Determinants of functional performance in long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD)

By: SA Mitchell, N Kline Leidy, KH Mooney, WN Dudley, SL Beck, PC LaStayo, EW Cowen, P Palit, LE Comis, MC Krumlauf, DN Avila, N Atlam, DH Fowler and SZ Pavletic

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Abstract:

This study examined factors accounting for functional performance limitations in 100 long-term survivors of allogeneic hematopoietic stem cell transplantation with chronic graft-versus-host disease (cGVHD). Functional performance, measured by the SF-36 physical component summary score, was substantially lower (mean = 36.8 ± 10.7) than the US population norm of 50 (P<0.001). The most severe decrements were in physical function (mean = 38.8 ± 10.9) and physical role function (mean = 37.88 ± 11.88); 68% of respondents exceeded the five-point threshold of minimum clinically important difference below the norm on these subscales. Controlling for age and gender, six variables explained 56% of the variance in functional performance: time since cGVHD diagnosis, cGVHD severity, intensity of immunosuppression, comorbidity, functional capacity (distance walked in 2 min, grip strength, and range of motion), and cGVHD symptom bother (F=11.26; P<0.001).Significant independent predictors of impaired performance were intensive systemic immunosuppression, reduced capacity for ambulation, and greater cGVHD symptom bother (P<0.05). Symptom bother had a direct effect on functional performance, as well as an indirect effect partially mediated by functional capacity (Sobel test, P = 0.004). Results suggest two possible mechanisms underlying impaired functional performance in survivors with cGVHD and underscore the importance of testing interventions to enhance functional capacity and reduce symptom bother. Bone Marrow Transplantation (2010) 45, 762–769; doi:10.1038/bmt.2009.238; published online 28 September 2009

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Article:

Introduction

Chronic graft-versus-host disease (cGVHD) affects 30–80% of individuals who survive for > 100 days after allogeneic hematopoietic stem cell transplant (HSCT) and causes significant morbidity and mortality.[1–3] This late complication of HSCT has heterogeneous, multisystem clinical manifestations including mucocutaneous, ocular, gastrointestinal, hepatic, musculoskeletal, and immunologic impairments. Chronic GVHD is also associated with a graft-versus-tumor effect that may confer a survival benefit .[4,5] Although our understanding of the basic biology of cGVHD is improving and therapeutic advances are being made, the clinical impact of cGVHD has not been well-characterized.

Studies of quality of life in survivors of allogeneic HSCT suggest that cGVHD is associated with impairments in functional status,[6–11] with specific effects on physical function; domestic and vocational role function; and marital, family, and social interaction.[1,12–14] Relative to transplant survivors without cGVHD, those with cGVHD have lower physical, sexual, and social functioning[14] and show impaired physical and psychosocial recovery 1 year after transplant [12,13,15] and beyond.[16–18] No prior studies have explicitly characterized functional performance or its predictors in a sample of HSCT survivors experiencing cGVHD. Existing studies of HSCT

survivors have focused on health-related quality of life, a broad, multidimensional outcome of which physical function is just one element. This literature suggests that age, gender [6,19–21] intensity of immunosuppression,[6] cGVHD severity, [12,16,22] time since the cGVHD diagnosis,1 [0,23] comorbidity,[1,17,22] and symptom distress[7,10,14,17] are factors that may be relevant to functional performance in allogeneic HSCT survivors with cGVHD. The purpose of this study was to determine the factors that account for variability in functional performance in long-term allogeneic HSCT survivors with cGVHD.

Materials and methods

Design, participants, setting

Data for this cross-sectional analysis were prospectively gathered from the first 100 sequentially recruited adults participating in a natural history study of cGVHD (clinicaltrials.gov; #NCT00331968). Data were collected from October 2004 until December 2007. Eligible study participants were referred from oncologists and allogeneic transplant centers from around the United States and were over age 18; were at least 100 days post transplant; had the diagnosis of cGVHD established through clinical signs and/or tissue biopsy of one or more organ systems;[24] and were literate in English or Spanish.

