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Clinical Characterization and Cytokine Profile of Fatigue in Hematologic Malignancy Patients with Chronic Graft-Versus-Host Disease

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Abstract

Limited information is available regarding clinical and biological properties of fatigue in patients with chronic graft-versus-host disease (cGvHD). Patients with moderate-to-severe cGvHD per NIH criteria were enrolled on a cross-sectional study and categorized as “fatigued” if SF-36 vitality score was <40. Clinical and laboratory parameters of fatigued (n=109) and non-fatigued patients (n=72) were compared. In univariate analysis, walk velocity, NIH joint-fascia score, human activity profile, and SF-36 physical and mental health self-report scales were correlates

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Conflict of Interest

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of fatigue. No cGvHD biomarkers were associated with fatigue. NIH joint score, Lee sleep and depression questions, and PG-SGA Activities and Function score jointly predicted fatigue. Though higher rates of depression and insomnia were reported in the fatigued group, antidepressant or sleep aid use did not differ between groups. Survival ratio was not significantly different by fatigue status.. Pathophysiology of fatigue in patients with cGvHD is complex and may involve mechanisms unrelated to disease activity. Patients with cGvHD experiencing fatigue had higher rates of untreated depression and insomnia, highlighting the need to focus clinical management of these conditions to improve health-related quality of life.

Keywords

graft-versus-host-disease; fatigue; biomarkers; hematopoietic cell transplantation

Introduction

Chronic graft-versus-host disease (cGvHD) is a leading late complication in patients after allogeneic hematopoietic stem cell transplantation (HSCT).[1] cGvHD is a systemic immune disease and affects multiple organs including skin, eyes, mouth, gastrointestinal tract (GI), genitalia, lungs, liver, joints and muscular fascia.[2] About 20–50% of HSCT survivors develop cGvHD.[3] In spite of recent new therapies approved by the United States Food and Drug Administration (FDA) for the treatment of steroid-resistant cGvHD, effective treatment for cGVHD remains a significant unmet need.[4, 5]

Immune-mediated multi-organ damage in cGvHD is associated with debilitating sequalae.[6] Patients with cGvHD have higher symptom burden and decreased health-related quality of life (HRQoL) among HSCT recipients.[3, 7] In addition, increasing cGvHD severity proportionally impacts HRQoL.[8] Studies exploring late effects of HSCT in patients have shown that presence of cGvHD substantially increases rates of fatigue and energy loss,[9, 10] with both acute and cGvHD being predictors of post-transplant fatigue.[9] Hence, the relationship of fatigue and cGvHD is worthy of attention in post-transplant cancer survivors as a possible clinical reflection of disease activity or progression which might then be targeted with novel therapies.

Cancer-related fatigue is a common condition experienced by cancer survivors[11] and it is different from the state of “being tired,” as it does not resolve with rest.[12] Many studies have looked at fatigue in cancer survivors and concluded that it is a multidimensional construct with a multifactorial etiology, mostly involving systemic mechanisms such as inflammation, alteration in mitochondrial function, dysfunction in hypothalamic-pituitary-adrenal axis, and impairment of circadian rhythm.[13–15] Majority of patients with cGvHD are cancer survivors transplanted after multiple lines of prior therapies. The exact relationship between pre- and post-HSCT treatment modalities and fatigue are also not well elucidated.

Causes of cancer-related fatigue and decreased physical functioning are multifactorial and also includes transplant conditioning regimen, total body irradiation and underlying disease.[9, 16] We have previously shown that fatigue symptom bother is prevalent in patients with cGvHD and was associated with lower HRQoL scores compared to the general

population.[17] This study investigates associations of patient self-reported fatigue with demographic, clinical, and behavioral data, task performances and cytokine biomarkers of cGvHD activity in a cross sectional observational study.[18–20] It also explored whether these associations influence the morbidity and mortality of patients with cGvHD.

