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

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Purpose/Objectives: To describe associations among symptoms, cytokines, and quality of life (QOL) of patients with chronic graft-versus-host disease (cGVHD).

Design: Prospective, cross-sectional, cohort.

Setting: The bone marrow transplantation unit at a National Cancer Institute–designated cancer center in Virginia.

Sample: 24 adults diagnosed with cGVHD.

Methods: Data were collected for demographic factors, symptoms, and QOL from medical record and validated questionnaires. Serum was analyzed for cytokine levels.

Main Research Variables: cGVHD, symptoms, cytokines, C-reactive protein, and QOL.

Findings: Participants reported multiple, concurrent symptoms. Cytokine levels were higher in participants with symptoms versus those without symptoms. Cytokine interleukin-6 correlated with lack of energy and dry mouth. Negative correlations were noted between QOL and symptoms.

Conclusions: Findings demonstrated multiple concurrent symptoms present in this sample and significant relationships among symptoms, cytokines, and QOL.

Implications for Nursing: cGVHD is a serious condition affecting QOL in many individuals after bone marrow transplantation for many different cancers. Results from this pilot study indicate that patients experience multiple symptoms, including sexual dysfunction, that adversely affect QOL. Better understanding of the interrelated symptoms of cGVHD and the biomarkers associated with these symptoms may lead to targeted symptom management interventions.

Key Words: chronic graft-versus-host disease; symptoms; cytokines; inflammation; C-reactive protein; quality of life; cancer; bone marrow transplantation

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Hematopoietic cell transplantation (HCT) is the only curative therapy for many patients with hematologic, metabolic, and immunologic disorders. The number and efficacy of transplantations has increased. The goal of HCT is to cure the underlying disease by replacing destroyed, unhealthy cells with healthy stem cells (Majhail et al., 2012). With an increase in the number of allogeneic HCTs and a decrease in mortality because of earlier transplantation, a resultant shift of focus to survivorship issues has occurred (Flowers et al., 2008). A major survivorship issue for patients receiving allogeneic HCT is the development of graft-versus-host disease (GVHD). About 40%–80% of long-term survivors of HCT experience chronic GVHD (cGVHD), which is a serious and often life-threatening condition. cGVHD may carry a high symptom burden for patients that may negatively affect functional status and quality of life (QOL) (Antin, 2002; Baird & Pavletic, 2006).

The incidence of cGVHD is rising as an increasing number of transplantations are being performed, particularly in older patients (Hahn et al., 2013; Veltri et al., 2013). Adequate assessment and targeted therapeutic interventions to mitigate distressing symptoms and long-term complications of this chronic condition are needed (Pérez-Simón, Sánchez-Abarca, Díez-Campelo, Caballero, & San Miguel, 2006). In addition, the identification of biomarkers associated with cGVHD is a priority for diagnosing and monitoring progression of cGVHD, as well as evaluating the efficacy of new therapies (Schultz et al., 2006).

Symptom management is a major concern for patients experiencing cGVHD (Lee, Cook, Soiffer, & Antin, 2002; Pérez-Simón et al., 2006). However, a gap in the literature remains that establishes the relationship between symptoms and QOL in individuals with cGVHD (Lynch Kelly, 2014). Little study has been performed on the relationship between symptoms and biologic markers of cGVHD despite that the interplay between biologic markers and symptoms may affect the frequency and severity of symptoms experienced by patients with cGVHD (Lynch Kelly, 2014). The

purpose of this study was to describe levels of symptoms, inflammation (cytokines and C-reactive protein levels), and QOL of patients diagnosed with cGVHD following allogeneic HCT and to examine the relationships among these variables.