Permission for the study was granted by the Institutional Review Board of the Intramural Research Program of the Center for Cancer Research, National Cancer Institute. Each subject participated in a 4-day, comprehensive, multidisciplinary evaluation. Self-report measures were administered via personal interview immediately after study enrollment. Measures of functional capacity, and demographic and clinical data were collected through clinical and diagnostic evaluations. On the basis of a series of multidisciplinary examinations and diagnostic testing, the severity of cGVHD involvement was scored using standardized criteria.[24]

Measures

Functional performance. Functional performance was evaluated using the physical component summary (PCS) score of the SF-36, version 2, a widely used and extensively validated [25,26] multidimensional generic measure of functional health and well-being. The 36 items of the SF-36 evaluate eight factors: physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional-role functioning, and mental health [.25,27–29] The PCS score and the mental component summary score [30] are derived by using a standard algorithm to aggregate scores across the eight subscales. Lower scores on the PCS indicate limitations in physical functioning and role participation, a high degree of bodily pain, and an unfavorable perception of general health .[30] The use of norm-based scoring[30] facilitates the interpretation of SF-36 scores such that any score below 50 is below the US population mean, and each point represents one-tenth of a standard deviation.

Functional capacity. Measures of functional capacity included the distance walked in 2 min, dominant hand grip strength (Jamar hydraulic hand dynamometer; Bissell Healthcare Corporation, Jackson, MI, USA), and upper and lower body range of motion (ROM). All measures were obtained in a single session by one of two rehabilitation professionals, and in accordance with written testing procedures [.31,32] The 2-min walk distance was chosen over the more commonly used 6-min walk because of a concern that study participants would have insufficient endurance to complete 6-min walk test procedures. Studies support the construct validity and responsiveness of the 2-min walk distance as a measure of functional capacity in other chronically ill populations [.33–35] Five of the 100 participants in this study were not ambulatory and were therefore excluded from 2-min walk distance procedures.

Active assisted ROM measurements in the supine position were taken using a standard goniometer. Participants' mean bilateral ROM measurements were converted to the percentage of normal ROM, using the American Academy of Orthopaedic Surgeons '[32] definition of normal ROM for each joint. Measurements that exceeded the maximum value were assigned a score of 100. Joints with fixed contractures were assigned a score of 0. An aggregate score [36] was calculated representing the patient's average degree of impairment in upper and lower body ROM.

Chronic GVHD symptom bother. The degree to which respondents have been bothered in the past month by each of 30 symptoms was assessed using the Lee cGVHD symptom scale.[37] A summary score was created by taking the mean of all items and linearly transforming that value to a0–100 scale.[37]

Comorbidity. Comorbidity was measured using the total score on the Functional Comorbidity Index .[38] The Functional Comorbidity Index has favorable psychometric properties when functional status is the outcome of interest .[39] In this study, the Functional Comorbidity Index was completed by a clinician, based on a comprehensive evaluation.

Clinician-rated cGVHD severity. Clinician-rated cGVHD severity and the number of sites involved with cGVHD were evaluated using the NIH consensus criteria.[24] The extent of involvement of each of eight organ systems typically affected by cGVHD (skin, mouth, eyes, lungs, GI tract, liver, joints/fascia, and in women, the genitalia) was rated, and a summative score reflecting cGVHD severity was calculated. This scoring was completed by a consistent team of organ system subspecialists (for example oral medicine, dermatology, gynecology) and other transplant experts, all of whom have extensive experience with cGVHD.

Intensity of immunosuppression. The intensity of current systemic immunosuppression was classified as follows: a low intensity regimen was defined as treatment with prednisone alone at a dose of < 0. 5 mg/kg/day. Moderately intense regimens included single agent prednisone at a dose ≥ 0.5 mg/kg/day, and/or any other single agent or modality. Regimens comprised of two or more agents or modalities (± prednisone ≥ 0.5 mg/kg/day), were categorized as highly intensive systemic immunosuppression. When scoring the intensity of systemic immunosuppression, the use of topical agents was not captured.

