Data Collected by (Please Print): _____

Location: _____

Data Collected

_____ **Demographic with Disease Profile**

_____ **MSAS**

_____ **Lee Symptom Bother**

_____ **PSS-10**

_____**Lifestyle Profile**

_____ **FACT-BMT**

_____ **BPI**

_____**HADS Score =** _____

_____ **BFI**

Blood Samples

_____ **Specimen delivered (1 small purple tube)**

_____

_____

Gift Card Information

_____ **Patient received Gift Card** _____ **Gift Card Number**

Other Information

_____

_____

_____

_____

_____

Data Collected by (Please Sign): _____ **Date:** _____

9059391051

cGVHD Study
Kelly, D.
Enrollment Form (Page 1 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

DEMOGRAPHIC PROFILE

Data Collector: _____

1. Enrollment Date: ☐☐ / ☐☐ / ☐☐ (mm/dd/yy)

2. Age (in years): ☐☐

3. Ethnicity:

- ○ Hispanic or Latino
- ○ Not-Hispanic or Latino

4. Race (select one):

- ○ American Indian/Alaska Native
- ○ Asian
- ○ Black or African-American
- ○ Native Hawaiian or Other Pacific Islander
- ○ White
- ○ More than one race
- ○ Other

5. Gender:

- ○ Male
- ○ Female

6. Education:

- ○ Didn't finish High School
- ○ High School Diploma
- ○ Any education beyond High School

cGVHD Study
Kelly, D.
Enrollment Form (Page 2 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

7. Marital Status:

- ○ Married/Partner
- ○ Divorced/Separated
- ○ Single, never married

8. Employment (select one):

- ○ Unemployed
- ○ Employed Part-time
- ○ Employed Full-time
- ○ Disabled
- ○ Retired
- ○ Student

9. Total household income:

- ○ Less than $15,000
- ○ Between $15,000 and $29,999
- ○ Between $30,000 and $44,999
- ○ Between $45,000 and $59,999
- ○ Between $60,000 and $74,999
- ○ Between $75,000 and $89,999
- ○ Between $90,000 and $104,9999
- ○ Greater than or equal to $105,000

cGVHD Study
Kelly, D.
Enrollment Form (Page 3 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

10. Weight in pounds: ☐☐☐.☐

11. Height in inches: ☐☐.☐

12. Body Mass Index: ☐☐.☐☐

DISEASE PROFILE

13. Diagnosis Date: ☐☐ / ☐☐ / ☐☐ (mm/dd/yy)

14. Type of Cancer:

- ○ AML
- ○ ALL
- ○ CML
- ○ MM
- ○ Burkett's Lymphoma
- ○ Hodgkins
- ○ Non Hodgkins
- ○ B-Cell Lymphoma
- ○ T-Cell Lymphoma
- ○ MDS

15. Transplant Date: ☐☐ / ☐☐ / ☐☐ (mm/dd/yy)

16. Date diagnosed with cGVHD: ☐☐ / ☐☐ / ☐☐ (mm/dd/yy)

cGVHD Study
Kelly, D.
Enrollment Form (Page 4 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

17. cGVHD type of onset:

- ○ De Novo
- ○ Quiescent
- ○ Progressive

18. cGVHD Type:

- ○ Classic
- ○ Overlap

19. Organ Systems Involved:

- ○ 0
- ○ 1
- ○ 2
- ○ 3

20. Overall NIH Global Rating Scale:

- ○ Mild
- ○ Moderate
- ○ Severe

LABORATORY VALUES

21. Platelet Count:

- ○ < 100,000
- ○ > 100,000

22. Erythrocyte Sedimentation Rate: ☐☐☐.☐☐

23. Serum Ferritin: ☐☐☐.☐☐

24. Hemoglobin: ☐☐☐.☐☐

cGVHD Study
Kelly, D.
Enrollment Form (Page 5 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