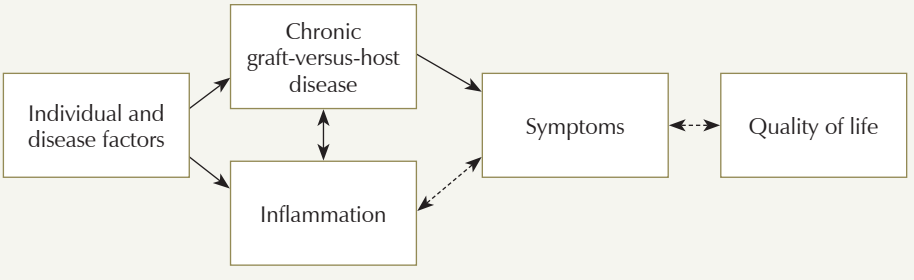
Literature Review

HCT is a standard treatment for many hematologic disorders, including acute leukemia, chronic leukemia, multiple myeloma, and myelodysplastic syndrome (Pidala, 2011). A 165% increase has occurred in the number of allogeneic HCTs from 1994–2005, and survival rates of more than 100 days after HCT have increased about 86% (Hahn et al., 2013). This increase in the use of HCT is partially related to advances in conditioning regimens with reduced intensity (known as a mini-transplantation), involving lower doses of chemotherapy and radiation and allowing HCT for individuals who may have once been ineligible (Hahn et al., 2013). Although notable survival gains have resulted from HCT, cGVHD remains one of the greatest issues for late-term mortality and morbidity. cGVHD is a serious long-term complication following allogeneic HCT, marked by immune dysregulation and debilitating clinical sequelae (Pérez-Simón et al., 2006). Manifestations of cGVHD usually appear several months after transplantation. Consequences associated with cGVHD include scleroderma, destruction of saliva and tear ducts, and liver and pulmonary dysfunction (Filipovich et al., 2005).

Acute GVHD usually appears within the first 100 days post-transplantation and involves different immune cell subsets and different cytokine profiles than cGVHD (Ratanatharathorn, Ayash, Lazarus, Fu, & Uberti, 2001). Acute GVHD is speculated to involve alloreactive memory T cells in donor cells. In contrast, symptoms of cGVHD usually occur 100 days or more post-transplantation. To date, the pathobiology of cGVHD is not well known (Pidala, 2011). Although the exact cause of cGVHD is unknown, cGVHD is speculated to involve mechanisms associated with proliferation and exaggeration of inflammation, as occurs with other autoimmune disorders (Baird & Montine, 2008; Bazzichi et al., 2007; Klimiuk, Sierakowski, Domyslawska, & Chwiecko, 2011). Because of the complexity of cGVHD and the need to standardize classification of cGVHD, 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). Risk factors for cGVHD include a history of acute GVHD, transplantation conditioning, donor match, and underlying disease process prior to transplantation (Flowers et al., 2011; Remberger et al., 2002). Any of the body systems can be affected by cGVHD. Cutaneous, ocular, and oral cGVDH are the most frequently occurring, but pulmonary and hepatic cGVHD have the highest mortality rates (Pidala et al., 2012).

Understanding symptoms of cGVHD, including the biologic underpinnings of symptoms, is a fundamental step toward managing symptoms effectively. Knowing the relationships among symptoms and QOL may provide insight about the impact of symptoms on QOL for patients with cGVHD. Therefore, the specific aims of this study were (a) to examine the levels of symptoms (cGVHD-specific, general, and cluster symptoms [pain, depression, and fatigue]); inflammation, including cytokines (interleukin [IL]-1β, IL-6, IL-10, tumor necrosis factor [TNF], and interferon-γ) and C-reactive protein (CRP); and QOL in patients diagnosed with cGVHD and (b) to assess the relationships between and among symptoms (top three general symptoms and cluster symptoms), inflammation, and QOL in individuals with cGVHD. Knowledge about symptoms and biologic 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.

An adaptation of the Theory of Unpleasant Symptoms (TOUS) (Lenz, Suppe, Gift, Pugh, & Milligan, 1995) provided the theoretical perspective to explore the relationships among symptoms, inflammation, and QOL in patients diagnosed with cGVHD. The TOUS assumes commonalities among symptoms while exhibiting uniqueness (Lenz



Note. A solid line with single arrow indicates influencing factor and bidirectional relationships, a solid line with two arrows indicates bidirectional relationship, and a dashed line with two arrows indicates hypothesized relationship.

Figure 1. Conceptual Model for Examining Symptoms, Cytokines, and Quality of Life of Patients Diagnosed With Chronic Graft-Versus-Host Disease

et al., 1995). The TOUS was modified (see 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, necessitating examining biologic correlates with behavioral manifestations.

Methods

Sample and Setting

This study used a prospective, cross-sectional, correlational design. Participants were recruited from a bone marrow transplantation (BMT) unit at Virginia Commonwealth University Massey Cancer Center in Richmond, an urban National Cancer Institute (NCI)–designated comprehensive cancer center with continued NCI funding since 1975. Patients were eligible for participation if they were aged 18 years or older, had a diagnosis of cGVHD, and could speak English. Patients were ineligible for participation if they had begun taking antidepressants within the past 30 days, were pregnant, or were incarcerated.