Other variables. Disease risk categories were classified using the definitions validated by Parimon et al.[40] Low-risk diseases included chronic myelogenous leukemia in chronic phase, refractory anemia, and aplastic anemia. Intermediate-risk diseases included chronic myelogenous leukemia in accelerated phase or in chronic phase after blastic phase, acute leukemia or lymphoma in remission, refractory anemia with excess blasts, chronic lymphocytic leukemia, and paroxysmal nocturnal hemoglobinuria. High-risk diseases included chronic myelogenous leukemia in blastic phase, juvenile chronic myelogenous leukemia, acute leukemia or lymphoma in relapse, refractory anemia with excess blasts in transformation, myeloma, solid tumor, and nonhematologic diseases.

Statistical analysis

Multiple regression analysis was performed to determine the contributions the following five blocks of variables make in explaining the variability in functional performance: demographic factors (age and gender); clinical- and treatment-related factors (cGVHD severity, time since cGVHD diagnosis, intensity of immunosuppression); comorbidity; functional capacity; and cGVHD symptom bother. All blocks were simultaneously entered into the model.

Post hoc hierarchical multiple regression analyses were conducted to explore whether mediation fully or partially explained the relationships among the significant predictor variables and the outcome of functional performance .41 SPSS version 15.0 was used for all analyses. The α level of significance was set at 0.05.

Results

Demographic and clinical characteristics

Sample characteristics are presented in Tables 1 and 2. Participants (N=100) were primarily Caucasian (90%), married (67%), and a mean age of 46 years (± 11.8). Males (52%) and females (48%) were approximately equally represented. Forty-one percent of the sample worked full time, were full-time students, or were homemakers. Participants were a mean of 42.6 months (± 37.5) post transplant (median, 31 months; range, 4–201 months). Chronic GVHD had been diagnosed a median of 25 months before their evaluation at study enrollment, and at the time of enrollment, all participants had evidence of cGVHD organ involvement as defined by the NIH consensus guidelines for diagnosis and staging.[24] Participants had a mean of 2.6 (± 1.5)

comorbidities or late effects of transplantation in addition to cGVHD. The most prevalent comorbidities were osteoporosis (53%), depression (43%), peripheral neuropathy (38%), upper gastrointestinal disease (21%), degenerative disc disease (20%), and obesity (body mass index > 30) (17%).

Table 1 Clinical and demographic characteristics of the sample ($N = 100$)

	n	%	*Mdn*	*Range*
Age (years)			47.00	20–66
Diagnosis				
Acute leukemia/myelodysplastic syndrome	40	40		
Chronic leukemia	23	23		
Lymphoma	22	22		
Multiple myeloma	8	8		
Aplastic anemia/myelofibrosis	4	4		
Other	3	3		
Disease risk				
Low	8	8		
Intermediate	55	55		
High	37	37		
Conditioning				
Myeloablative	57	57		
Reduced intensity	43	43		
Donor				
HLA-identical sibling	69	69		
HLA-mismatched related donor	4	4		
10/10 allele-matched unrelated donor	17	17		
9/10 allele-matched unrelated donor	10	10		
Stem cell source				
Mobilized blood	80	80		
Marrow	18	18		
Unspecified	2	2		

Table 2 cGVHD characteristics of the sample ($N = 100$)

	n	%	M	±*s.d.*	*Range*
Months since allogeneic transplant			42.6	37.5	4–201
Months since cGVHD diagnosed			35.6	37.0	1–196
cGVHD onset type					
De novo	40	40			
Quiescent	17	17			
Progressive	43	43			
Number of sites involved with cGVHD[a]					
2	11	11			
3	18	18			
4	24	24			
5–8	46	47			
NIH cGVHD global severity					
Mild	5	5			
Moderate	45	45			
Severe	50	50			
Clinician-scored cGVHD severity (0–100)			32.2	10.4	7.4–55.6
Lee cGVHD symptom bother score			28.4	13.5	0.7–68.6
Change in cGVHD over past month					
Better	19	19			
About the same	34	34			
Worse	47	47			
Intensity of current immunosuppression					
None	22	22			
Low[b]	9	9			
Moderate[c]	33	33			
High[d]	36	36			

[a] $n = 99$.
[b] Single agent prednisone < 0.5 mg/kg/day.
[c] Single agent prednisone ≥ 0.5 mg/kg/day and/ or any single agent/ modality.
[d] 2 or more agents/modalities ± prednisone ≥ 0.5 mg/kg/day.