DONOR

25. Gender Match:

○ No

○ Yes

26. Age Match:

○ No

○ Yes

27. HLA Match:

○ No

○ Yes

28. Related:

○ No

○ Yes

29. Transplant Regimen: _____

cGVHD Study
Kelly, D.
Enrollment Form (Page 6 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

MEDICATION PROFILE

30. Immunosuppressive Medications:

○ No
○ Yes

If yes, please select all that apply:

○ Systemic
○ Topical

31. Pain Medications:

○ No
○ Yes

32. Psychotropic Medications:

○ No
○ Yes

33. Antihypertensive Medications:

○ No
○ Yes

34. Cardiac Medications:

○ No
○ Yes

cGVHD Study
Kelly, D.
Enrollment Form (Page 7 of 7)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

35. Vitamins and Minerals:

○ No

○ Yes

36. Herbal Supplements:

○ No

○ Yes

37. Other medications: _____

PERFORMANCE STATUE

38. ECOG: ☐☐

2483158001

cGVHD Study
Kelly, D.
Lifestyle Profile (Page 1 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

Directions: This questionnaire contains statements about your present way of life or personal habits. Please respond to each item as accurately as possible, and try not to skip any item. Indicate the frequency with which you engage in each behavior by filling in the corresponding bubble.

	Never	Sometimes	Often	Routinely
1. Discuss my problems and concerns with people close to me.	①	②	③	④
2. Choose a diet low in fat, saturated fat, and cholesterol.	①	②	③	④
3. Report any unusual signs or symptoms to a physician or other health professional.	①	②	③	④
4. Follow a planned exercise program.	①	②	③	④
5. Get enough sleep.	①	②	③	④
6. Feel I am growing and changing in positive ways.	①	②	③	④
7. Praise other people easily for their achievements.	①	②	③	④
8. Limit use of sugars and food containing sugar (sweets).	①	②	③	④
9. Read or watch TV programs about improving health.	①	②	③	④
10. Exercise vigorously for 20 or more minutes at least three times a week (such as brisk walking, bicycling, aerobic dancing, using a stair climber).	①	②	③	④
11. Take some time for relaxation each day.	①	②	③	④
12. Believe that my life has purpose.	①	②	③	④
13. Maintain meaningful and fulfilling relationships with others.	①	②	③	④
14. Eat 6-11 servings of bread, cereal, rice and pasta each day.	①	②	③	④

cGVHD Study
Kelly, D.
Lifestyle Profile (Page 2 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Directions: This questionnaire contains statements about your present way of life or personal habits. Please respond to each item as accurately as possible, and try not to skip any item. Indicate the frequency with which you engage in each behavior by filling in the corresponding bubble.

	Never	Sometimes	Often	Routinely
15. Question health professionals in order to understand their instructions.	①	②	③	④
16. Take part in light to moderate physical activity (such as sustained walking 30-40 minutes 5 or more times a week).	①	②	③	④
17. Accept those things in my life which I can not change.	①	②	③	④
18. Look forward to the future.	①	②	③	④
19. Spend time with close friends.	①	②	③	④
20. Eat 2-4 servings of fruit each day.	①	②	③	④
21. Get a second opinion when I question my health care provider's advice.	①	②	③	④
22. Take part in leisure-time (recreational) physical activities (such as swimming, dancing, bicycling).	①	②	③	④
23. Concentrate on pleasant thoughts at bedtime.	①	②	③	④
24. Feel content and at peace with myself.	①	②	③	④
25. Find it easy to show concern, love and warmth to others.	①	②	③	④
26. Eat 3-5 servings of vegetables each day.	①	②	③	④
27. Discuss my health concerns with health professionals.	①	②	③	④
28. Do stretching exercises at least 3 times per week.	①	②	③	④