Methods

Patients

Patients were enrolled in the NIH cGVHD natural history study (NCT00092235) (Supplementary Figure 1) It is a cross-sectional study that entails a single visit evaluation and protocol-driven prospective data collection of adult (age ≥18 years) cGvHD patients by a multiple-disciplinary team of specialists (dermatology, dentistry, rehabilitation medicine, occupational therapy, gynecology, pain and palliative care, hematology/oncology and ophthalmology). Demographic, clinical, and laboratory data were collected at evaluation. A complete list of variables examined in this study are listed in Supplementary Tables 1 **and**2. The rationale for selecting these specific cytokines cGvHD serum biomarkers has been described previously.[21] Symptoms were assessed using patient reported outcome questionnaires: Lee Symptom Scale (LSS)[22], Functional Assessment of Cancer Therapy – Bone Marrow Transplant score (FACT-BMT)[23], Human Activity Profile (HAP)[24] and Short Form 36 Health Survey Questionnaire (SF-36).[25] A patient was classified as fatigued if SF-36 vitality scale score was <40 based on a prior analysis of a large population data set from the Medical Outcomes Study showing that a 10-point-lower score from a SF-36 vitality score of 50 was associated with hazard ratios varying from 1.21 to 2.39 for short-term mortality and from 1.10 to 1.54 for long-term mortality.[26] Performance tests included a pulmonary function test, 2-minute (2MWT) and 6-minute walking tests (6MWT). Overall survival (OS) was defined as the total time from the date of enrollment until death or last follow-up. Patient survival after enrollment was ascertained by follow-up calls to patients or referring physicians. The patient-generated-subjective assessment tool (PG-SGA) score was used to evaluate weight, intake, symptoms, functional status, disease state, metabolic stress and nutritional physical examination of the patient.[27]

Statistical Methods

Factors reported as a continuous parameter were compared between two groups using a Wilcoxon rank sum test. Ordered categorical parameters were compared between the two groups using a Cochran-Armitage test for trend. Dichotomous parameters were compared between the two groups using Fisher's exact test. Unordered categorical parameters were compared between two groups using Mehta's modification to Fisher's exact test. Continuous parameters were compared according to ordered categorical parameters using a Jonckheere-Tersptra test for trend. P-values <0.005 demonstrate a very strong relationship while 0.005 < p <0.05 suggest a weaker relationship as a function of the magnitude of the p-value.

Patients were categorized into three groups based on their time from cGvHD diagnosis to study consent: 0–2 years, 2–4 years, and >4 years. The levels of the seven cytokines were then compared between each group. Strength and direction of association of SF-36

scores and corresponding changes in biomarker levels was tested by Spearman's rank-order correlation.

In the multivariable model analysis, all parameters with $p \leq 0.1$ in univariate analysis were examined in logistic regression model with backward elimination.

Results

Chronic GvHD patients (n=181) with a median age of 49 years (range, 18–70) were enrolled and included in this analysis; 44% were female. The majority (73%) of patients had severe cGvHD per NIH criteria and median number of involved organs was 5 (1–8). Median time of evaluation was 36 months (range, 12–646) post-HSCT with the median time of cGvHD onset 8 months (4–360). Patients were treated with median 4 (0–9) prior systemic immunosuppressive therapies.

Forty percent of patients were classified as fatigued based on the SF-36 vitality scores. SF-36 PCS (28 vs 39) and MCS (41 vs 51) scores were significantly lower in the fatigued group (p=0.0001). In addition, the median LSS energy subscore was 25 (0–9) and 50 (1–12) in non-fatigued and fatigued individuals (p=0.0001), respectively.

Patients with any increased joint involvement were more likely to be fatigued (72% vs 60%, p=0.0067). Fatigued individuals had higher LSS skin-, breathing-, muscle/joints-, and mental-related symptom bother subscores. Among laboratory variables, only hemoglobin was found to differ significantly between fatigued (12.4 g/dL) and non-fatigued (12.9 g/dL) individuals (p=0.03). Antidepressant or sleep medication use did not differ significantly between the two groups (p=0.63 and p=0.51, respectively), although patients reporting depression ($p < 0.0001$) and sleep problems ($p < 0.0001$) were more likely to be in the fatigued group. Results of other examined measures are listed in Table 1 and Table 2.

