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Symptom Distress Predicts Long-Term Health and Well-Being in Allogeneic Stem Cell Transplantation Survivors

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The number of survivors after allogeneic hematopoietic stem cell transplantation (HSCT) continues to increase, yet their survivorship experience has not been fully characterized. This study examines the health status and health-related quality of life (HRQL) of HSCT survivors. The aims of the study were to: (1) explore the baseline and change over time in these health outcomes, and (2) characterize subgroups experiencing adverse outcomes. In this longitudinal study, adults who survived >3 years from date of allogeneic HSCT completed a series of patient-reported outcome measures annually, including measures of health status, HRQL, and symptoms. Data were analyzed using hierarchical linear modeling. Subjects (N = 171) were on average 44 (±13.5) years of age and primarily male (62.6%); 40% were Hispanic. Mean scores for physical and mental health and HRQL were preserved relative to population norms. Hierarchical linear modeling revealed no significant change in the mean trajectories of these outcomes, although significant between-individual variability was observed. When controlling for demographic and clinical factors, physical symptom distress negatively affected all outcomes. The impact of symptom distress on physical health varied based on time since HSCT; impairment in physical health was greatest in survivors experiencing high symptom distress and who were within the first decade post transplantation. Extended treatment with systemic immunosuppressive therapy also predicted inferior physical health. These findings suggest that patient-centered outcomes are preserved relative to normative values and are generally stable after allogeneic HSCT, although survivors with persistent symptoms and those receiving systemic immunosuppression experience impairments in health status and HRQL.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) has become a curative treatment for patients with a wide variety of diseases [1,2], with approximately 25,000 allogeneic HSCTs performed annually worldwide [3]. The increasing number of stem cell transplantations performed reflects a greater availability of donors from acceptable transplant sources (umbilical cord, unrelated donors, haploidentical donors) and the breadth of indications for this treatment. The availability of reduced-intensity conditioning regimens has also extended this treatment option to individuals who are older and those with comorbidities. At the same time, improvements in human leukocyte antigen (HLA) matching, prevention, and treatment of post-transplantation infections, and more effective management of acute and chronic graft-versus-host disease (cGVHD) have played a significant role in extending HSCT survivorship [4]. Although survivorship after life-threatening illness is a benefit, at the same time, late effects of HSCT including cGVHD, opportunistic infections, and the management of minimum residual disease, are challenges that can be difficult to manage and contribute to the need for specialized long-term follow-up [5].

Beyond the clinical aspects of recovery, survivorship also entails a reintegration back into domestic and professional roles and meaningful routines and activities that generate a sense of well-being and quality of life. The assessment of health-related quality of life (HRQL) includes biological factors along with functional status, symptom experience, general health perceptions, and overall quality of life [6]. Several recent reviews have examined HRQL after transplantation [7,8], including 1 focused specifically on the experiences of long-term survivors of allogeneic HSCT [9]. Although current evidence suggests that most survivors experience a relatively good HRQL when compared with healthy populations or to other chronically ill populations, a subset of survivors report impaired physical or emotional function [10-13]. Major

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demographic, clinical, and treatment factors influencing variation in HRQL outcomes are well described [14], including the unique complications and late effects, such as cGVHD and infections associated with prolonged immunosuppression therapy, which substantially shape the recovery experienced by long-term survivors [15-17]. However, no prior studies have evaluated physical and mental health status and HRQL longitudinally in a diverse sample of allogeneic HSCT recipients during a period of extended survival. This study characterizes patterns of recovery according to health status and HRQL in a diverse population of survivors ≥3 years after allogeneic HSCT and identifies predictors of impairment in these outcomes.

MATERIALS AND METHODS

Study Design and Participants

The design of this prospective longitudinal study has been previously described [18]. This study was approved by the National Heart, Lung and Blood Institute intramural Institutional Review Board and all patients provided written informed consent before participation. Patients who were 3 years after first allogeneic HSCT (after receiving either a myeloablative [19] or reduced-intensity [20-22] conditioning regimen) at the National Institutes of Health Clinical Center were accrued consecutively. Eligible study participants were at least 18 years old, carried a life expectancy of at least 6 months, and spoke and read English or Spanish. Those with a life expectancy less than 6 months and individuals who had undergone a second allogeneic HSCT procedure were excluded from participation. Those who agreed to join the study completed a survey packet annually within 60 days of their annual clinical follow-up.

Study Procedures

Paper and pencil questionnaires, which took approximately 45 minutes to complete, were administered to outpatients in a private area. In some instances, the questionnaires were mailed with instructions for completion and a postage-paid return envelope. If the questionnaires were not returned within 2 weeks, a follow-up phone call was made to confirm receipt of the questionnaires and respond to any questions or concerns about completion. Permission to contact participants by phone and e-mail was obtained during the consenting process.

Measures

Physical and mental health status were measured using the Medical Outcomes Study Short Form 36-Version 2 [23]. The Short Form-36 is a 36-item self-report measure of physical and mental health, evaluating 8 subscales including physical functioning, physical role functioning, emotional role functioning, social functioning, bodily pain, mental health, vitality, and general health. In addition to the individual subscale scores, a Physical Component Score (PCS) and Mental Component Score (MCS) are computed through aggregation of the subscales. To facilitate comparison with US healthy population values, summary and subscale scores were transformed to a *T*-score metric, with a mean of 50 and standard deviation of 10. Higher scores indicate better outcomes [23]. Summary scores that are 3 or more points above or below the norm-based score of 50, the minimum important difference indicating clinical relevance, are considered outside the average range for the US healthy population. The Short Form-36 was translated into Spanish through the International Quality of Life Assessment Project. Strong evidence of internal consistency reliability and construct validity has been documented in Spanish-speaking samples [24-27].