3260158005

cGVHD Study
Kelly, D.
Lifestyle Profile (Page 3 of 4)
V. 06/20/13

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	Never	Sometimes	Often	Routinely
29. Use specific methods to control my stress.	①	②	③	④
30. Work toward long-term goals in my life.	①	②	③	④
31. Touch and am touched by people I care about.	①	②	③	④
32. Eat 2-3 servings of milk, yogurt or cheese each day.	①	②	③	④
33. Inspect my body at least monthly for physical changes/danger signs.	①	②	③	④
34. Get exercise during usual daily activities (such as walking during lunch, using stairs instead of elevators, parking ccar away from destination and walking).	①	②	③	④
35. Balance time between work and play.	①	②	③	④
36. Find each day interesting and challenging.	①	②	③	④
37. Find ways to meet my needs for intimacy.	①	②	③	④
38. Eat only 2-3 servings from the meat, poultry, fish, dried beans, eggs, and nuts group each day.	①	②	③	④
39. Ask for information from health professionals about how to take good care of myself.	①	②	③	④
40. Check my pulse rate when exercising.	①	②	③	④
41. Practice relaxation or meditation for 15-20 minutes daily.	①	②	③	④
42. Am aware of what is important to me in life.	①	②	③	④

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cGVHD Study
Kelly, D.
Lifestyle Profile (Page 4 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

Directions: This questionnaire contains statements about your present way of life or personal habits. Please respond to each item as accurately as possible, and try not to skip any item. Indicate the frequency with which you engage in each behavior by filling in the corresponding bubble.

	Never	Sometimes	Often	Routinely
43. Get support from a network of caring people.	①	②	③	④
44. Read labels to identify nutrients, fats, and sodium content in packaged food.	①	②	③	④
45. Attend educational programs on personal health care.	①	②	③	④
46. Reach my target heart rate when exercising.	①	②	③	④
47. Pace myself to prevent tiredness.	①	②	③	④
48. Feel connected with some force greater than myself.	①	②	③	④
49. Settle conflicts with others through discussion and compromise.	①	②	③	④
50. Eat breakfast.	①	②	③	④
51. Seek guidance or counseling when necessary.	①	②	③	④
52. Expose myself to new experiences and challenges.	①	②	③	④

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cGVHD Study
Kelly, D.
Perceived Stress Scale 10 Form (Page 1 of 1)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

Directions: The questions below ask you about your feelings and thoughts during the LAST MONTH. Please fill in the corresponding bubble that best describes how often you felt or thought like the statement. There is no right or wrong answer.

In the last MONTH, how often have you...

	Never	Almost never	Sometimes	Fairly often	Very often
1. Been upset because of something that happened unexpectedly.	⓪	①	②	③	④
2. Felt that you were unable to control the important things in your life.	⓪	①	②	③	④
3. Felt nervous and "stressed".	⓪	①	②	③	④
4. Felt confident about your ability to handle your personal problems.	⓪	①	②	③	④
5. Felt that things were going your way.	⓪	①	②	③	④
6. Found that you could not cope with all the things that you had to do.	⓪	①	②	③	④
7. Been able to control irritations in your life.	⓪	①	②	③	④
8. Felt that you were on top of things.	⓪	①	②	③	④
9. Been angered because of things that happened that were outside of your control.	⓪	①	②	③	④
10. Felt difficulties were piling up so high that you could not overcome them.	⓪	①	②	③	④

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cGVHD Study
Kelly, D.
MSAS (Page 1 of 3)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

Instructions: We have listed 24 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how OFTEN you had it, how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by filling in the corresponding bubble. If you DID NOT HAVE the symptom, fill in the bubble under "DID NOT HAVE."