Although levels of selected serum cGvHD biomarkers did not differ between the fatigued and non-fatigued groups, after stratifying patients based on their time from cGvHD diagnosis to study consent, as expected, BAFF showed a decline with increased cGvHD duration (p=0.015) (Figure 1, Supplementary Figure 2, Supplementary Table 3). Higher BAFF levels had a positive correlation with cGvHD activity, intensity of immunosuppression, higher NIH joint and fascia and skin scores, and lower Karnofsky performance status, but not with fatigue (Supplementary Table 4). In the multivariable model, four variables retained significance as independent correlates of fatigue: higher NIH joint score (p=0.03), higher symptom bother in Lee sleep question (p=0.0004), Lee depression question (p=0.03), and higher PG-SGA activities and function score (p=0.0007) (Table 3).

Overall survival by fatigue status is shown in Figure 2 (p=0.074 by log-rank test). When adjusted for parameters previously found to predict death in this population (higher NIH lung score, lower Karnofsky performance status[28]) in Cox multivariable modeling, survival was lower among fatigued patients, but this was not statistically significant (HR_{death}=1.45, 95% CI 0.88–2.40, p=0.14). Known risk factors for mortality including low platelets at

onset, progressive onset and overlap with GI involvement at diagnosis were not associated with mortality (data not shown).

Discussion

Fatigue is a common problem in cGvHD associated with decreased HRQoL. Patients with cGvHD are more likely to experience fatigue and have SF-36 PCS scores 10 points lower than the general population.[10, 17, 28] However, studies addressing mechanism and clinical characteristics of fatigue in transplant survivors with cGvHD are conspicuously rare. This analysis used a widely accepted component of the SF-36 scale, the vitality score, to define patients with fatigue among those with moderate and severe cGvHD. Several clinical characteristics and patient self-report scores were shown to be associated with fatigue in patients with cGvHD. None of the cGvHD-associated biomarkers showed any correlation with fatigue, including BAFF, which was shown to be associated with measures of disease activity. [29, 30]

Reversible factors known to be associated with fatigue in the general population including thyroid function, statin use, and vitamin D levels were not associated with fatigue in this current study.[31–33] Fatigued individuals with cGvHD had slightly lower hemoglobin levels than non-fatigued ones but without statistically significant difference in multivariable analysis. Similarly, fatigued individuals with cGVHD had a trend of having lower vitamin D levels than non-fatigued ones (median 29 vs 31 ng/mL), with fatigued ones having insufficient levels (defined 20–30 ng/mL. Further research should be conducted to determine relationship between vitamin D levels and fatigue in cGVHD.

Our study did not show a difference in the levels of inflammatory markers (ESR and CRP) between fatigued and non-fatigued patients unlike reported by Im et al.[17] This may be due to the fact that patient population used in our analysis was slightly different from the one in that study, as our study only incorporates patients with biomarker data. In addition, both studies failed to show a difference in the markers of inflammation in the multivariable analysis. Neither prior nor subsequent relapse of malignancy was correlated with fatigue (data not shown). Fatigue was predicted by higher NIH joint scores, which could be explained by the restricted movement and impaired mobility associated with worse joint and fascia symptoms. Severe joint and muscle symptoms along with fear of muscle use due to pain, may discourage patients from continued exercise and activity, and subsequently lead to muscle atrophy and deconditioning which could potentially aggravate the existing fatigue.[34] Furthermore, most patients were on systemic steroids (56%) and other immunosuppressive medications that are known to cause myopathy. However, the intensity of immunosuppression was notably similar between the two groups, thus suggesting fatigue as not reflective of the immunosuppression used at the time of cGvHD treatment.