Procedure

This study was approved by Virginia Commonwealth University Massey Cancer Center Protocol Review Monitoring Committee and the institutional review board at Virginia Commonwealth University. Patients were referred to the study by the transplantation center's medical director in consultation with other attending physicians and clinical coordinators. Written consent was obtained from all participants. Individual and disease factors were collected from 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 about one hour to complete, and participants received a $25 Visa card after completing the study.

Measures

All individual and disease factors were collected by chart review and 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. Disease factors included date of cGVHD onset, NIH global rating, blood platelet and hemoglobin counts, and immunosuppressive therapy.

The Lee cGVHD Symptom Scale (Lee et al., 2006) consists of seven subscales (skin, eye and mouth, breathing, eating and digestion, muscles and joints, energy, and mental and emotional), each based on the body system that may be affected by cGVHD. Items are rated using a five-point Likert-type scale, with higher scores indicating a greater level of the symptom. A summary score is created by linearly transforming the mean of all items to a 0–100 scale. This measure has demonstrated Cronbach alphas ranging from 0.79–0.9 and has good convergent validity (Lee et al., 2006). The Cronbach alpha for this study was 0.79.

The Memorial Symptom Assessment Scale (MSAS) was used to assess dimensions (frequency, severity, and distress) of 32 prevalent physical and psychological symptoms (Portenoy et al., 1994). Each item is assessed for the presence or absence of a particular symptom during the past week and uses a four-point Likert-type scale to score each dimension. An average total symptom score is calculated based on the scale, with higher scores indicating higher symptom presentation. This measure has demonstrated Cronbach alphas ranging from 0.76–0.88 (Chang, Hwang, Feuerman, Kasimis, & Thaler, 2000; Portenoy et al., 1994). The Cronbach alpha for this study was 0.89.

The Brief Pain Inventory (BPI) was used to assess pain severity and interference within the past 24 hours (Cleeland, 2009). Each item is rated on an 11-point Likert-type scale, with higher scores indicating greater levels of pain. 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 Cronbach alphas ranging from 0.8–0.87 for pain severity items and from 0.89–0.92 for interference items (Cleeland, 2009). The Cronbach alpha for this study was 0.95.

The depression subscale of the Hospital Anxiety and Depression Scale (HADS) was used to assess depressive symptoms (Zigmond & Snaith, 1983). The depression subscale is comprised of seven items. Each item is rated on a four-point Likert-type scale, with higher scores indicating a greater level of the symptom. The score is the sum of all items for the subscale. The measure has demonstrated Cronbach alphas ranging from 0.82–0.9 (Mykletun, Stordal, & Dahl, 2001). The Cronbach alpha for this study was 0.77.

The Brief Fatigue Inventory (BFI) was used to assess fatigue severity and interference during the past 24 hours (Mendoza et al., 1999). Each item is rated on an 11-point Likert-type scale, with higher scores indicating greater levels of fatigue. A mean score is calculated for each subscale and the total measure (Mendoza et al., 1999; Seyidova-Khoshknabi, Davis, & Walsh, 2011). The measure has demonstrated Cronbach alphas ranging from 0.95–0.96 (Mendoza et al., 1999, Mendoza, Mayne, Rublee, & Cleeland, 2006). The Cronbach alpha for this study was 0.93.

Table 1. Sample Characteristics (N = 24)

Characteristic	n
Gender	
Female	14
Male	10
Race	
Caucasian	21
African American	3
Ethnicity	
Non-Hispanic	22
Hispanic	2
Married	
Yes	19
No	5
Employment	
Unemployed	12
Full-time	10
Part-time	2
Diagnosis	
Acute myelogenous leukemia	7
Myelodysplastic syndrome	4
Chronic myeloid leukemia	3
Multiple myeloma	3
Other[a]	7
Conditioning	
Reduced intensity radiation or chemotherapy	13
Total body irradiation	11
Gender-matched donor	
Yes	14
No	10
Donor type	
Related	19
Unrelated	5
ECOG score	
0	2
1	17
2	5
cGVHD onset	
Never had acute GVHD	17
Resolved cGVHD	4
Progressed from acute GVHD to cGVHD	3
NIH cGVHD global rating	
Mild	4
Moderate	12
Severe	8
Number of organs involved in cGVHD	
1	4
2	8
3 or greater	12
Platelet count[b]	
Less than 100,000	4
100,000 or greater	20
Immunosuppressive therapy	
Systemic	11
Topical	5
Both	6
None	2

[a] Other diagnoses included non-Hodgkin lymphoma, B-cell lymphoma, and T-cell lymphoma.