DURING THE PAST WEEK Did you have any of the following symptoms?		**IF YES** How OFTEN did you have it?				**IF YES** How SEVERE was it usually?				**IF YES** How much did it DISTRESS or BOTHER you?				
	DID NOT HAVE	Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much
1. Difficulty Concentrating	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
2. Pain	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
3. Lack of energy	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④

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cGVHD Study
Kelly, D.
MSAS (Page 1 of 3)
V. 06/20/13

Subject ID ____ - ____
Date __ / __ / __

DURING THE PAST WEEK Did you have any of the following symptoms?		**IF YES** How OFTEN did you have it?				**IF YES** How SEVERE was it usually?				**IF YES** How much did it DISTRESS or BOTHER you?				
	DID NOT HAVE	Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much
4. Cough	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
5. Feeling nervous	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
6. Dry mouth	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
7. Nausea	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
8. Feeling drowsy	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
9. Numbness/tingling in hands/feet	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
10. Difficulty sleeping	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④

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cGVHD Study
Kelly, D.
MSAS (Page 1 of 3)
V. 06/20/13

Subject ID ____ - ____
Date __ / __ / __

DURING THE PAST WEEK Did you have any of the following symptoms?	IF YES How OFTEN did you have it?				IF YES How SEVERE was it usually?				IF YES How much did it DISTRESS or BOTHER you?				
	DID NOT HAVE	Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much
11. Feeling bloated	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
12. Problems with urination	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
13. Vomiting	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
14. Shortness of breath	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
15. Diarrhea	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
16. Feeling sad	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
17.Sweats	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④

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cGVHD Study
Kelly, D.
MSAS (Page 1 of 3)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

DURING THE PAST WEEK Did you have any of the following symptoms?	**IF YES** How OFTEN did you have it?				**IF YES** How SEVERE was it usually?				**IF YES** How much did it DISTRESS or BOTHER you?				
	DID NOT HAVE	Rarely	Occasionally	Frequently	Almost Constantly	Slight	Moderate	Severe	Very Severe	Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much
18. Worrying	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
19. Problems with sexual interest or activity	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
20. Itching	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
21. Lack of appetite	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
22. Dizziness	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
23. Difficulty swallowing	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④
24.Feeling irritable	○	①	②	③	④	①	②	③	④	⓪	①	②	③	④

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cGVHD Study
Kelly, D.
MSAS (Page 1 of 3)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

Section 2
Instructions: We have listed 8 symptoms below. Read each one carefully. If you have had the symptom during this past week, let us know how SEVERE it was usually and how much it DISTRESSED or BOTHERED you by filling in the corresponding bubble. If you DID NOT HAVE the symptom, fill in the bubble under "DID NOT HAVE."

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DURING THE PAST WEEK Did you have any of the following symptoms?	DID NOT HAVE	**IF YES** How SEVERE was it usually?				**IF YES** How much did it DISTRESS or BOTHER you?				
		Slight	Moderate	Severe	Very Severe	Not At All	A Little Bit	Somewhat	Quite A Bit	Very Much
25. Mouth sores	○	①	②	③	④	⓪	①	②	③	④
26. Change in the way food tastes	○	①	②	③	④	⓪	①	②	③	④
27. Weight loss	○	①	②	③	④	⓪	①	②	③	④
28. Hair loss	○	①	②	③	④	⓪	①	②	③	④
29. Constipation	○	①	②	③	④	⓪	①	②	③	④

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Kelly, D.
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V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

DURING THE PAST WEEK **Did you have any of the following symptoms?**	DID NOT HAVE	**IF YES** **How SEVERE was it usually?** Slight (1)	Moderate (2)	Severe (3)	Very Severe (4)	**IF YES** **How much did it DISTRESS or BOTHER you?** Not At All (0)	A Little Bit (1)	Somewhat (2)	Quite A Bit (3)	Very Much (4)
30. Swelling of arms or legs	○	○	○	○	○	○	○	○	○	○
31. "I don't look like myself"	○	○	○	○	○	○	○	○	○	○
32. Changes in skin	○	○	○	○	○	○	○	○	○	○

IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE LIST BELOW AND INDICATE HOW MUCH THE SYMPTOM HAD DISTRESSED OR BOTHERED YOU.

Other:_____	○	○	○	○	○
Other:_____	○	○	○	○	○
Other:_____	○	○	○	○	○

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cGVHD Study
Kelly, D.
Chronic GVHD Symptom Scale (Page 1 of 2)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Directions: By filling in one bubble per line, please indicate how much you have been bothered by the following problems in the past month.