The profiles of functional capacity and performance are presented in Table 3 and Figure 1. As seen in Figure 1, the mean PCS and seven of eight SF-36 subscale scores were significantly lower than the US general population normative value of 50 ($P<0.001$). Moreover, based on a minimum clinically important difference of three points for the PCS and five points for the subscales,[30,42] 78% of the sample reported clinically important functional performance limitations, with a substantial portion showing meaningful impairment in physical function (68%), physical role function (68%), social function (72%), vitality (54%), and role-emotional function (44%).

Linear regression model of functional performance

As shown in Table 4, the linear combination of demographic and clinical variables accounted for over half (56%) of the variation in functional performance. All of the blocks of variables, the demographic intensity of immunosuppression, the distance walked in 2 min, and cGVHD symptom bother were significant independent predictors of functional performance, and explained 3, 21, and 19% of the variance, respectively, while controlling for the remaining variables.

Mediation model of functional performance

To determine whether symptom bother leads directly to decrements in functional performance, or whether functional capacity is an intermediary in this relationship, the mediation model depicted in Figure 2 was estimated using hierarchical multiple regression. Significant results for all three regression equations are interpreted as evidence of mediation.[41,43] *Post hoc* probing to determine whether the mediation path was significantly greater than zero was conducted using Sobel's equation.[41,44] In all analyses, intensity of immunosuppression was used as a covariate.

Controlling for intensity of immunosuppression, cGVHD symptom bother was significantly associated with functional performance, explaining 38% (adjusted $R^2 = 0.38$) of the variation in functional performance.

Chronic GVHD symptom bother was also significantly associated with functional capacity, when the effect of intensity of immunosuppression was controlled. Finally, when controlling for both symptom bother and intensity of immunosuppression, functional capacity was associated with functional performance; and simultaneously, the association of functional performance and symptom bother, controlling for intensity of immunosuppression, remained significant. The indirect path between symptom bother and functional performance through functional capacity was significant (Sobel test, P=0.004). Thus, functional capacity partially mediated the relationship between cGVHD symptom bother and functional performance, with 26% of the variation in functional performance explained by symptom bother accounted for by the mediation pathway through functional capacity.

Table 3 Functional capacity measures

	n	*Mean*	*s.d.*	*Range*
Functional capacity				
2-min walk distance (meters/2 min)	95	171.8	40.2	47.2–235.9
Grip strength (kg)	98	26.8	11.4	4.6–55
Upper body ROM (% of norm)	99	91.0	9.1	66.0–100.0
Lower body ROM (% of norm)	99	76.8	16.1	0–100.0

Abbreviation: ROM = range of motion.

Table 4 Regression analysis predicting functional performance

Block	*b*	*SE b*	β	t	*Significance*
Constant	38.25	12.84		2.98	0.004
1. Demographic					
Age	0.016	0.066	0.018	0.242	0.81
Gender	−0.873	1.673	−0.041	−0.522	0.60
2. Treatment					
cGVHD severity	−0.149	0.094	−0.145	−1.588	0.12
Intensity immunosupp.	−1.587	0.696	−0.173	−2.279	0.03
Time since cGVHD Dx	0.012	0.022	0.043	0.567	0.57
3. Comorbidity	−0.814	0.558	−0.117	−1.458	0.15
4. Functional capacity					
Distance walked in 2 min	0.034	0.007	0.433	4.945	< 0.001
Grip strength	−0.026	0.017	−0.122	−1.512	0.14
Upper body ROM	−0.024	0.102	−0.020	−0.233	0.82
Lower body ROM	0.031	0.068	0.039	0.453	0.65
5. Symptom bother	−0.284	0.067	−0.360	−4.268	<0.001
Full model	Adjusted R^2 = 0.56 F = 11.26 P < 0.001				

Abbreviations: b = non-standardized coefficient; β = standardized coefficient; ROM = range of motion; s.e. = standard error of the unstandardized regression coefficient.