One important finding in this study is the association of fatigue with LSS depression-related symptom question in the multivariable analysis. Depression is commonly seen in cancer survivors and has been negatively associated with HRQoL, survival, and coping mechanisms.[35, 36] For this reason, screening for this problem and addressing it earlier may improve CRF in cGvHD. In this study, it was also shown that patients with higher scores

on Lee sleep symptom questions were more likely to be classified as fatigued. Notably, no difference was observed between the groups in terms of antidepressant or sleep aid use, even though more patients in the fatigued group reported depression and insomnia. This could be explained by variable efficacy of measures to treat depression. Alternatively, fatigued patients may be less willing or motivated to seek medical help to address their mental health challenges. Prior studies have found that the majority of the transplant survivors were not on any sleep medications[37, 38] and non-pharmacological interventions including cognitive behavioral therapy for insomnia and yoga were found to improve clinically relevant insomnia and CRF in cancer survivors.[39–41] In addition, some studies analyzing fatigue among cancer survivors with clinical depression showed that treatment of depression and/or insomnia with SSRIs and other antidepressants may help ameliorate the effects of CRF.[42–44] More longitudinal studies and randomized controlled trials incorporating all these variables and understanding the relationship between fatigue, depression and insomnia in cGvHD is needed.

None of the biomarkers considered as diagnostic or prognostic for cGvHD were predictive of fatigue in this cohort. However, after stratifying patients based on their time from diagnosis, irrespective of their fatigue status, it was seen that BAFF is the only cytokine with a significant decrease in its levels over time post-transplant reflecting its known role as a marker of disease activity.[21] In addition, B cell counts are known to be higher in patients with longstanding cGvHD which may contribute to lower BAFF levels, as B cells remove BAFF from the plasma[21, 45]In addition to BAFF, elevated levels of IL-6 and CCL2 have been shown to prime microglial cells and increase sensitivity to inflammatory signals in the brain, driving fatigue in cancer, depression and many rheumatological diseases.[30] However, we found no significant association in this study. BAFF levels are known to suppressed by high dose steroid use, but intensity of immunosuppression was not significantly different between fatigued and non-fatigued patients cGVHD, suggesting a different mechanism. Chronic GvHD-related fatigue is probably multifactorial and may involve central rather than peripheral pathways[30, 46]. An extended biomarker panel accounting for central mechanisms should be used in further attempts to determine the pathophysiology of fatigue in cGvHD[47].

This study delineates potential areas for intervention for fatigue in patients with cGvHD. Many pre-clinical and clinical studies suggest that initiating a structured exercise regimen before or after transplant may not only decrease the deconditioning rate and fatigue but also improve HRQoL and survival.[48–50] Poor sleep has been shown to be associated with reduced cognitive functioning, pain and fatigue.[12] cGvHD is associated with worse mental and physical functioning[16], so awareness and screening for depression and insomnia should be done diligently. As only 27% of the HSCT survivors return to their original center for cancer related care, it is of critical importance to alert providers of these potential areas for intervention.[51]

This study has several limitations that should be taken into consideration. First, it is a cross-sectional study, so a longitudinal assessment of fatigue complaints is not possible. It would be important for future studies to include non-cGvHD allotransplant controls and patients after autologous HSCT to allow deciphering factors related to cancer therapy versus allotransplant or cGvHD. This study did not include some putative cGvHD biomarkers,

including osteopontin and matrix metallopreinase (MMP) necessitating a wider cytokine panel to yield more insight about the biological properties of fatigue in cGvHD.[20] Finally, there is no universally accepted standard method to characterize fatigue in cancer and HSCT survivors. Many instruments and scoring methods including FACT-F, SF-36 and PROMIS have been used to assess fatigue and many studies adopt different cutoffs or criteria to define fatigue.[52, 53] This also explains why some clinical variables including anxiety and insomnia are predictive of fatigue in some studies and not in the others. It is essential for researchers and clinicians to agree on a standardized methodology to assess fatigue outcome in patients with cGvHD to develop better treatments for fatigue-related symptoms.