	Not at all	Slightly	Moderately	Quite a bit	Extremely
SKIN:					
1. Abonrmal skin color	⓪	①	②	③	④
2. Rashes	⓪	①	②	③	④
3. Thickened skin	⓪	①	②	③	④
4. Sores on skin	⓪	①	②	③	④
5. Itchy skin	⓪	①	②	③	④
EYES AND MOUTH:					
6. Dry eyes	⓪	①	②	③	④
7. Need to use eye drops frequently	⓪	①	②	③	④
8. Difficulty seeing clearly	⓪	①	②	③	④
9. Need to avoid certain foods due to mouth pain	⓪	①	②	③	④
10. Ulcers in mouth	⓪	①	②	③	④
11. Receiving nutrition from an intravenous line or feeding tube	⓪	①	②	③	④
BREATHING:					
12. Frequent cough	⓪	①	②	③	④
13. Colored sputum	⓪	①	②	③	④
14. Shortness of breath with exercise	⓪	①	②	③	④
15. Shortness of breath at rest	⓪	①	②	③	④
16. Need to use oxygen	⓪	①	②	③	④

cGVHD Study
Kelly, D.
Chronic GVHD Symptom Scale (Page 2 of 2)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Directions: By filling in one bubble per line, please indicate how much you have been bothered by the following problems in the past month.

	Not at all	Slightly	Moderately	Quite a bit	Extremely
EATING AND DIGESTION:					
17. Difficulty swallowing solid foods	⓪	①	②	③	④
18. Difficulty swallowing liquids	⓪	①	②	③	④
19. Vomiting	⓪	①	②	③	④
20. Weight loss	⓪	①	②	③	④
MUSCLES AND JOINTS:					
21. Joint and muscle aches	⓪	①	②	③	④
22. Limited joint movement	⓪	①	②	③	④
23. Muscle cramps	⓪	①	②	③	④
24. Weak muscles	⓪	①	②	③	④
ENERGY:					
25. Loss of energy	⓪	①	②	③	④
26. Need to sleep more/take naps	⓪	①	②	③	④
27. Fevers	⓪	①	②	③	④
MENTAL AND EMOTIONAL:					
28. Depression	⓪	①	②	③	④
29. Anxiety	⓪	①	②	③	④
30. Difficulty sleeping	⓪	①	②	③	④

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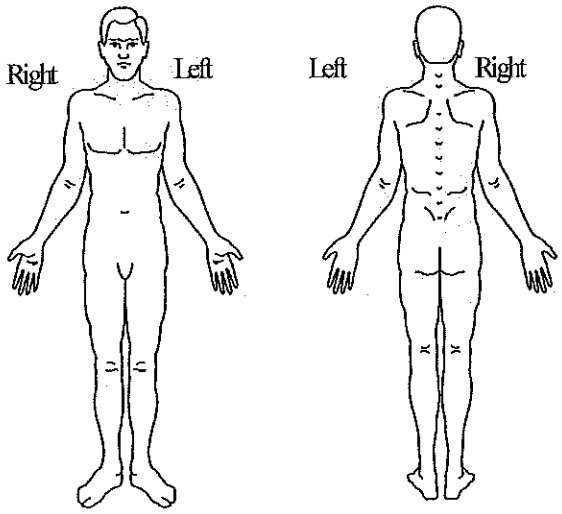
cGVHD Study
Kelly, D.
Brief Pain Inventory (Page 1 of 3)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today ? ○ Yes ○ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by filling in the one circle that best describes your pain at its WORST in the last 24 hours.