[b] Platelets were measured in microliters of whole blood.

cGVHD—chronic graft-versus-host disease; ECOG—Eastern Cooperative Oncology Group; NIH—National Institutes of Health

Note. ECOG scores range from 0–5, with higher scores indicating patients who are more disabled.

Blood was collected in a 3 ml ethylenediaminetetraacetic acid tube and transported on ice to the research laboratory. The blood was centrifuged at 1,030 rpm for 10 minutes at 4°C. Plasma was aliquoted to three microfuge tubes (500 mcl each), and samples were stored in a –80°C freezer until processed for analysis. Serum cytokine levels were analyzed using the Bio-Plex® multiplex assay, which allows for the simultaneous measurement of multiple cytokines in a single biologic sample. Dual-laser technology allows for the detection of multiple analytes across numerous fluorescent spectra, which provides accurate quantification of cytokines. Serum CRP levels were measured using the American Laboratory Products Company high-sensitivity CRP enzyme–linked immunosorbant assay per manufacturer's protocol.

The Functional Assessment of Cancer Treatment–BMT (FACT-BMT) was used to measure QOL (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 (seven items), social and family well-being (six items), emotional well-being (six items), and functional well-being (seven items). The trial outcome index is the sum of the physical and functional well-being and the BMT subscales. Each item is rated on a five-point Likert-type scale, with higher scores indicating more truth to an item during 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 subscales. Higher scores indicate greater QOL. The measure has demonstrated Cronbach alphas of 0.84 for physical well-being, 0.69 for social and family well-being, 0.67 for emotional well-being, and 0.78 for functional well-being. The Cronbach alpha was 0.88 for the FACT-G and 0.89 for the FACT-BMT (Kopp et al., 2000; Lau et al., 2002). The Cronbach alpha for the FACT-BMT for this study was 0.91.

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 biologic 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 JMP®, version 10.0. Alpha was set at 0.05 for the analysis.

Results

Examining Levels of Symptoms

The first aim of this study was to examine the levels of symptoms (cGVHD-specific, general, and cluster symptoms [pain, depression and fatigue]); inflammation, including cytokines (IL-1β, IL-6, IL-10, TNF, and interferon-γ) and CRP; and QOL in patients diagnosed with cGVHD. Individual and disease factors are detailed in Table 1. The majority of participants were female (58%), Caucasian (88%), and married (79%). Half of the participants were not employed. The median age of participants was 54 years, and age ranged from 28–73 years. The median time from transplantation to cGVHD diagnosis was 191 days (range = 123–702). The mean hemoglobin level was 12.5. All participants in this study had a cancer diagnosis for which they received a BMT as a curative measure. The largest percentage (29%) of participants had a diagnosis of acute myelogenous leukemia. Most participants received stem cells from a relative (79%) and were gender matched (59%). Based on criteria from the Eastern Cooperative Oncology Group, functional impairment (score of greater than 0) was noted in 92% of participants.

Most participants had multiple cGVHD symptoms (see Table 2). The most frequently reported dermatologic symptom was change in skin color (50%). Dry eyes was the most reported symptom from the eyes and mouth subscale symptom (83%). About half (49%) of participants were either "quite a bit" or "extremely bothered" by dry eyes, and 75% were bothered by having to use eye drops frequently. Shortness of breath was reported by 50% of participants. Two participants reported being "extremely" bothered by the need to use supplemental oxygen. All participants were able to receive nutrition without any IV or feeding tube supplementation. Being bothered by limited joint movement and "aches" was reported by 50% of participants. Loss of energy was reported by 79% of participants, and the need to sleep more was bothersome for 67% of participants. Difficulty sleeping was the most reported symptom (58%) on the mental and emotional subscale.

Most participants also reported multiple general symptoms (see Table 3). The most frequently reported symptom was lack of energy (83%), followed by dry mouth (67%). 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 majority of participants (54%) reported having pain, and about half (46%) reported interference with activity because of pain. Ninety-six percent of participants reported having some depressive symptoms. Most participants (88%) reported fatigue, and the same high percentage reported interference with daily activity because of fatigue (see Table 4).

