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Determinants and Clinical Significance of Musculoskeletal Symptoms in Patients With Chronic Graft-Versus-Host Disease

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ABSTRACT

Musculoskeletal symptoms in chronic graft-versus-host disease (cGVHD) are rare manifestations contributing to disease burden. This study assesses the frequency of muscle cramps, joint and muscle aches, and muscle weakness in a cohort of patients severely affected by cGVHD. Three hundred thirty-four patients participated in the NCI natural history study of cGVHD (NCT00092235) from October 2004 to March 2017. Five-point Lee cGVHD Symptom Scale was dichotomized (less symptom bother—0, 1, 2; severe symptom bother—3, 4) and tested for associations with: Short Form 36 (SF36), 2-minute walk test, grip strength, joint range of motion, and human activity profile, clinical and laboratory data. Seventy-five point four percent of patients reported joint and muscle aches (36.8% severe, Lee Symptom Scale score 3–4), 74.3% muscle cramps (33.5% severe), and 82.34% muscle weakness (45.51% severe), which were associated with reduced functional capacity (SF36 Physical Component Scale, $P < 0.0001$). Muscle cramps were associated with limited joint movement ($P < 0.0001$) and skin manifestations (skin thickening, $P = 0.0008$; itchy skin, $P = 0.0003$). Muscle cramps did not show association with potential causative agents, such as concomitant calcineurin inhibitors therapy, statins, or use of antidiabetic drugs. Joint and muscle aches showed associations with multiple variables (including strong associations with mood symptoms and fatigue, $P < 0.0001$). Muscle weakness was not associated with steroid dose, but was significantly associated with depression ($P < 0.0001$) and anxiety ($P = 0.0009$). This study documents a high frequency of musculoskeletal symptoms in a cohort of adult patients with cGVHD. The multivariable logistic regression models showed that a joint set of factors were moderately well associated with musculoskeletal symptoms in this study.

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) is a disabling and life-threatening condition due to immune dysregulation that affects about half of patients after allogeneic hematopoietic stem cell transplantation (allo-HSCT).[1] cGVHD-related muscle involvement,[2,3] its clinical features, and pathophysiology are poorly understood. Musculoskeletal involvement is captured by the 2005 and 2014 National Institutes of Health (NIH) cGVHD Consensus Organ Scoring Scale, Joint and Fascia score,[4,5] which measures the extent to which joint tightness impacts usual and daily activities. The updated 2014 criteria also recommend assessment using photographic range of motion (P-ROM) of the shoulder, elbow, wrist, and ankle joints. Diagnostic features of musculoskeletal cGVHD are fasciitis, joint stiffness, and contractures, whereas distinctive features include myositis and polymyositis. The NIH cGVHD organ scoring system records the presence of other musculoskeletal cGVHD-related features, including peripheral neuropathy and polymyositis, but these do not contribute to the total scoring of disease severity. Edema, muscle cramps, and arthralgias are also classified as "other" features, not captured in the NIH scoring or response criteria.[4,5] However, the Lee cGVHD Symptom Scale, a self-report measure of cGVHD symptom bother, addresses musculoskeletal symptoms including joint and muscle pain, joint restrictions, muscle cramps, and muscle weakness into its scoring, thereby providing valuable insight into the burden of cGVHD-related

musculoskeletal symptoms that might not otherwise be captured or evaluated.[6]

Muscle cramps are a common symptom in clinical practice, but as a feature of cGVHD are relatively underinvestigated. It is also unclear whether muscle cramps are a primary feature of cGVHD or a consequence of other causes.[7] Neurological symptoms frequently found among hematological patients undergoing transplant are "positive" sensory symptoms (neuropathic pain, paraesthesia), "negative" sensory symptoms (loss of any kind of sensation, especially cold and warm sensation), and autonomic symptoms (dry mouth or eyes, dry skin, erectile dysfunction, obstipation, diarrhea, urinary bladder control, sweating disturbances). Some of those symptoms may overlap with musculoskeletal symptoms, but they can also share some of the underlying pathophysiological mechanisms. A large proportion of cGVHD patients (77.8%) have small fiber neuropathy where A-delta fibers are more frequently affected.[8] Whether this is a specific subtype of cGVHD neuropathy associated with specific symptoms (muscle cramps or neuropathic pain) is to be determined. Since it is known that prolonged muscle pain may include broader neuropathic pain syndrome components (such as depression, anxiety, and sleep disturbances), it is often considered when tailoring pain treatment for cGVHD patients (for example opting for antiepileptics and antidepressants).