No Pain										**Pain as bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

4. Please rate your pain by filling in the one circle that best describes your pain at its LEAST in the last 24 hours.

No Pain										**Pain as bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

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cGVHD Study
Kelly, D.
Brief Pain Inventory (Page 2 of 3)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

5. Please rate your pain by filling in the one circle that best describes your pain on the AVERAGE.

No Pain										**Pain as bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

6. Please rate your pain by filling in the one circle that tells how much pain you have RIGHT NOW.

No Pain										**Pain as bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please fill in the one circle that shows how much RELIEF you have received.

No Relief										**Complete Relief**
0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
○	○	○	○	○	○	○	○	○	○	○

cGVHD Study
Kelly, D.
Brief Pain Inventory (Page 3 of 3)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

9. Fill in the one circle that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

B. Mood

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

C. Walking ability

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

D. Normal work (includes both work outside the home and daily chores)

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

E. Relations with other people

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

F. Sleep

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

G. Enjoyment of life

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

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cGVHD Study
Kelly, D.
HADS (Page 1 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐

Date ☐☐ / ☐☐ / ☐☐

Directions: Please fill in the corresponding bubble that best describes how you currently feel.

1. I feel tense or "wound up":

O Most of the time

O A lot of the time

O From time to time, occasionally

O Not at all

2. I still enjoy the things I used to enjoy:

O Definitely as much

O Not quite so much

O Only a little

O Hardly at all

3. I get a sort of frightened feeling as if something awful is about to happen:

O Very definitely and quite badly

O Yes, but not too badly

O A little, but it doesn't worry me

O Not at all

4. I can laugh and see the funny side of things:

O As much as I always could

O Not quite so much now

O Definitely not so much now

O Not at all

cGVHD Study
Kelly, D.
HADS (Page 2 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Directions: Please fill in the corresponding bubble that best describes how you currently feel.

5. Worrying thoughts go through my mind:

O A great deal of the time

O A lot of the time

O From time to time, but not too often

O Only occasionally

6. I feel cheerful:

O Not at all

O Not often

O Sometimes

O Most of the time

7. I can sit at ease and feel relaxed:

O Definitely

O Usually

O Not often

O Not at all

8. I feel as if I am slowed down:

O Nearly all the time

O Very often

O Sometimes

O Not at all

cGVHD Study
Kelly, D.
HADS (Page 3 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Directions: Please fill in the corresponding bubble that best describes how you currently feel.

9. I get a sort of frightened feeling like "butterflies" in the stomach :

O Not at all
O Occasionally
O Quite often
O Very often

10. I have lost interest in my appearance:

O Definitely
O I don't take as much care as I should
O I may not take quite as much care
O I take just as much care as ever

11. I feel restless as I have to be on the move:

O Very much indeed
O Quite a lot
O Not very much
O Not at all

12. I look forward with enjoyment to things :

O As much as I ever did
O Rather less than I used to
O Definitely less than I used to
O Hardly at all

cGVHD Study
Kelly, D.
HADS (Page 4 of 4)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Directions: Please fill in the corresponding bubble that best describes how you currently feel.

13. I get sudden feelings of panic:

O Very often indeed

O Quite often

O Not very often

O Not at all

14. I can enjoy a good book or radio or TV program :

O Often

O Sometimes

O Not often

O Very seldom

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cGVHD Study
Kelly, D.
Brief Fatigue Inventory (Page 1 of 2)
V. 06/20/13

Subject ID ☐☐☐☐ - ☐
Date ☐☐ / ☐☐ / ☐☐

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? ○ Yes ○ No

1. Please rate your fatigue (weariness, tiredness) by filling in the one circle that best describes your fatigue right NOW.

No fatigue										**As bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

2. Please rate your fatigue (weariness, tiredness) by filling in the one circle that best describes your USUAL level of fatigue during the past 24 hours.

No fatigue										**As bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

3. Please rate your fatigue (weariness, tiredness) by filling in the one circle that best describes your WORST level of fatigue during the past 24 hours.