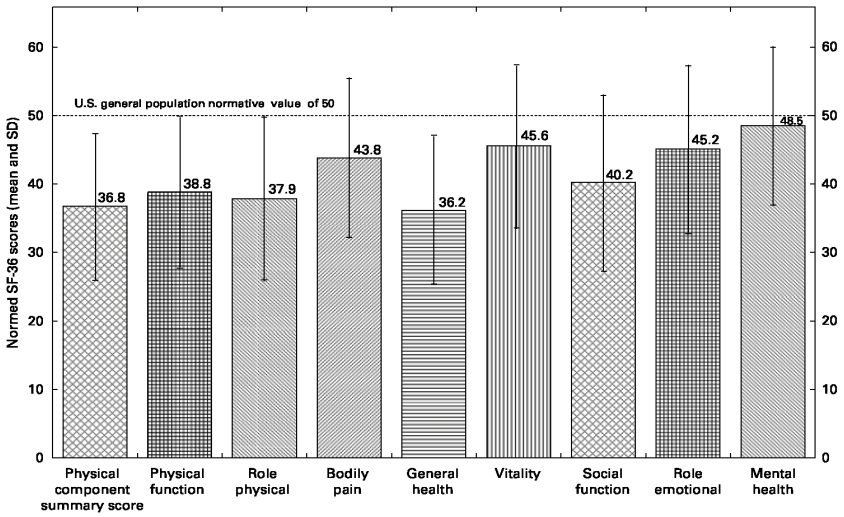

Figure 1 Norm-based SF-36 scores in allogeneic HSCT survivors with cGVHD.

Discussion

This study explored functional performance limitations in patients with cGVHD by testing two types of models designed to examine the direct and indirect effects of selected clinical and demographic factors on this outcome in a sample of 100 long-term survivors with cGVHD after allogeneic HSCT.

Consistent with earlier research, [16,17,22] participants in this study showed substantial impairment in both functional capacity and performance, showing a level of functional performance that was significantly inferior to US population norms. The normed-means on the SF-36 for physical function, physical role function, bodily pain, and general health were also 6–15 points lower than the normed-means reported in a small sample of very long-

term (median of 17.5 years post transplant) allogeneic HSCT survivors, only 50% of whom were noted to have cGVHD .[45] Our results suggest that individuals with moderate-to-severe cGVHD requiring treatment with moderate-to-high levels of immunosuppression experience significant functional limitations. These limitations climbing stairs, walking distances, and performing moderately vigorous activities, as well as reduced endurance for household tasks and other work, and unfavorable perceptions of general health.

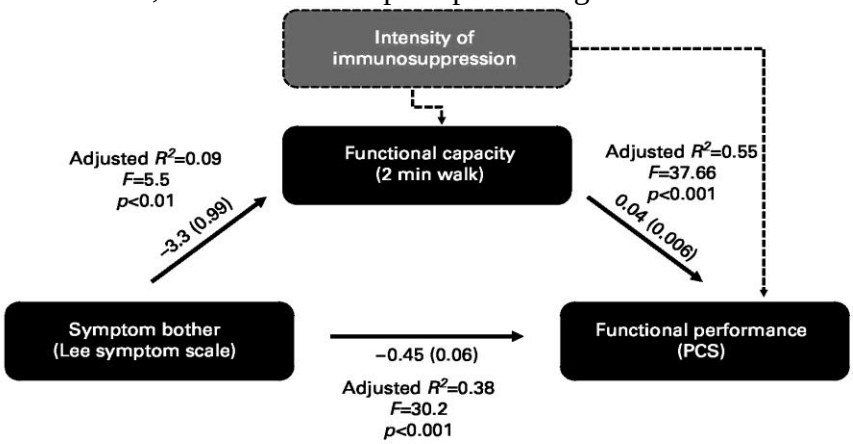

Figure 2 Functional capacity partially mediates the relationship between cGVHD symptom bother and functional performance, controlling for intensity of immunosuppression. Numbers outside parentheses represent the raw partial coefficient (*b*); numbers in parentheses represent the standard error of the raw partial coefficient (*b*).