In summary, this report shows high prevalence of fatigue in patients with cGvHD using SF-36 vitality scale. Clinical characteristics such as NIH joint score, PG-SGA activity and function scores and Lee sleep and depression scores are significantly associated with presence of fatigue in cGvHD indicating points for targeted therapeutic interventions. None of the commonly suggested cGvHD biomarkers are associated with fatigue, probably reflecting a multifactorial etiology and complex pathophysiology in these patients. Studies with longitudinal analyses and planned interventions are needed for better understanding fatigue in patients with cGvHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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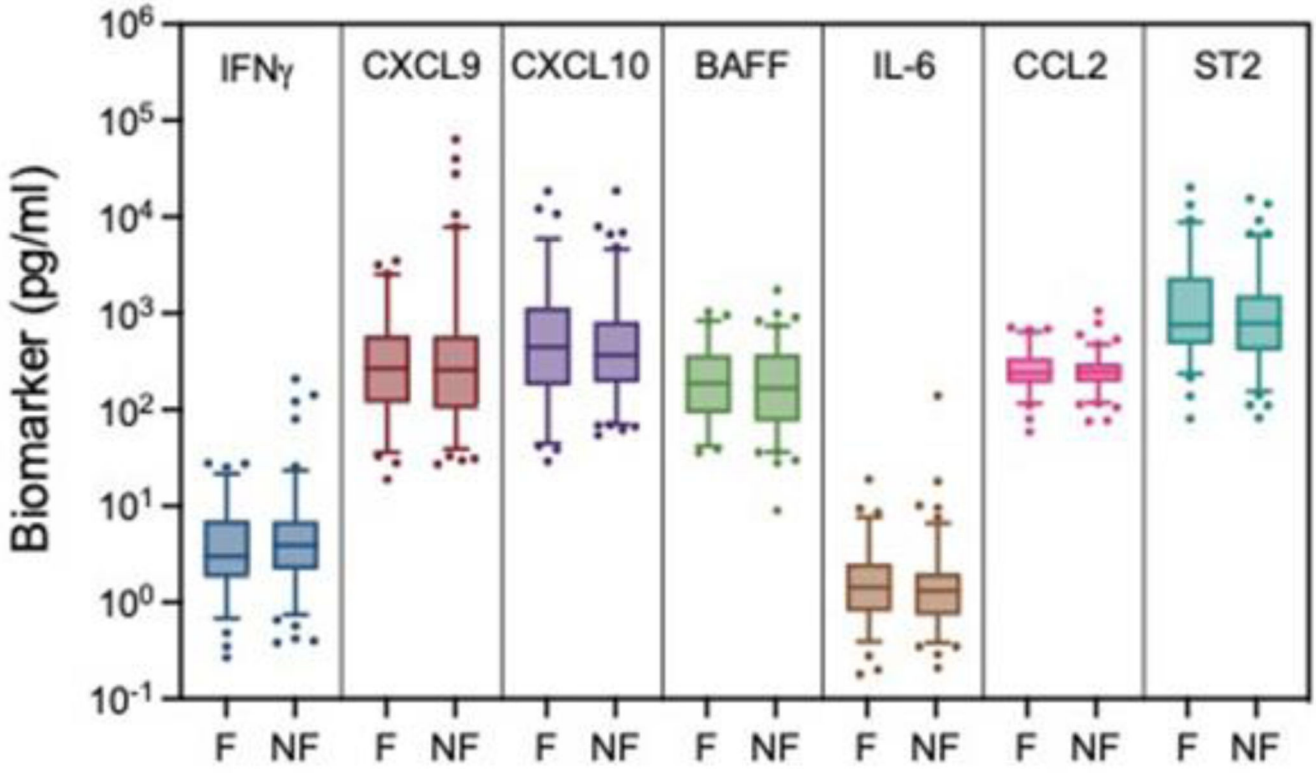

Figure 1: Levels of potential cGvHD biomarkers in fatigued and non-fatigued individuals

Figure 1: Figure comparing the levels of potential cGvHD biomarkers (IFNγ, CXCL9, CXCL10, BAFF, IL-6, CCL2 and ST2 between fatigued (F) and non-fatigued (NF) individuals. Vertical axis is represented in the logarithmic scale. None of the biomarkers were found to be significantly different between the 2 groups.