HRQL was measured with the Functional Assessment of Cancer Therapy—General Version 4 (FACT-G) [28]. The FACT-G is a 27-item self-report cancer-specific quality of life questionnaire. Scores are summed to yield a FACT-G Total Score, which can range from 0 to 108. Higher scores indicate better HRQL. The US healthy population value for the FACT-G total score is 80.1 (±18.1) and a 5-point difference is considered clinically meaningful [29]. The Spanish version of the FACT-G (version 4) has demonstrated construct validity and evidence of strong internal consistency reliability [30,31].

Physical symptom distress was assessed with the physical symptom distress scale (PSDS) of the Rotterdam Symptom Checklist [32]. The PSDS consists of 23 items evaluating the bother experienced in the past 30 days from a range of physical symptoms. Total PSDS scores range from 23 to 92; higher scores indicate more symptom distress. The PSDS raw scores were linearly transformed into scores on a 100-point scale; previously published data [32] suggest 3 cut-points that may be used to aid interpretation. Thus, a transformed score of <10 was considered "low" (eg, healthy population), 10 to 15 as "mild/moderate" (ie, disease free population, newly diagnosed), and >15 as "high" (ie, active treatment, high symptom burden cancer type). The Spanish version of the Rotterdam Symptom Checklist has demonstrated strong internal consistency reliability and construct validity in Spanish-speaking cancer patients [10].

Demographic (age, gender, race, ethnicity, years post transplantation, country of residence, marital status, educational attainment, and employment) and clinical (intensity of conditioning, HLA compatibility, stem cell source, primary disease, stage of disease, and comorbidity score) variables were collected at time of study enrollment. Transplantation risk status was classified based on an expanded version of published guidelines [33] to yield 3 risk categories based on type of malignancy/disease and stage at the time of transplantation: standard, intermediate, high/very high. Comorbidities at time of transplantation were retrospectively scored using the hematopoietic stem cell transplantation—comorbidity index [34], and categorized according to whether 0, 1 to 2, or ≥3 comorbidities were present. Several additional clinical variables were also collected annually and modeled as time-varying factors. These variables included Eastern Cooperative Oncology Group performance status, evidence of disease, current treatment with systemic immunosuppression, and physical symptom distress. Evidence of disease was coded based on molecular, hematopathologic, or radiographic evidence of disease and whether treatment had been administered for their primary disease in the past year. Only subjects in complete remission and who had not received treatment for their primary disease in the past year were coded as "no evidence of disease." If a subject was receiving any immunosuppressive therapy, including single-agent prednisone, they were classified as positive for the presence of immunosuppression (compared to none) [17,35-37].

Statistical Analysis

Descriptive statistics were used to describe clinical and demographic characteristics of subjects and to summarize health status, HRQL, and physical symptom distress scores at each year after allogeneic HSCT. Hierarchical linear modeling (HLM) was used to analyze within-individual (level-1) and between-individual (level-2) changes. The main goal of HLM models was to examine changes over time in longitudinal data, and therefore time was included in all models.

For each of the 3 outcomes variables (PCS, MCS, and FACT-G) HLM was performed in 2 steps. First, 3 unconditional models were specified: unconditional means model (no time effect), unconditional linear model (linear time effect), and unconditional quadratic model (quadratic time effect). The main purpose of fitting the unconditional means models is to estimate level-1 and level-2 variance components. This allows for a determination of whether significant between-individual variability exists in the trajectories for physical health, mental health, or HRQL, which may be accounted for by level-2 covariates [38]. If the level-2 variance components are significant, suggesting substantial between-individual variability in the intercept or trajectory, demographic and clinical variables significant in the uncontrolled model, along with the baseline clinical factors, are then examined in an adjusted model. The deviance goodness-of-fit test was used to compare the model fit of the linear and quadratic time effect models. Subsequently, each time-invariant (age, gender, education, ethnicity, marital status, disease risk status, conditioning type, and hematopoietic stem cell transplantation—comorbidity index category) and time-varying (evidence of disease, treatment with systemic immunosuppression, and physical symptom distress) covariate was tested one by one to see if it alone was a significant level-2 predictor of the outcome. Two HLM models were specified to sequentially investigate the association of the covariates with the 3 outcomes. Model 1 included the following demographic and baseline clinical variables: age, gender, ethnicity, transplantation risk status, comorbidity, and conditioning type. The final model (model 2) included all other time-invariant and time-varying variables that were significant at the intercept or linear term in the individual models, in addition to the covariates from model 1.

All models were estimated using full information maximum likelihood estimation. The unstructured covariance matrix was used for random intercepts and slopes in each model. A P value <.05 indicated statistical significance. All data analyses were performed using SAS 9.3 [39].

RESULTS

Study Participants

Beginning in August 2005, 227 HSCT survivors were screened and 173 agreed to participate and completed the enrollment (baseline) survey. Fifty-four patients were not enrolled because of lack of interest (n = 10), clinical acuity/second HSCT (n = 16), <18 years of age (n=4) limited literacy, or speaking a language other than English or Spanish