The frequency of musculoskeletal symptoms in cGVHD, and their associations with specific risk factors, and consequences for health-related quality of life and functional capacity measures have not been well characterized.[9] Herein this study investigates the burden of musculoskeletal symptoms not reflected in the NIH cGVHD severity scoring criteria in a large patient cohort severely affected by cGVHD.

METHODS

Patients

Patients were enrolled in the NIH cross-sectional cGVHD Natural History study protocol "Prospective Assessment of Clinical and Biological Factors Determining Outcomes in Patients with Chronic Graft-Versus-Host-Disease" (NCT00092235), after signing a National Cancer Institute Institutional Review Board-approved consent form. The patients were assessed, and data collected in case report forms predetermined by the study protocol during a 1-week multidisciplinary comprehensive evaluation. Patients were assessed and graded per the 2005 NIH cGVHD Diagnostic and Staging Criteria.[4] The self-reported symptom bother subscale for muscle cramps, muscle weakness, joint, or muscle aches from the Lee Symptom Scale (LSS) was used as the primary outcome for the analysis.[6]

Study measures

All patients had pulmonary function tests performed, energy expenditure and health-related quality of life measurements, and laboratory blood draw collected, as well as biopsies (skin, oral mucosa, and salivary gland) and imaging studies as clinically indicated at the time of evaluation. The self-reported symptom bother subscale for muscle cramps, muscle weakness, joint, or muscle aches from the LSS was used for the analysis.

Lee Symptom Scale is a validated self-assessment tool for patients with cGVHD, it assesses symptom bother of skin, eyes, and mouth, difficulties in breathing and eating/digestion, musculoskeletal symptoms, fatigue, and asthenia, as well as the emotional and mental burden of the disease.[6] Each symptom is described on a scale 0–4 (0-not at all, 1-slightly, 2-moderately, 3-quite a bit, 4-extremely), which was dichotomized for this analysis (0–2 as mild and 3–4 as severe) for each symptom of interest. This dichotomization of symptom severity categories was based on clinical judgement. Since the severity is self-reported and subjective, by separating higher scores from milder ones we minimized the possibility of clinically irrelevant symptoms affecting the analysis. This dichotomization was used for all statistical analyses. These categories were then tested to see if they were individually and then potentially jointly associated with muscle cramps, joint and muscle aches, and muscle weakness. Following outcome measures were also used in the analysis health-related quality of life: Short Form 36 (SF36, Physical and Mental Component Scales),[10] functional assessment of cancer therapy-bone marrow transplant (FACT-BMT),[11] energy expenditure and physical activity/function: human activity profile—maximal and adjusted activity score (HAP MAS/AAS), 2-minute walk distance, and grip strength.[12] HAP is a 94-item self-report measure of energy expenditure or physical fitness. SF36 is a 36-item self-report questionnaire examining multiple domains, including physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. It has 2 summary subscales, the Physical Component Score (PCS) and Mental Component Score (MCS), both of which are normalized to the general American population with a mean of 50 and a standard deviation of 10.[13] Patients were also assessed for clinician therapeutic intent in terms of cGVHD management at the time of assessment as a measure of cGVHD disease activity. A "non-active" therapeutic intent is defined as a decrease in systemic therapy because cGVHD is better, no change in therapy because GVHD is stable, or altering therapy due to toxicity. "Active" therapeutic intent is defined as an increase in systemic therapy due to worsening of GVHD, substituting therapy due to lack of response, or withdrawal of therapy due to lack of response; other—not meeting any of the criteria.[14] Intensity of immunosuppression was also evaluated and graded (mild-single agent prednisone up to 0.5 mg/kg/day, moderate-single agent prednisone >0.5 mg/kg/day, or any single agent modality and high-two or more agents/modalities ± prednisone > 0.5 mg/kg/day).[15] A list of concomitant medications for each patient were also retrospectively extracted from their electronic medical records by a team member (AZK).

