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Quality of Life after Allogeneic Hematopoietic Cell Transplantation According to Affected Organ and Severity of Chronic Graft-versus-Host Disease

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A B S T R A C T

Knowing the impact of chronic graft-versus-host disease (GVHD) on quality of life (QoL) after allogeneic hematopoietic stem cell transplantation (allo-HCT) by GVHD type and severity is critical for providing care to transplant survivors. We conducted a cross-sectional questionnaire study to examine the relationship between patient-reported QoL as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey, Functional Assessment of Cancer Therapy-Bone Marrow Transplant, and visual analogue scale (VAS) and chronic GVHD defined by the National Institutes of Health (NIH) criteria. Recipients of allo-HCT for hematologic disease between 1995 and 2009 aged ≥ 16 years at transplant and ≥20 years at the time of the survey who were relapse-free were eligible. A total of 1140 pairs of patient and physician questionnaires were included in the analysis. By NIH global severity score, QoL scores in all aspects were significantly lower in patients with higher global and organ-specific severity grades, independent of background variables. Compared with patients without GVHD symptoms, those with mild symptoms had impaired physical and general QoL according to global severity score and organ-specific scores except for the genital tract. Mild symptoms in the lungs, gastrointestinal tract, and joints and fascia were associated with clinically meaningful deterioration of physical QoL. VAS scores provided by physicians were generally higher than those provided by patients. Differences between scores reported by patients and physicians were larger for patients with no or mild GVHD symptoms. Our findings based on more than 1000 long-term survivors after HCT enabled us to identify a target of care, informing survivorship care protocols to improve post-transplantation QoL.

INTRODUCTION

Advances in allogeneic hematopoietic cell transplantation (allo-HCT) and expanding indications for its use in recent years have resulted in a growing number of transplant

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survivors [1-5]. Quality of life (QoL) after allo-HCT and long-term survivorship care have been receiving more attention [6-10].

Chronic graft-versus-host disease (GVHD) is a major late complication after allo-HCT. Approximately 30% to 70% of patients who receive allo-HCT develop chronic GVHD, which leads to late mortality and impaired QoL in long-term survivors [11-13]. Chronic GVHD can manifest in various sites, including the skin, mouth, eyes, gastrointestinal (GI) tract, lungs, joints and fascia, and genital tract [14-18]. Its diverse symptoms and associated disability are major targets of treatment and care in the long-term follow-up clinic. With a growing awareness, emerging reports on the impact of chronic GVHD on QoL have shown not only that GVHD impairs QoL but also that among patients with chronic GVHD, QoL may differ by severity [11] or affected site [19-21]. However, it is still unclear how chronic GVHD clinically affects QoL by affected site and severity, especially in comparison with those who do not have GVHD symptoms.

To provide optimal care for transplant survivors physically, mentally, and socially, it is of great importance to know the change in QoL after allo-HCT. Considering the burden of QoL measures tasked to patients, we may also need to evaluate the validity and usefulness of the assessment of QoL by proxies [22]. Several studies have reported that patient–proxy agreement was better for concrete, observable aspects, such as daily activities [22,23]. However, agreement was reported to be poor for more subjective domains such as psychosocial functioning [24,25].

To address the relationship between patient-reported QoL and chronic GVHD based on the National Institutes of Health (NIH) criteria, we conducted a nationwide cross-sectional questionnaire study. We also investigated the degree of agreement between the visual analogue scale (VAS) provided by patients and physicians to see if the degree differs among patients with different GVHD status.

METHODS

Study Design and Participants

Eligibility criteria included receipt of allo-HCT for hematologic disease between 1995 and 2009, age ≥ 16 years at transplant and ≥20 years at the time of the survey, and relapse-free status at the time of the survey. A total of 3301 eligible patients registered from 47 participating centers were identified in the national transplant registry database [26,27]. Participants were enrolled between December 2012 and September 2014 at the outpatient visit to each participating center. The protocol was approved by the institutional review boards of the National Cancer Center Hospital and each participating center. All subjects provided informed consent in accordance with the Declaration of Helsinki.

QoL Measures, Chronic GVHD Assessment, and Other Data Sources

The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), and VAS were administered to assess patient-reported QoL at 1 time point. For all these scales, higher scores indicate better QoL.