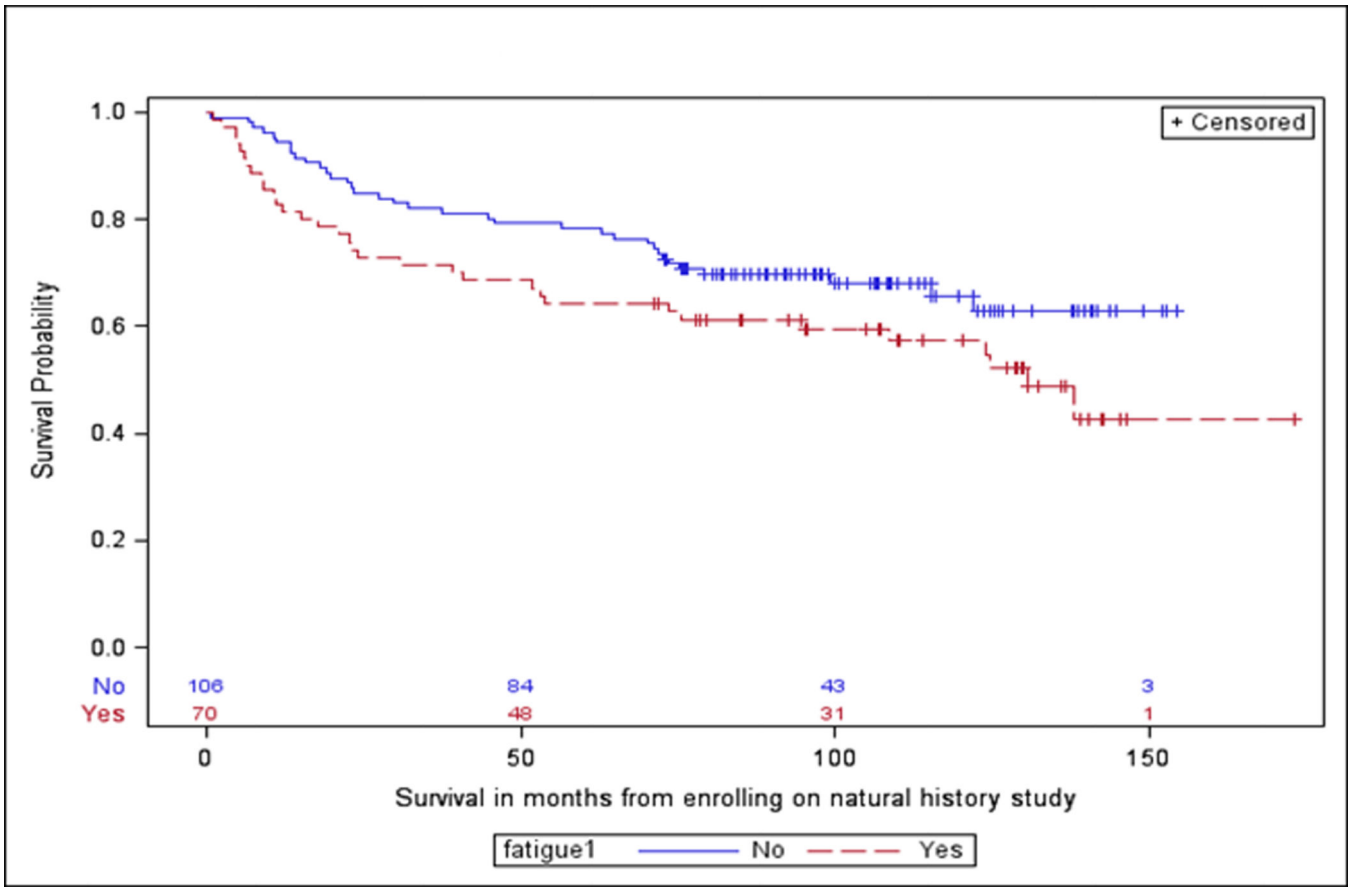

Figure 2: Overall Survival in Fatigued vs Non-Fatigued Patients

Figure 2: Kaplan-Meier plot comparing fatigued (dashed line) vs non-fatigued (solid line) patients with cGvHD. Median survival among fatigued patients was 130.6 months (95% CI: 75.5, upper bound not estimable) while median survival among non-fatigued patients was not reached. Overall survival did not differ by group (p=0.74 by log-rank test) but did following adjustment for NIH lung score and Karnofsky Performance Status (HR^{death}=1.45, 95% CI 0.88–2.40, p=0.14).