No fatigue										**As bad as you can imagine**
0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

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4. Fill in the one circle that describes how, during the past 24 hours, fatigue has interfered with your:

A. General Activity

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

B. Mood

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

C. Walking ability

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

D. Normal work (includes both work outside the home and daily chores)

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

E. Relations with other people

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

F. Enjoyment of life

Does not interfere **Completely interferes**

0	1	2	3	4	5	6	7	8	9	10
○	○	○	○	○	○	○	○	○	○	○

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Date ☐☐ / ☐☐ / ☐☐

Below is a list of statements that other people with your illness have said are important. By filling in one (1) circle per line, please indicate your response as it applies to the past 7 days.

PHYSICAL WELL-BEING

		Not at all	A little bit	Some what	Quite a bit	Very much
GP1	I have lack of energy	⓪	①	②	③	④
GP2	I have nausea	⓪	①	②	③	④
GP3	Because of my physical condition, I have trouble meeting the needs of my family	⓪	①	②	③	④
GP4	I have pain	⓪	①	②	③	④
GP5	I am bothered by side effects of treatment	⓪	①	②	③	④
GP6	I feel ill	⓪	①	②	③	④
GP7	I am forced to spend time in bed	⓪	①	②	③	④

SOCIAL/FAMILY WELL-BEING

		Not at all	A little bit	Some what	Quite a bit	Very much
GS1	I feel close to my friends	⓪	①	②	③	④
GS2	I get emotional support from my family	⓪	①	②	③	④
GS3	I get support from my friends	⓪	①	②	③	④
GS4	My family has accepted my illness	⓪	①	②	③	④
GS5	I am satisfied with family communication about my illness	⓪	①	②	③	④
GS6	I feel close to my partner (or the person who is my main support)	⓪	①	②	③	④
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer, please check this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	⓪	①	②	③	④

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EMOTIONAL WELL-BEING

		Not at all	A little bit	Some what	Quite a bit	Very much
GE1	I feel sad	○ 0	○ 1	○ 2	○ 3	○ 4
GE2	I am satisfied with how I am coping with my illness	○ 0	○ 1	○ 2	○ 3	○ 4
GE3	I am losing hope in the fight against my illness	○ 0	○ 1	○ 2	○ 3	○ 4
GE4	I feel nervous	○ 0	○ 1	○ 2	○ 3	○ 4
GE5	I worry about dying	○ 0	○ 1	○ 2	○ 3	○ 4
GE6	I worry that my condition will get worse	○ 0	○ 1	○ 2	○ 3	○ 4

FUNCTIONAL WELL-BEING

		Not at all	A little bit	Some what	Quite a bit	Very much
GF1	I am able to work (include work at home)	○ 0	○ 1	○ 2	○ 3	○ 4
GF2	My work (include work at home) is fulfilling	○ 0	○ 1	○ 2	○ 3	○ 4
GF3	I am able to enjoy life	○ 0	○ 1	○ 2	○ 3	○ 4
GF4	I have accepted my illness	○ 0	○ 1	○ 2	○ 3	○ 4
GF5	I am sleeping well	○ 0	○ 1	○ 2	○ 3	○ 4
GF6	I am enjoying the things I usually do for fun	○ 0	○ 1	○ 2	○ 3	○ 4
GF7	I am content with the quality of my life right now	○ 0	○ 1	○ 2	○ 3	○ 4

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ADDITIONAL CONCERNS

		Not at all	A little bit	Some what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

Vita

Debra Lynch Kelly was born on January 19, 1966, in Fairfax, Virginia and is an American citizen. She graduated from Langley High School, McLean, Virginia in 1984. She received her Associates of Arts degree from Northern Virginia Community College in 1992 and her Bachelor of Science with a major in Nursing from Virginia Commonwealth University's School of Nursing in 1996. She worked as an RN in Virginia Commonwealth University Health System from 1996 until 2013. She received her oncology nurse certification in 2012. She has been a Project Coordinator for two nationally funded R-01 breast cancer studies from 2009 until current. She received the Stoke's Doctoral Fellowship award of $11,000.00 to aid in the funding of her dissertation in 2012.