Table 2. Frequency of Symptom Bother by Body System and Total Scores From the cGVHD Symptom Scale (N = 24)

	Score				
Symptom	**1**	**2**	**3**	**4**	**5**
Cutaneous					
Abnormal skin color	12	3	4	3	2
Rashes	14	6	2	2	–
Thickened skin	20	–	1	–	3
Sores on skin	18	4	2	–	–
Itchy skin	13	2	5	3	1
Ocular and oral					
Dry eyes	4	3	5	7	5
Need to use eye drops frequently	5	1	3	5	10
Difficulty seeing clearly	7	3	7	3	4
Need to avoid certain foods because of mouth pain	17	4	–	1	2
Ulcers in mouth	22	–	1	–	1
Receiving nutrition from an IV line or feeding tube	24	–	–	–	–
Pulmonary					
Frequent cough	14	1	4	4	1
Colored sputum	18	3	2	–	1
Shortness of breath with exercise	6	6	4	5	3
Shortness of breath at rest	18	3	1	2	–
Need to use oxygen	22	–	–	–	2
Digestive					
Difficulty swallowing solid foods	16	5	2	–	1
Difficulty swallowing liquids	23	–	–	1	–
Vomiting	21	1	2	–	–
Weight loss	21	–	3	–	–
Muscular					
Joint and muscle aches	8	7	5	2	2
Limited joint movement	13	4	3	3	1
Muscle cramps	12	6	2	1	3
Energy					
Loss of energy	5	6	7	4	2
Need to sleep more or take naps	8	5	7	2	2
Fevers	23	1	–	–	–
Mental and emotional					
Depression	17	3	4	–	–
Anxiety	12	8	4	–	–
Difficulty sleeping	10	4	5	1	4

1—not at all bothered; 2—slightly bothered; 3—moderately bothered; 4—quite a bit bothered; 5—extremely bothered; cGVHD—chronic graft-versus-host disease

Table 3. Memorial Symptom Assessment Scale Results (N = 24)

Symptom	n	Frequency		Severity		Distress or Bother		Total	
		$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Change in taste	3	–	–	1	0	2	0	1.5	0
Constipation	3	–	–	3	1.73	2.33	2.08	2.67	1.89
Cough	14	2.29	0.91	1.64	0.63	1.41	1.23	1.69	0.78
Diarrhea	2	2.5	0.71	1.5	0.71	1.5	0.71	1.83	0.71
Difficulty concentrating	13	2.25	0.87	1.42	0.67	1.42	1.31	1.69	0.86
Difficulty sleeping	12	2.76	0.93	2	0.91	1.46	1.2	2.06	0.87
Difficulty swallowing	7	2.14	0.69	1.86	0.69	2.14	1.57	2.05	0.91
Dizziness	2	2	0	1.5	0.71	1.5	0.71	1.67	0.47
Do not look like self	7	–	–	2.14	1.07	2.57	0.98	2.36	0.99
Dry mouth	16	3.5	0.63	2.31	0.95	2.06	1.24	2.63	0.78
Feeling bloated	5	3.4	0.55	2.2	1.1	2.8	1.1	2.8	0.84
Feeling drowsy	14	2.07	0.62	1.64	0.63	1	0.88	1.57	0.48
Feeling irritable	8	1.63	0.74	1.25	0.46	1.5	1.41	1.46	0.69
Feeling nervous	8	1.88	0.35	1.14	0.38	0.86	0.38	1.29	0.23
Feeling sad	6	1.83	0.41	1.33	0.52	1.5	0.55	1.56	0.34
Hair loss	5	–	–	2.4	1.52	2	1.58	2.2	0.91
Itching	8	2.38	0.92	1.5	0.76	1.38	1.19	1.75	0.89
Lack of appetite	2	3.5	0.71	3	1.41	3	1.41	3.17	1.18
Lack of energy	20	2.84	0.9	2.16	0.9	2.11	1.41	2.37	0.9
Mouth sores	3	–	–	1.33	0.58	1.33	1.53	1.33	1.04
Nausea	4	1.5	0.58	1.75	0.5	1.5	1	1.58	0.57
Numbness or tingling in hands and feet	13	2.54	1.05	1.31	0.48	1.08	0.95	1.64	0.66
Pain	12	2.92	1	2.6	1	2.08	1.16	2.7	0.82
Problems with urination	4	2.5	0.58	1.25	0.5	2.25	1.5	2	0.61
Sexual dysfunction	11	2.73	1.1	2.55	1.29	2.82	1.25	2.47	1.31
Shortness of breath	13	2.53	1	1.92	0.86	1.85	1.34	2.1	0.99
Skin changes	8	–	–	2.25	1.04	2.34	1.06	2.31	1
Sweats	6	2.67	0.52	1.67	0.52	1.83	1.67	2.06	0.71
Swelling in arms or legs	7	–	–	2	0.58	2	1.5	2	0.71
Vomiting	2	2	0	2	1.41	2.5	2.12	2.17	1.18
Weight loss	2	–	–	1.5	0.71	1.5	2.12	1.5	1.4
Worrying	14	1.79	0.58	1.36	0.5	1	0.56	1.38	0.45

Note. Scores are based on a four-point Likert-type scale, with 4 indicating the highest symptom presentation.