It was surprising to find that neither comorbidity nor objectively scored cGVHD severity was a significant predictor of functional performance limitations in our sample of allogeneic HSCT survivors. As a prior report observed a small, positive association between comorbidity and functional status in patients with cancer,[46] it is possible that comorbidity and cGVHD severity may have a function in limiting functional performance in transplant survivors with cGVHD, and this should be explored in a larger sample.

Earlier studies indicate that the presence of immunosuppressive therapy may not have an adverse effect on health-related quality of life .[6] However, our study measured the intensity of systemic immunosuppressive therapy, not just its presence/absence, and showed a significant relationship with functional performance. From a clinical perspective, more intensive immunosuppression regimens, particularly regimens containing high doses of corticosteroids, may contribute to a side-effect profile,[47,48] including tremor and muscle weakness, that results in impaired physical function, though this hypothesis has not yet been empirically tested in HSCT survivors receiving immunosuppression for cGVHD.

Other investigators have also observed an association between the occurrence of multiple symptoms and adverse functional performance .[49–51] However, our study results are novel in showing that in long-term allogeneic HSCT survivors with cGVHD, the adverse effects of symptoms on functional performance are both direct, and indirect mediated through decrements in functional capacity.

Several limitations must be considered in the interpretation of our study results. The sample size was relatively small, and the cross-sectional design did not permit a conclusion that the observed relationships are solely the result of cGVHD. Individuals seen at our referral center may also have more severe, intractable, or heterogeneous manifestations of cGVHD, and the observations and associations may not hold if the relationships were examined in another setting or in individuals with less severe or less intractable cGVHD manifestations. Caution should be used in generalizing these results to patients with mild or subclinical cGVHD.

With these caveats in mind, this study fills an important gap in knowledge by examining the effects of symptoms, functional capacity, and clinical- and treatment-related factors on functional performance in a sample comprised exclusively of allogeneic HSCT survivors with cGVHD. These results may be helpful in planning interventions for this patient population, a population shown in prior research to be at particular risk for morbidity and mortality. For example, the findings underscore the importance of close follow-up of patients with cGVHD to ensure thorough evaluation of functional capacity and symptom bother, and to provide

rehabilitative interventions targeted to improve functional capacity. Interventions to evaluate and effectively manage cGVHD symptoms and reduce symptom bother are also essential and may contribute to better functional performance directly, as well as indirectly by elevating functional capacity. Study results also suggest that patients receiving intensive immunosuppression are at particular risk for impairments in functional performance and represent a group who might benefit from early intervention.

These study results also support the utility of three instruments recommended by the National Institutes of Health for use as dimensions of therapeutic response evaluation in cGVHD:[52] the SF-36, the distance walked in 2 min, and the Lee chronic GVHD symptom bother scale. Measures of functional performance and functional capacity offer complementary information about functional status in this patient population, and the inclusion of differing dimensions of function and contrasting methodologic approaches to measuring functional outcomes in clinical trials of new therapies appears warranted.

Results suggest several directions for future research. Specifically, longitudinal studies are needed to determine whether early declines in functional capacity produce subsequent performance limitations, and to test whether interventions specifically designed to elevate functional capacity and ameliorate symptom bother lead to improvements in functional performance. Research is indicated to develop and refine screening measures that can be used to identify cGVHD patients with clinically significant symptom bother, declines in functional capacity, and deterioration in performance of activities in daily life.

Conflict of interest

The authors declare no conflict of interest.

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