Laboratory variables collected included serum creatinine-phosphokinase, aldolase, sodium, potassium, chloride, magnesium, phosphate, calcium, C-reactive protein, erythrocyte sedimentation rate, C3, and C4 complement, total complement, TSH, lactate dehydrogenase, aspartate aminotransferase, albumin, and autoantibodies: antinuclear antibodies, anticitrulline antibodies (antiCCP), rheumatoid factor, and antimitochondrial antibodies.

Statistical analysis methods

Factors reported as a continuous parameter were compared between 2 groups using a Wilcoxon rank-sum test. Ordered categorical parameters were compared between the 2 groups using a Cochran-Armitage test for trend.[16] Dichotomous parameters were compared between the 2 groups using Fisher's exact test. Unordered categorical parameters were compared between 2 groups using Mehta's modification to Fisher's exact test.[17]

After an initial univariate analysis (done on all patients), multivariable logistic regression was performed to identify a set of factors that could jointly be associated with each dichotomized musculoskeletal symptom. In an effort to provide an evaluation of parameters on a modestly large number of subjects as well as to explore whether the associations would also apply in an independent group of study subjects, the data from 334 total subjects were divided in an alternating fashion into a training set of 167 observations and a testing set of 167 observations; the latter would be considered an independent group from the training set. Since the data were sequential based on enrollment date, this would distribute patients evenly over time. Based on the univariate screening results, the parameters with $P < 0.05$ from the overall set of 334 subjects were used to evaluate the significance of the parameter within the training set, initially using univariate logistic regression. A multivariable regression

model was then created on the training set and evaluated in the testing set as follows: once the parameters for the training set were identified, backward selection was used to identify the final set of parameters for inclusion in the model. The parameters in the final model and their coefficients were used to construct a model for classifying patients according to the outcome selected; that is, to decide how likely it would be for the joint set of factors to indicate that a patient could have lesser or greater symptoms. The classification rule developed was applied to the 167 patients in the training set to demonstrate the association under ideal conditions, in which the same subjects used to create the model were used to identify the probability of correctly identifying that a combination of factors was associated with the outcome. Then the same model was applied to the testing set for validation of the model, which would then consist entirely of different patients. As the model was developed on a separate set of data, it would be expected that the classification on the testing set would be less accurate than what was arrived at on the training set; the overall results of classification further assist in the interpretation. All P values from reported tests are 2-tailed and presented without any formal adjustment for multiple comparisons. Given the number of univariate tests performed, P values such that $P < 0.005$ could be considered statistically significant, whereas $0.005 < P < 0.05$ would represent strong trends.

RESULTS

Patient population characteristics

The patient population (**Table 1**; **Suppl. Table S1**) was composed of 46% female and 54% male patients, median of age of 49 years. The majority of patients received an allogeneic hematopoietic stem cell transplant for hematologic malignancy, with peripheral blood stem cell grafts from HLA-matched related donors. Patients were evaluated at a median of 24 months after diagnosis of cGVHD, at which time 72% of patients had severe cGVHD according to NIH 2005 staging criteria. Relevant concomitant medication and supplement use was as follows: 46% calcineurin inhibitor, 29% supplemented magnesium, 39% statin, and 15% an antidiabetic agent (oral drugs or insulin).

Musculoskeletal symptoms

Frequency

In this cohort, 75.4% of patients reported joint and muscle aches (36.8% severe, LSS score 3–4), 74.3% muscle cramps (33.5% severe), and 82.34% muscle weakness (45.51% severe) (**Figure 1**).

Cramps

In the univariate analysis, severe symptom bother of muscle cramps was associated with lower SF36 Physical Component Score and MCS, higher Lee modified total score (total score reduced by the scores for muscle cramps, joint, and muscle aches, and muscle weakness), skin sclerosis and with a higher burden of the following symptoms reported by the LSS (skin thickening, itchy skin, limited joint movement, shortness of breath with exercise, loss of energy, need to sleep more, depression, anxiety, and difficulty sleeping), time from HSCT to enrollment and number of previous therapeutic lines for cGVHD (**Suppl. Table S2** shows factors with $P < 0.05$). Multivariable logistic regression analysis jointly identified variables (limited joint movement, shortness of breath with exercise, itchy skin, **Table 2**) as being moderately well associated with the outcome in both training and testing sets of patients. In the training set, using the model developed and a cutoff identified by examining the receiver operating characteristic curve, 40 of 61 (65.6%) of those with cramps and 80 of 105 (76.2%) of those without cramps could be correctly identified, where in all cases which are described below, correct identification is the term used to indicate when there is consistency between what a model would indicate and the way the patients' symptoms were classified into 2 categories. Applying the model to the testing set, 25 of 50 (50%) of those with cramps and 88 of 116 (75.9%) of those without cramps could be correctly identified. Overall, a total of 72.3% (95% CI, 64.8-78.9%) of patients were correctly identified for whether they had severe cramps or not in the training set, and 68.1% (95% CI, 60.4-75.1%) of patients were correctly identified for whether they had severe cramps or not in the testing set. Interestingly, the self-reported muscle cramp severity did not show associations with concomitant calcineurin