Serum cytokine levels were obtained for all participants (N = 24). Individual cytokine levels varied among participants; however, the median scores for IL-10 (24), TNF-α (27), and interferon-γ (126.6) appear to be above established norms for these cytokines (see Table 5). Serum CRP levels were reported for 22 participants. Two participants had values that were out of range. Most participants (n = 21) had CRP levels above the normal range of less than 1,000 ng/ml, with a reported median level for the group of greater than 6,000 ng/ml. Only one participant had a level within the normal range. In addition, participants with moderate or severe cGVHD had higher levels of CRP than those with only mild cGVHD. Cytokine levels varied among participants.

The FACT-BMT scores demonstrated impaired QOL for many participants (see Table 6). The functional well-being subscale had the lowest mean of all scales measured by the FACT-BMT, followed by the physical well-being subscale. The trial outcome index 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 Quality of Life

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

Table 4. Mean Scores of Cluster Symptoms

Measure	$\bar{X}$	SD	Median	Range
Brief Pain Inventory		–		
Total	–	–	0.3	0–6.4
Interference	–	–	0	0–8.3
Severity	–		0.8	0–5.8
HADS	4.1	3.5	–	0–11
Brief Fatigue Inventory				
Total	3	2.4	–	0–8
Interference	2.4	2.6	–	0–9.5
Severity	4	2.5	–	0–9.3

HADS—Hospital Anxiety and Depression Scale

with cGVHD. Six symptoms (i.e., pain, lack of energy, dry mouth, difficulty sleeping, shortness of breath, and sexual dysfunction) were identified by the MSAS that were present in more than 30% of participants, with a total mean score of greater than 2 out of 4. Significant correlations were noted among the MSAS items pain, lack of energy, dry mouth, and sexual dysfunction. The MSAS pain item significantly correlated with the BPI total pain score ($r = 0.78$, $p < 0.01$). The MSAS lack of energy item significantly correlated with the MSAS items dry mouth ($r = 0.48$, $p = 0.02$) and sexual dysfunction ($r = 0.53$, $p < 0.01$). The MSAS item lack of energy also showed significant correlations with cluster symptoms in the HADS depression subscale ($r = 0.65$, $p < 0.01$) and the BFI total fatigue score ($r = 0.78$, $p < 0.01$). The MSAS sexual dysfunction item significantly correlated with the BFI severity subscale ($r = 0.43$, $p = 0.03$). Dimensions of cluster symptoms demonstrated some significant correlations with each other. The BPI did not demonstrate significant correlations with the BFI. The HADS depression subscale demonstrated significant positive correlations with the BPI interference subscale and all scales of the BFI.

Multiple correlations were found among levels of inflammation and measures of symptoms. Cytokine IL-1β had significant positive correlations with TNF ($r = 0.78$, $p < 0.01$), interferon-γ ($r = 0.97$, $p < 0.001$), IL-6 ($r = 0.44$, $p = 0.031$), and IL-10 ($r = 0.79$, $p < 0.001$). Cytokine IL-6 showed significant correlations with interferon-γ ($r = 0.58$, $p < 0.01$), the MSAS item lack of energy ($r = 0.42$, $p = 0.04$), the MSAS item dry mouth ($r = 0.42$, $p = 0.04$), and near significance with the emotional well-being subscale ($r = –0.4$, $p = 0.05$). Cytokine IL-10 showed significant positive correlations with interferon-γ ($r = 0.78$, $p < 0.01$), TNF ($r = 0.82$, $p < 0.01$), and the MSAS item difficulty sleeping ($r = 0.43$, $p = 0.03$). TNF was significantly correlated with interferon-γ ($r = 0.73$, $p < 0.01$). CRP was significantly correlated with the social and family well-being subscale ($r = –0.56$, $p < 0.01$) and was nearing significance with the MSAS item sexual dysfunction ($r = 0.41$, $p = 0.05$).

