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Patient-Reported Outcomes and Socioeconomic Status as Predictors of Clinical Outcomes after Hematopoietic Stem Cell Transplantation: A Study from the Blood and Marrow Transplant Clinical Trials Network 0902 Trial

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A B S T R A C T

This secondary analysis of a large, multicenter Blood and Marrow Transplant Clinical Trials Network randomized trial assessed whether patient-reported outcomes (PROs) and socioeconomic status (SES) before hematopoietic stem cell transplantation (HCT) are associated with each other and predictive of clinical outcomes, including time to hematopoietic recovery, acute graft-versus-host disease, hospitalization days, and overall survival (OS) among 646 allogeneic and autologous HCT recipients. Pretransplantation Cancer and Treatment Distress (CTXD), Pittsburgh Sleep Quality Index (PSQI), and mental and physical component scores of the Short-Form 36 were correlated with each other and with SES variables. PROs and SES variables were further evaluated as predictors of clinical outcomes, with the PSQI and CTXD evaluated as OS predictors ($P < .01$ considered significant given multiple testing). Lower attained education was associated with increased distress ($P = .002$), lower income was related to worse physical functioning ($P = .005$) and increased distress ($P = .008$), lack of employment before transplantation was associated with worse physical functioning ($P < .01$), and unmarried status was associated with worse sleep ($P = .003$). In this large heterogeneous cohort of HCT recipients, although PROs and SES variables were correlated at baseline, they were not associated with any clinical outcomes. Future research should focus on HCT recipients at greater psychosocial disadvantage.

INTRODUCTION

Previous research has shown that baseline patient-reported outcome (PRO) and socioeconomic status (SES) measures predict morbidity and mortality after hematopoietic cell transplantation (HCT) [1-6]. In contrast to that for other cancer populations, there is minimal published research investigating more proximal clinical events or immunologic determinants to suggest candidate biobehavioral mechanisms that might explain this relationship [7,8]. Lower levels of optimism and increased anxiety, depression, and post-traumatic symptoms in the peri-transplantation period are associated with impaired white blood cell recovery after HCT [9-11]. Increased anxiety has also been associated with acute graft-versus-host disease (GVHD) [12], and depression has been associated with increased inflammation [10]. Finally, absence of spirituality has been associated with greater

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incidence of infection, sepsis, and GVHD [5]. However, these studies have been limited by small sample sizes derived from single institutions, retrospective designs, and utilization of a variety sampling measures, some of which are nonvalidated.

Social factors, including SES, confer risk for adverse HCT outcomes [2,13,14]. In other cancer populations, such as laryngeal and prostate cancer as well as multiple myeloma, SES-related outcome disparities persist after controlling for differences in access to care and health behaviors [15-19]. The mechanisms by which SES and social factors affect outcomes are not well defined. Lifestyle and stress associated with low SES can activate psychobiological processes that lead to altered neural, endocrine, and immune activation [20,21]. A recent study suggests that low SES among unrelated donor HCT recipients is associated with increased gene expression patterns representative of chronic adversity [22]. This gene profile is predictive of adverse clinical outcomes, including increased relapse and decreased leukemia-free survival [22].

The purpose of the current study was to evaluate whether PROs and SES factors influence morbidity and mortality outcomes among HCT recipients from a large Blood and Marrow Transplant Clinical Trials Network (BMT CTN) randomized controlled trial [23]. The randomized controlled trial was a 2 × 2 factorial trial of whether an exercise and/or a stress intervention versus usual care for each improved quality of life (QOL) after HCT, in which participants additionally reported survey data before HCT and randomization. The primary aim of the current study was to examine the relationship between self-reported pre-HCT PROs and SES and determine whether these factors were associated with time to hematopoietic recovery. Secondary endpoints included acute GVHD (aGVHD), days of life out of the hospital within the first 100 days, and overall survival (OS). Specifically, we hypothesized that (1) worse pretransplantation PROs (including distress, sleep quality, and physical and mental health–related QOL) would be associated with adverse SES factors; and (2) better pretransplantation PROs and SES would predict decreased time to hematopoietic recovery, decreased incidence and severity of aGVHD, increased days of life out of the hospital within the first 100 days, and better OS.