Table 1.

Patient Characteristics

	N (% or Range)
Total number of patients	334
Median age, y	48.3 (18–75)
Median months from cGVHD diagnosis to consent	24 (0–222)
Sex	
Male	190 (56.8)
Female	144 (43.2)
Disease	
Acute leukemias and myelodysplasia	155 (46.4)
Myeloproliferative diseases	42 (12.6)
Chronic lymphocytic leukemia	22 (6.6)
Hodgkin and Non-Hodgkin lymphomas	82 (24.6)
Multiple myeloma	17 (5.1)
Aplastic anemia, paroxysmal night hemoglobinuria	9 (2.7)
Other	7 (2)
Conditioning regimen	
Myeloablative	152 (45.5)
Nonmyeloablative	179 (53.5)
Unknown	3 (1)
Stem cell source	
Bone marrow	58 (17)
Peripheral blood	273 (82)
Cord blood	3 (1)
Donor relationship status	
Related	129 (38.6)
Unrelated	204 (61.1)
Unknown	1 (0.3)
cGVHD onset	
Progressive	124 (37)
Quiescent	96 (28.7)
De novo	113 (34)
Unknown	1 (0.3)
Intensity of immunosuppression	
None/mild	78 (23.4)
Moderate	127 (38)
High	127 (38)
Unknown	2 (0.6)
Presence of skin erythema	180 (53)
Presence of skin sclerosis	195 (58)
NIH 2005 cGVHD severity (mild, moderate, severe)	
Mild	6 (1.8)
Moderate	86 (25.7)
Severe	242 (72.5)
Organs affected per 2005 NIH cGVHD criteria	
Eyes	273 (81.7)
Skin	264 (79)
Lung	252 (75.4)
Mouth	153 (45)
Joint and Fascia	214 (64)
Liver	164 (49)
Genital tract (females only)	84 (25)
Gastrointestinal tract	146 (43.7)

cGVHD = chronic graft-versus-host disease.

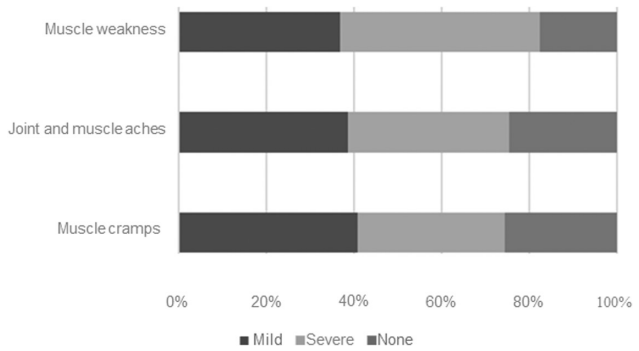

Figure 1. Distribution of self-reported severity of muscle cramps, joint and muscle aches and muscle weakness (as per Lee symptom scale: 1–2—mild, 3–4—severe).

inhibitor treatment, level of magnesium, use of statins or antidiabetic agents.