In a comparison of participants with and without reported symptoms, participants reporting lack of energy had significantly elevated (difference of 2.23, standard error [SE] = 0.98, 95% confidence interval [CI] [0.19, 4.27]) serum levels of IL-6 compared to individuals who did not report lack of energy ($df = 22$, $t = 2.07$, $p = 0.03$). Participants reporting problems with urination had significantly higher (difference of 1.81, SE = 0.73, 95% CI [0.3, 3.31]) serum levels of IL-1β compared to individuals who did not report problems with urination ($df = 22$, $t = 2.07$, $p = 0.02$). Participants reporting swelling of arms and legs had significantly lower (difference of 1.18, SE = 0.54, 95% CI [0.06, 2.3]) of serum IL-10 compared to individuals who did not report swelling of arms and legs ($df = 22$, $t = 2.07$, $p = 0.04$).

Significant correlations were found among QOL and pain, as well as depression and fatigue. The MSAS pain item significantly correlated with the physical well-being subscale ($r = –0.57$, $p < 0.01$). The MSAS item lack of energy showed significant correlations with the physical well-being subscale ($r = –0.7$, $p < 0.01$), the functional well-being subscale ($r = –0.53$, $p < 0.01$), the BMT subscale ($r = –0.71$, $p < 0.01$), the FACT-G subscale ($r = –0.64$, $p < 0.01$), and the FACT-BMT ($r = –0.68$, $p < 0.01$). The MSAS dry mouth item correlated to the BMT subscale ($r = –0.55$, $p < 0.01$), the trial outcome index subscale ($r = –0.41$, $p = 0.04$), and the FACT-BMT ($r = –0.42$, $p = 0.04$). The MSAS sexual dysfunction item correlated with the social and family well-being subscale ($r = –0.44$, $p = 0.03$) and the BMT subscale ($r = –0.44$, $p = 0.03$). Cluster symptoms of pain, depression, and fatigue showed significant correlations with the FACT-BMT and the subscales of FACT-G, trial outcome index, and BMT.

Discussion

This study examined the levels of symptoms, inflammation, and QOL, as well as associations among these variables in a sample of patients diagnosed with

Table 5. Cytokine and CRP Distributions

Inflammatory Marker	$\bar{X}$	SD	Median	Range
Cytokines				
IL-1β	4.7	4.31	–	0.03–14.93
IL-6	23.7	20.2	–	0.01–85.5
IL-10	–	–	16	0.5–109.08
TNF	27.05	25.17	–	1.27–96.16
IFN-γ	126.56	124.3	–	2.03–508.17
CRP	–	–	6.42	0.53–90

CRP—C-reactive protein; IFN—interferon; IL—interleukin; TNF—tumor necrosis factor

Note. Cytokines are reported in pg/ml, and CRP is reported in mg/ml.

Table 6. Quality-of-Life Scores From the FACT-BMT

Measure	$\bar{X}$	SD	Range	Measure Range
FACT-BMT (0–148)	113.28	20.9	58–136	0–148
FACT-G	83.89	16.15	41–101	0–108
BMT	29.38	5.44	17–38	0–40
TOI	69.08	16.76	30–88	0–96
PWB	20.66	6.59	6–27	0–28
SWB	23.99	3.68	12–28	0–28
EWB	20.21	3.18	10–24	0–24
FWB	19.04	6.16	5–28	0–28

BMT—bone marrow transplantation; EWB—emotional well-being; FACT—Functional Assessment of Cancer Therapy; FWB—functional well-being; G—General; PWB—physical well-being; SWB—social and family well-being; TOI—trial outcome index

cGVHD following allogeneic HCT. A high number of psychological and physical manifestations of symptoms that were associated with cGVHD were demonstrated in this sample.

In this study, the most pronounced symptoms 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 (Visvanathan & Nix, 2010). A positive association was found between dry mouth and inflammatory marker IL-6, which has been associated with Sjögren'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 Sjögren's syndrome may be a clinical sequela of cGVHD (Kawanami et al., 2012). This association supports findings by Fall-Dickson et al. (2010), identifying 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. 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 of patients, including assessment of shortness of breath, is essential for early detection of pulmonary complications. After allogeneic HCT, more frequent monitoring may be indicated for individuals with dyspnea. 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).