Table 1:

Univariate Analysis of Clinical Variables in Fatigued and Non-Fatigued Patients

Clinical Characteristics	Fatigued (n=72) (SF-36 vitality<40)	Non-Fatigued (n=109) (SF-36 vitality≥40)	p-value
Age (median, range)	46 (18–69)	50 (18–70)	0.29
Sex (n, %)			
Male	39 (54)	63 (58)	0.65
Female	33 (46)	46 (42)	
Karnofsky Performance Status (median, range)	70 (40–100)	80 (30–100)	**0.0003**
Underlying disease (n, %)			
Lymphoid	26 (36)	39 (36)	0.78
Myeloid	44 (61)	64 (59)	
Other	2 (3)	6 (5)	
Myeloablative conditioning regimen (n, %)			
No	34 (47)	54 (50)	0.88
Yes	38 (53)	55 (50)	
Total body irradiation (n, %)			
No	58 (67)	74 (68)	1.00
Yes	24 (33)	35 (32)	
Stem cell source (n, %)			
Bone Marrow	17 (24)	15 (14)	0.14
Peripheral blood	53 (74)	93 (85)	
Umbilical cord	2 (3)	1 (1)	
HLA Match (n, %)			
Match	61 (85)	93 (85)	1.00
Mismatch	11 (15)	16 (15)	
cGVHD characteristics			
NIH global severity (n, %)			
Moderate	16 (22)	30 (28)	0.49
Severe	56 (78)	77 (71)	
Number of prior therapies (median, range)	4 (0–8)	4 (1–9)	0.26
Prior acute GVHD (n, %)			0.55
No	27 (37)	25 (32)	
Yes	45 (63)	74 (68)	0.55
Months from cGVHD onset to enrollment (median, range)	22 (0–215)	25 (0–207)	0.83
NIH average organ score (median, range)	1.2 (0.9–1.4)	1 (0.1–2)	0.06

Clinical Characteristics	Fatigued (n=72) (SF-36 vitality<40)	Non-Fatigued (n=109) (SF-36 vitality≥40)	p-value
NIH organ score*, organ involvement (n, %)			
Skin	59 (82)	83 (76)	0.19
Mouth	50 (69)	69 (63)	0.69
Eyes	57 (79)	88 (81)	0.81
Gastrointestinal tract	37 (51)	46 (42)	0.85
Liver	38 (53)	55 (50)	0.93
Lung	62 (86)	80 (74)	0.23
Joints and fascia	52 (72)	65 (60)	**0.0067**
Genital (female only)	22 (54)	23 (37)	0.40
Lee symptom total score** (median, range)	36 (16–72)	25 (2–66)	**0.0001**
Lee subscale scores, median (range)			
Skin	40 (0–100)	25(0–100)	**0.026**
Eyes and mouth	38 (0–75)	33 (0–92)	0.88
Breathing	20 (0–100)	15 (0–75)	**0.022**
Eating and digestion	13 (0–88)	6 (0–69)	0.10
Muscles and joints	56 (0–75)	31 (0–100)	**0.0001**
Energy	50 (8–100)	25 (0–75)	**0.0001**
Mental and emotional	42 (0–100)	25 (0–92)	**0.0001**
Predicted grip strength (%; median, range)	60 (5.7–122.2)	64.5 (21.5–105.8)	0.25
2-minute walk test distance (feet; median, range)	532.5 (228–724)	593.8 (82–994.1)	**0.0002**
HAP MAS** (median, range)	69 (9–93)	78.5 (42–94)	**0.0001**
HAP AAS** (median, range)	52.5 (8–92)	66 (26–94)	**0.0001**
SF-36 PCS** (median, range)	28 (15–56)	39 (16–58)	**0.0001**
SF-36 MCS** (median, range)	41 (6–61)	51 (31–73)	**0.0001**
PG-SGA*** total score (median, range)	8 (2–26)	5 (2–20)	**0.001**

Additional clinical variables that were not significant: intensity of immunosuppression, FEV1, presence of acute GVHD subtypes, and statin use.