Muscle aches

In univariate analysis, severe joint and muscle aches were significantly associated with multiple variables, including reduced 2-minute walk, HAP AAS, SF36 PCS, and MCS score, Karnofsky performance status, and with greater LSS score for skin rash, skin thickening, limited joint movement, loss of energy, need to sleep more, depression, anxiety, and difficulty in sleeping (**Suppl. Table S3** shows factors with $P < 0.05$). Factors jointly identified by multivariable logistic regression (SF36 PS, need to avoid certain foods due to mouth pain, limited joint movement, depression) were predictive in both training and testing sets. The multivariable model is shown in **Table 3**. Based on the 167 patients in the training set used to develop the model, 52 of 63 (82.5%) with severe joint and muscle aches were correctly identified and 85 of 104 (81.7%) without severe joint and muscle aches were correctly identified. In the testing set, 33 of 58 (56.9%) of those with aches and 87 of 103 (84.5%) without aches were correctly identified. Overall, in the training set, 82.0% (95% CI, 75.4-87.5%) were correctly identified as having severe joint and muscle aches or not. Based on the 161 independent observations in the testing set, the overall fraction correctly identified for having severe joint and muscle aches or not was 74.5% (95% CI, 67.1-87.1%). The percentage of subjects correctly classified by the testing set was below that for the training set, as expected, but the results do not invalidate the findings found in the training set.

Muscle weakness

Self-reported muscle weakness showed association with numerous variables in univariate and multivariable analysis, which is summarized in **Suppl. Table S4** (contains univariate results for factors with $P < 0.05$) and **Table 4** (for multivariable model results). Based on the multivariable logistic regression model, in the training set, 54 of 66 (81.8%) with muscle weakness were correctly identified as well as 78 of 92 (84.8%) without muscle weakness. In the testing set, 43 of 71 (60.6%) with muscle weakness were correctly identified as well as 66 of 80 (82.5%) without weakness. The overall percentage of correctly identified patients having severe muscle weakness or not was 83.5% (95% CI, 76.8-89.0%) in the training set and 72.2% (95% CI, 64.3-79.2%) in the testing set. More importantly, muscle weakness was not associated with serum creatine kinase level, electrolyte levels (potassium, magnesium, and chloride), steroid dose, magnesium supplementation, or statin use in the multivariate analysis, even though there was a statistically significant association in the univariate analysis.

Table 2.

Multivariable Logistic Regression Analysis of Muscle Cramps (Training Set)

	P	Odds Ratio (95% Confidence Interval)
Lee Symptom Scale—itchy skin	0.0076	1.42 (1.10-1.83)
Lee Symptom Scale—limited joint movement	0.012	1.35 (1.07-1.70)
Lee Symptom Scale—shortness of breath with exercise	0.049	1.29 (1.00-1.67)
Intercept	<0.0001	

Table 3.

Multivariable Logistic Regression Analysis of Joint and Muscle Aches (Training Set)

	P	Odds Ratio (95% Confidence Interval)
SF36 physical component scale	0.020	0.95 (0.91-0.99)
Lee Symptom Scale—limited joint movement	<0.0001	2.96 (2.00-4.39)
Lee Symptom Scale—depression	0.013	1.56 (1.10-2.22)
Lee Symptom Scale—need to avoid certain food	0.0084	1.59 (1.13-2.23)
Intercept	0.033	

DISCUSSION

The multifactorial nature of musculoskeletal symptoms[18] in cGVHD presents a diagnostic and therapeutic challenge, even though some studies show that the majority of those is indeed cGVHD-related.[19] Although muscle cramping has been described,[7,20] it is still not well characterized in the cGVHD literature. In this study of moderately and severely affected cGVHD patients, over 70% of patients reported muscle cramps, and over one-third described the symptom burden of muscle cramping as severe. The prevalence and severity of muscle cramps in this cohort was not associated with NIH overall cGVHD severity or level of cGVHD clinical activity, which suggests that the NIH cGVHD scoring systems are not capturing muscle involvement adequately. Also, there was no significant association with potential causative agents and medication. Nonetheless, neither of the symptoms of interest showed a statistically significant association with creatine kinase levels. Muscle cramps did not show any association with levels of electrolytes, which does not exclude electrolyte disturbances as a potential factor since the

Table 4.

Multivariable Logistic Regression Analysis of Muscle Weakness (Training Set)