Another notable symptom of cGVHD was sexual dysfunction in men and women. Sexual dysfunction among individuals with cGVHD has focused primarily on women with vaginal cGVHD. Advancements have been made in treatments and strategies to mitigate this symptom; however, it remains problematic. In a study of 23 women diagnosed with genital cGVHD, 21 women were unable to remain sexually active because of complications such as pain, scarring, and strictures (Stratton et al., 2007). In the current study, of the 11 participants reporting sexual dysfunction, two of seven female participants were diagnosed with vaginal cGVHD. Therefore, this appears to be an issue to assess for all individuals with cGVHD (Wong et al., 2013). To date, little study has been done on sexual dysfunction in men with cGVHD.

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 this cluster of symptoms in this sample. This finding suggests that further study of this cluster in larger samples is indicated.

Cytokines play a major role in influencing and regulating inflammatory responses. Dysregulation of cytokines has been associated with autoimmune 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 interferon-γ. This finding is consistent with the cytokine pathways (Kishimoto, 2010). A significant increase in serum IL-6 levels between patients with and without lack of energy was found; however, no difference was noted in IL-6 levels of patients with mild, moderate, or severe cGVHD. A study conducted by Rohleder, Aringer, and Boentert (2012) found increased IL-6 levels in individuals with impaired sleep and fatigue. The positive correlations among symptoms and cytokines IL-6, IL-10, and CRP merit examination in a larger sample.

The National Institute of Nursing Research (2011) recognizes the negative impact that symptoms have on QOL and supports research to improve understanding symptoms and the biologic mechanisms underlying symptoms, the goal of which is to improve QOL through better symptom management. In studies of patients who received HCT, patients without cGVHD one to two years following HCT did not report having impaired QOL, whereas patients with cGVHD reported QOL scores below that of population norms and other patients with cancer (Baker & Fraser, 2008; Fall-Dickson et al., 2010; Webster, Cella, & Yost, 2003). Some participants in the current study had QOL scores that were below general U.S. population and cancer population normative values. Although this study reports mean QOL 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, 2012). Findings of the significant negative correlations among symptoms and QOL suggest that symptoms may be a predictor of QOL outcomes, but this needs to be examined further.

Limitations

The current study was limited by small sample size and lack of a comparison group. This study was conducted at a single site, limiting the number of participants eligible for this study. In addition, the study was conducted at a long-term follow-up clinic. As such, patients are monitored closely and consistently for complications and may receive intervention earlier and more frequently than individuals in other institutions that perform BMT without a long-term follow-up clinic. This may partially explain the low pain scores and higher mean QOL scores noted in this study. No eligibility criteria were set for the length of time since diagnosis, but this was captured as an individual and disease factor. In addition, the length of time that participants had been living with cGVHD was highly varied. Some participants may have adapted to their symptoms over time. The cross-sectional design does not permit the examination of changes over time.

Implications for Nursing Practice

cGVHD is a serious condition that affects QOL in many individuals after BMT for hematologic and other types of cancer. Results from this pilot study indicate that patients experience multiple symptoms, including sexual dysfunction, that adversely affect QOL. By thoroughly assessing symptoms, nurses are poised to advocate for adequate management of symptoms for patients with cGVHD that may otherwise go unreported or unnoticed. Measures may include coordination for proper referral and treatment for individuals who are experiencing sexual dysfunction.

Fatigue was noted more than any other symptom in this study and was significantly negatively associated with QOL. Participants with fatigue had significantly elevated levels of IL-6. Education about fatigue and management strategies to combat fatigue may be crucial for these patients because mitigating fatigue may increase QOL and decrease inflammation for these patients.

Other implications for nursing include anticipatory guidance for individuals and caregivers about the potential to experience several symptoms and the necessity to report symptoms to healthcare providers when they are first occurring and not delay treatment. One symptom may potentiate others, and a multiplicative effect could occur on symptoms and inflammation. Better understanding of the interrelated symptoms present in individuals with cGVHD and biologic mechanisms associated with these symptoms may lead to targeted symptom management interventions.

Knowledge Translation

Sexual dysfunction was reported by men and women, but it has been primarily assessed in women.

Shortness of breath was noted with pulmonary chronic graft-versus-host disease regardless of severity.

A significant difference in cytokine interleukin-6 levels was noted between individuals with and without fatigue regardless of cGVHD severity.

Conclusion

The findings of this study provide a profile of the symptoms, inflammation, and QOL of patients diagnosed with cGVHD and associations among those variables. Evidence of associations were noted among symptoms and inflammation, and significant negative associations were noted 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. A larger sample with comparison group would be useful to compare levels of symptoms and biologic markers between groups, with the possibility of stratification by those with high levels of symptoms. The presence of symptoms that 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 to developing targeted interventions aimed at mitigating symptoms of cGVHD.

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