*NIH organ scores are reported on a 0 to 3 scale indicating no, mild, moderate, and severe cGVHD. Patients with score of 1–3 were considered to have involvement of a given organ. P-values determined by the Cochran-Armitage test for trend across all ordered categories.

**Lee Chronic GVHD Symptom Scale - higher score indicates higher symptom burden; HAP, MAS - Human Activity Profile, Maximum Activity Score indicates highest activity still performed; HAP, AAS - Human Activity Profile, Adjusted Activity Score indicates MAS minus total number of activities stopped less intense than maximally-intense activity still performed; SF-36, PCS - Physical Component Score; SF-36, MCS - Mental Component Score

***PG-SGA: Scored Patient-Generated Subjective Global Assessment

Table 2:

Univariate Analysis of Laboratory Variables Associated with Fatigue

Laboratory Measure (median, range)	**Fatigued (n=72)**	**Non-Fatigued (n=109)**	**p-value**
Platelets (cells/μL)	255 (34–555)	228 (52–561)	0.34
CRP (mg/L)	1.88 (0.4–160)	1.97 (0.26–91.1)	0.50
ESR (mm/h)	18 (2–80)	14 (1–113)	0.22
C3 (mg/dL)	138 (64–222)	132 (75–210)	0.43
C4 (mg/dL)	28 (14–49)	26.5 (13–61)	0.86
Albumin (g/dL)	3.6 (2.3–4.8)	3.7 (1.9–4.4)	0.47
TSH (mIU/L)	1.67 (0.06–7.37)	1.17 (0.02–18.4)	0.26
25-OH-vit D (ng/mL)	29 (8–74)	31 (9–86)	0.095
Hemoglobin (g/dL)	12.4 (7.5–17.1)	12.9 (8.4–17)	**0.031**
CD3 (cells/μL)	701 (23–4439)	806 (89–15530)	0.17
CD4 (cells/μL)	354.5 (10–2420)	355 (33–5599)	0.23
CD8 (cells/μL)	298 (8–3712)	375 (36–9498)	0.08
CD19 (cells/μL)	95 (0–6307)	115 (0–4784)	0.36

Cytokine (pg/mL; median, range)	Fatigued (n=72)	Non-Fatigued (n=109)	p-value
IFN-γ	3 (0.27–28)	3.91 (0.38–209)	0.17
IL-6	1.44 (0.18–19)	1.32 (0.21–139)	0.47
CXCL10	446 (29–18482)	366 (54–146996)	0.63
CCL2	241 (59–710)	246 (76–1052)	0.76
CXCL9	267 (19–3498)	258 (27–63570)	0.99
BAFF	188 (36–1037)	166 (8.6–1743)	0.45
ST2	763 (81–20214)	782 (82–15542)	0.52

Table 3:

Multivariable analysis of factors associated with fatigue

Parameter	OR (95% CI)	p-value
NIH Joint-Fascia Score	1.49 (1.04, 2.15)	0.03
Difficulty sleeping *	1.82 (1.30, 2.54)	0.0004
Depression *	1.48 (1.04, 2.11)	0.03
PG-SGA Activities and Function score	2.05 (1.35, 3.10)	0.0007

Estimates are per unit increase in severity (NIH Joint-Fascia Score; 0–3), unit increase in symptom bother (Difficulty Sleeping, Depression), and unit increase in score (PG-SGA Activities and Function score); Abbreviations: CI - confidence interval, OR - odds ratio, PG-SGA - Patient-Generated Subjective Global Assessment

* patients reported symptom bother related to depression (question bb.) and difficulty sleeping (question dd.) on the Lee Symptom Scale as ‘not at all’, ‘slightly’, ‘moderate’, ‘quite a bit’, or ‘extremely’