	P	Odds ratio, 95% Confidence Interval
NIH average score	0.019	0.19 (0.05-0.76)
SF36 PS	0.015	0.91 (0.85-0.98)
Lactate dehydrogenase	0.017	1.01 (1.00-1.01)
Intensity of immunosuppression	0.0016	3.74 (1.65-8.51)
Karnofsky performance scale	0.048	1.07 (1.00-1.13)
Lee Symptom Scale—sores on skin	0.0053	1.82 (1.20-2.78)
Lee Symptom Scale—difficulty swallowing solid foods	0.0077	2.03 (1.21-3.42)
Lee Symptom Scale—weight loss	0.0065	2.12 (1.23-3.65)
Lee Symptom Scale—limited joint movement	0.0014	1.91 (1.29-2.84)
Lee Symptom Scale—need to sleep more	0.0024	2.19 (1.32-3.62)
Lee Symptom Scale—depression	0.0005	3.82 (1.79-8.17)
Lee Symptom Scale—anxiety	0.014	0.45 (0.24-0.85)
Intercept	0.035	

levels analyzed are measured in a single time point. Notably, severe muscle cramping was associated with joint stiffness and skin manifestations (erythema and sclerosis), which may suggest a shared underlying pathophysiologic mechanism. This cohort of subjects is enriched for skin cGVHD manifestations (53% of patients have skin erythema and 58% have skin sclerosis).

Over 70% of patients reported joint and muscle aches, and over 30% described those as severe. Severe joint and muscle aches, in contrast to muscle cramps, showed association with a broader array of symptoms reported in the Lee cGVHD Symptom Scale, without any prominent organ or organ system. As expected, joint and muscle aches were strongly associated with limited joint movement and reduced health-related quality of life measurements.

In comparison, muscle weakness was associated with numerous variables (such as self-reported depression, anxiety, need to sleep more), both in univariate and multivariable analysis. Self-reported muscle weakness was not associated with steroid dose, the intensity of immunosuppression, number of previous therapeutic lines, underlying disease, or overall NIH cGVHD severity. Muscle weakness was also heavily associated with the component of the LSS assessing mental and emotional burden, reflecting the toll this symptom takes on mental health, which could be partially due to inaccurate self-reporting of perceived symptoms or significant overlapping of those symptoms, even though in this cohort, magnesium levels may be a potential additive etiological factor, due to a statistically significant association in the univariate analysis.[21–23] Fatigue, depression, and anxiety are known to be associated and can influence the way physical symptoms are perceived.[21,22,24]

Study limitations

This cohort consists of a cross-sectional cohort of patients who are heavily pretreated and with severe cGVHD. Capturing the complexity of these patients and their symptoms is limited by the one-time assessment without systematic work-up and longitudinal follow-up. Specific clinical tools, such as electromyoneurography (EMNG) was not used routinely in this specific cohort of cGVHD patients. However, even though peripheral neuropathies are gaining recognition as a valid cGVHD manifestation, prospective, targeted studies should be undertaken by neurologists versed in EMNG and experienced in cGVHD. Also, antismooth muscle antibodies were not analyzed in this specific cohort. Multivariable logistic regression models showed that a joint set of factors were only moderately well associated with muscle cramps, joint and muscle aches, and muscle weakness, without elucidating reliable predictors for these symptoms. The models are useful despite this, as they help identify a more limited set of factors which could be most associated with the outcomes when they are considered jointly. These models should not be considered for prediction in a strict sense, since the symptoms may have had multiple and potentially unknown etiologies.

CONCLUSIONS

In conclusion, this study documents a high frequency of muscle cramping, joint and muscle aches, and muscle weakness in a cohort of adult patients with cGVHD, and the impact of these symptoms on health-related quality of life. Musculoskeletal symptoms are very common and perhaps under-reported in clinical studies of cGVHD. Future research should focus on elucidating which interventions improve performance-based measures of activities of daily life in patients affected with musculoskeletal symptoms of cGVHD.[25,26] Continued research is necessary to improve understanding of the complex relationship of musculoskeletal manifestations in the context of cGVHD biology.

AUTHOR CONTRIBUTIONS

AZK, FP, SG, and LP-W did data gathering and extraction. SMS did statistics. SM, LC, NH, EB, EC, DP, GJ, LC, AI, AB, DP, KB, RG, and SP did methodology and clinical input. RG and SP did senior authors and overview. All authors contributed to article preparation.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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REFERENCES