The SF-36 Version 2 is a comprehensive scale that consists of a 36-item questionnaire that assesses self-reported health. SF-36 normative scores for the Japanese general population enabled us to compare the scores of allo-HCT recipients with those of the general population. For the SF-36, we used a 3-component model that was validated to have a better fit for Asian populations [28,29]. Thus, in addition to 8 subscale scores and physical (PCS) and mental (MCS) component summary scores, we also calculated a role/social component summary score (RCS).

The FACT-BMT Version 4.0 is a disease-specific scale that consists of a 37-item self-reported questionnaire. It includes the 27-item FACT-General (FACT-G) and the 10-item subscale that assesses concerns related to transplantation (bone marrow transplant subscale: BMTS). The FACT-G has 4 QoL domains including physical, social/family, emotional, and functional well-being [30]. The VAS is used to rate health on a scale with the endpoints labeled "best imaginable health state" at the top and "worst imaginable health state" at the bottom, with numeric values of 100 and 0, respectively.

Participating patients' own physicians graded overall and organ-specific (skin, mouth, eyes, lungs, GI tract, liver, joints and fascia, and genital tract) severity of chronic GVHD at the time of the survey based on NIH criteria [31]. Physicians also provided information on oral immunosuppressant (IS) use and VAS of respective patients. Clinical information including disease type, gender, age at HCT, date of HCT, donor type, preparative regimen, GVHD prophylaxis, performance status at HCT, and number of HCTs were extracted from the national transplant registry database.

Statistical Analysis

Standard algorithms were used to compute scores for the SF-36 [28,29] and FACT-BMT [30]. Multivariable models were constructed to examine the relationship between QoL scores and types and severity of chronic GVHD after controlling for background covariates, including age at survey (5-level scale by decade), gender, disease (myeloid leukemia/myelodysplastic syndrome/myeloproliferative disease/chronic myeloid leukemia, lymphoid leukemia, lymphoma, myeloma, and nonmalignant disease), time from allo-HCT (<5, 5 to 6, 7 to 9, and ≥10 years), donor type (related bone marrow, related peripheral blood, HLA well-matched unrelated bone marrow, HLA-mismatched unrelated bone marrow, and unrelated cord blood), preparative regimen (myeloablative and others), GVHD prophylaxis (cyclosporine-based and tacrolimus-based), performance status at HCT, and number of HCTs (1 and ≥2). Adjusted mean SF-36 summary scores were obtained as norm-based scores (mean = 50 [standard deviation = 10] based on the Japanese general population) after adjusting for the same covariates. Interclass correlation coefficients (ICCs) were calculated to evaluate the degree of agreement between VAS provided by patients (VASpt) and physicians (VASdoc).

Given multiple testing, we considered $P < .01$ to be statistically significant. Minimum clinically meaningful differences in QoL scores were defined as half of a standard deviation [32], as shown in Supplementary Table 1. Data were analyzed with SPSS statistical software (version 15.0; SPSS, Chicago, IL) and SAS/STAT software (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of the Patient Cohort and Baseline QoL Scores

We found a total of 3301 eligible patients registered from 47 participating centers in the national transplant registry database. Mostly because no outpatient visit occurred during the study period, 2051 patients were not informed of the study. Of the 1250 patients informed of the study, consent was obtained from 1216 patients (97%) at 45 of 47 participating centers, and 1149 patients (95% among those who consented) returned the questionnaires. Two centers had no participating patients. Nine patients were excluded because of a time lag of 4 months or longer between patient-completed questionnaires and physician-completed reports. Physicians' reports were obtained for all participants. Consequently, 1140 pairs of patient and physician questionnaires were included in the analysis (36% of 3178 eligible patients registered from 45 centers; Figure 1). Over 99% of each domain was valid for analysis except for the FACT trial outcome index (98.4%), FACT-G (98.3%), FACT-BMT total (97.9%), and VASpt (95.5%).

Table 1 presents the baseline demographic, disease, and transplantation characteristics of the 1140 patients. Men accounted for 52%. The median age at the time of survey was 51 years (range, 20 to 77). The median time after allo-HCT was 7.1 years (range, 3.3 to 18.9). Donor types were related bone marrow in 22% of patients, related peripheral blood in 21%, unrelated bone marrow in 40%, and unrelated cord blood in 17%.

Table 2 shows the information provided by physicians on type and severity of chronic GVHD according to NIH criteria and IS use at the time of the survey. By global severity score, 34% of patients did not have GVHD, 29% had mild, 25% had moderate, and 9% had severe chronic GVHD. Frequently affected organs were the eyes (31%), skin (25%), and mouth (21%). In general, a small number of patients had severe