METHODS

Participants

The current study was a secondary analysis of BMT CTN protocol 0902, a randomized trial of the effect of self-directed exercise and stress management on QOL in HCT recipients (ClinicalTrials.gov identifier: NCT01278927, protocol available at www.bmtctn.net) [23]. BMT CTN 0902 inclusion criteria as follows: age ≥18 years, ability to exercise at low-to-moderate intensity (as judged by self-reported ability to walk up 1 flight of stairs), no requirement for supplemental oxygen, and autologous or allogeneic transplantation to occur within 6 weeks of trial enrollment. Exclusion criteria included orthopedic, neurologic, or other problems that prevented safe ambulation or adherence to the protocol; participation in another trial with health-related QOL or functional status as a primary endpoint; planned donor lymphocyte infusion within 100 days after HCT; planned tandem transplantation; and planned anticancer therapies other than tyrosine kinase inhibitors or rituximab within 100 days after HCT. The 0902 trial was designed to be broadly representative of the general HCT population. A protocol review committee appointed by the National Heart, Lung and Blood Institute and all participating transplantation center institutional review boards or ethics committees approved the research protocol. All participants provided written informed consent. Eligible participants for this secondary analysis were those from the BMT CTN 0902 trial (n = 711) who completed the baseline assessment and had Center for International Blood and Marrow Transplantation pretransplantation and post-transplantation essential data forms completed. The final analysis included 310 allogeneic HCT recipients and 336 autologous HCT recipients; this final sample (n = 646) included patients from the original study who were evaluable for multivariate analysis and were not missing data on pertinent major variables. The parent study did not show an effect of the intervention on the primary outcomes, which were the physical and mental component summary (PCS and MCS) scores of the Medical Outcomes Study Short Form 36 at day +100 [23]. Therefore, we did not anticipate that the intervention would confound our interpretation of the prognostic ability of our selected PRO measures to predict clinical outcomes.

Data Collection Instruments

The pretransplantation PRO measures completed at study enrollment included the following: (1) Cancer and Treatment Distress (CTXD) [24,25], a 27-item measure of distress with subscales of uncertainty, health burden, family strain, identity, and managing the medical system, as well as distress interference with function; (2) Pittsburgh Sleep Quality Index (PSQI) [26,27], a 7-item measure of sleep patterns and difficulties, such as sleep quality, sleep latency, sleep efficiency, and use of sleeping medications; and (3) the Medical Outcomes Study Short Form 36, a 36-item, generic multidimensional health-related QOL measure with 2 summary domains, a physical (PCS) and a mental (MCS) component and 8 subscales. The age- and sex-adjusted normal population mean for both the MCS and PCS is 50 with a standard deviation of 10. A clinically meaningful change is considered to be .5 standard deviation, or 5 points, with higher scores indicating better health-related QOL. For the CTXD and PSQI, higher scores indicate greater symptom burden; a CTXD score of >1.1 is indicative of more clinically significant distress [28], and a PSQI score of >5 indicates disturbed sleep as adjusted for cancer populations [26,27].

Measurements of SES included patient-reported marital status, education level, employment status, and household income in the past year. Data collection was performed through the BMT CTN and the Center for International Blood and Marrow Transplantation [23].

Study Outcomes

The primary outcomes were time to hematopoietic recovery, defined as time to absolute neutrophil count $> .5 \times 10^9$/L sustained for 3 consecutive days for neutrophil engraftment, and time to achieve a platelet count of $>20 \times 10^9$/L independent of platelet transfusions for 7 consecutive days for platelet engraftment. Secondary outcomes included days of life out of the hospital within the first 100 days after HCT and incidence of grades II to IV aGVHD (among allogeneic recipients), defined as occurrence (yes versus no) of stages II to IV skin, gastrointestinal, or liver abnormalities fulfilling the National Institutes of Health Consensus criteria of aGVHD by 6 months. OS was evaluated as death from any cause, with the time to this event defined as the days from HCT to death or last follow-up.

Statistical Analyses

As a first step, linear regression was used to define associations between each pretransplantation PRO on SES and clinical variables. Data on all 646 patients were used for fitting these linear models.

Next, generalized linear models were used to assess whether PRO and SES measures predicted time to neutrophil and platelet engraftment, incidence of aGVHD by day 180 after transplantation, number of days out of the hospital in the first 100 days after transplantation, and OS. The PRO MCS and PCS were not assessed as predictors of OS in these models, as these results have been previously reported by Wood et al. [6]. Cox proportional hazards models were used for the time-to-event outcomes (OS, engraftment), logistic regression was used to model the probability of having aGVHD (allogeneic recipients only) by day 180, and Poisson and negative binomial regression were used to model the number of days out of hospital in the first 100 days. Separate models were constructed for autologous and allogeneic HCT patients.

Each of these models adjusted for the 4 SES factors and other relevant clinical variables. Tested clinical variables included age, baseline Karnofsky performance score (KPS; site reported, not validated by independent review), alcohol use (yes/no), tobacco use (yes/no), body mass index at baseline, hematopoietic cell transplantation–specific comorbidity index [29], disease risk index [30], prior transplantation (yes/no), conditioning regimen (myeloablative or not), and graft type (bone marrow, peripheral blood, or cord blood). Additional clinical variables analyzed for allogeneic transplantations included cytomegalovirus status, degree of donor/recipient matching, antithymocyte globulin/use, and GVHD prophylaxis. Stepwise variable selection at a .05 significance level was used to identify the clinical variables to include in the final linear and generalized linear models. Because they were found to affect the PROs, the 4 SES variables were included in all final models, regardless of their statistical significance.

The correlation between each pair of SES and PRO variables was checked to assess for collinearity between predictors. The final assessment of whether the PRO and SES variables affected the outcomes in these models was made using a significance level of .01. This stricter criterion was chosen to help