1. Bachier CR, Aggarwal SK, Hennegan K, Milgroom A, Francis K, Rotta M. Epidemiology and real-world treatment of chronic graft-versus-host disease post allogeneic hematopoietic cell transplantation: a US Claims Analysis. *Blood*. 2019;134(Supplement_1):2109–2109.
2. Oda K, Nakaseko C, Ozawa S, et al.; Kanto Study Group for Cell Therapy (KSGCT). Fasciitis and myositis: an analysis of muscle-related complications caused by chronic GVHD after allo-SCT. *Bone Marrow Transplant*. 2009;43:159–167.
3. New-Tolley J, Smith C, Koszyca B, et al. Inflammatory myopathies after allogeneic stem cell transplantation. *Muscle Nerve*. 2018;58:790–795.
4. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2005;11:945–956.
5. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. the 2014 diagnosis and staging working group report. *Biol Blood Marrow Transplant*. 2015;21:389–401.e1.
6. Lee Sk, Cook EF, Soiffer R, et al. Development and validation of a scale to measure symptoms of chronic graft-versus-host disease. *Biol Blood Marrow Transplant*. 2002;8:444–452.
7. Kraus PD, Wolff D, Grauer O, et al. Muscle cramps and neuropathies in patients with allogeneic hematopoietic stem cell transplantation and graft-versus-host disease. *PLoS One*. 2012;7:e44922.
8. Bilic E, Delimar V, Desnica L, et al. High prevalence of small- and large-fiber neuropathy in a prospective cohort of patients with moderate to severe chronic GvHD. *Bone Marrow Transplant*. 2016;51:1513–1517.
9. Herzberg PY, Heussner P, Mumm FH, et al. Validation of the human activity profile questionnaire in patients after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2010;16:1707–1717.
10. Perić Z, Desnica L, Duraković N, et al. Which questionnaires should we use to evaluate quality of life in patients with chronic graft-vs-host disease? *Croat Med J*. 2016;57:6–15.
11. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant*. 1997;19:357–368.
12. Pidala J, Chai X, Martin P, et al. Hand grip strength and 2-minute walk test in chronic graft-versus-host disease assessment: analysis from the Chronic GVHD Consortium. *Biol Blood Marrow Transplant*. 2013;19:967–972.
13. Baker F, Haffer SC, Denniston M. Health-related quality of life of cancer and noncancer patients in Medicare managed care. *Cancer*. 2003;97:674–681.
14. Grkovic L, Baird K, Steinberg SM, et al. Clinical laboratory markers of inflammation as determinants of chronic graft-versus-host disease activity and NIH global severity. *Leukemia*. 2012;26:633–643.
15. Mitchell SA, Leidy NK, Mooney KH, et al. Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). *Bone Marrow Transplant*. 2010;45:762–769.
16. Agresti A. *Categorical Data Analysis*. 2nd ed. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2002.
17. Mehta CR, Patel NR. A network algorithm for performing Fisher's exact test in r × c contingency tables. *J Am Stat Assoc*. 1983;78

18. Sauter A, Bethge W, Vogel U, et al. Cervical fascial and muscular involvement in chronic GVHD after allo-SCT and radiation therapy. *Bone Marrow Transplant*. 2009;44:451–452.
19. Kuzmina Z, Joe GO, Baird K, et al. Prevalence of isolated joint involvement in chronic graft-versus-host disease: Comment on the article by Inamoto et al [Internet]. *Arthritis and Rheumatology*. 2014;66:2646–2648.
20. Carroll CB, Hilton DA, Hamon M, et al. Muscle cramps and weakness secondary to graft versus host disease fasciitis. *Eur J Neurol*. 2005;12:320–322.
21. Trivedi MH. The link between depression and physical symptoms. *Prim Care Companion J Clin Psychiatry [Internet]*. 2004;6(Suppl 1):12–6.
22. Vassend O, Røysamb E, Nielsen CS, et al. Fatigue symptoms in relation to neuroticism, anxiety-depression, and musculoskeletal pain. A longitudinal twin study. *PLoS One*. 2018;13:e0198594.
23. Kenzik K, Huang IC, Rizzo JD, et al. Relationships among symptoms, psychosocial factors, and health-related quality of life in hematopoietic stem cell transplant survivors. *Support Care Cancer*. 2015;23:797–807.
24. Hartman JM, Berger A, Baker K, et al. Quality of life and pain in premenopausal women with major depressive disorder: the POWER Study. *Health Qual Life Outcomes*. 2006;4:2.
25. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2015;21:984–999.
26. Bevans M, El-Jawahri A, Tierney DK, et al. National Institutes of Health hematopoietic cell transplantation late effects initiative: the patient-centered outcomes working group report. *Biol Blood Marrow Transplant*. 2017;23:538–551.