Biol Blood Marrow Transplant 20 (2014) 946–950

Risk Factors for Depression in Patients Undergoing Hematopoietic Cell Transplantation

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Article history:
Received 27 November 2013
Accepted 10 March 2014

Key Words:
Hematopoietic stem cell transplantation
Depression
Hematopoietic cell transplantation
Bone marrow transplantation
Quality of life

A B S T R A C T

Despite the prevalence and known adverse impacts of depression after hematopoietic cell transplantation (HCT), little is known about the trajectory of depression occurring after HCT, or which pretransplantation risk factors might help predict new or worsening post-HCT depression. This secondary analysis evaluated the relationships between pre-HCT patient-reported outcomes and demographic characteristics and post-HCT depression. A total of 228 adult HCT patients were evaluated pre-HCT (T1) and again at 6 to 7 weeks post-HCT (T2), using touch-screen computers in the transplantation clinic during participation in a larger trial. Measures evaluated included the Symptom Distress Scale, the EORTC QLQ-C30 for quality of life, a single-item pain intensity question, and the Patient Health Questionnaire 9 for measurement of depression. At T1, rates of depression were quite low, with only 6% of participants reporting moderate or higher depression. At T2, however, the prevalence of moderate or higher depression was 31%. We observed a strong linear relationship in PHQ-9 scores between T1 and T2 ($P < .0001$). Depression score at T1 was a significant predictor of depression score at T2 ($P = .03$), as was poorer emotional function at T1 ($P < .01$). Our results indicate that post-HCT depression is common, even in patients with a low pre-HCT depression score. Frequent screening for symptoms of depression at critical time points, including 6 to 7 weeks post-HCT, are needed in this population, followed by referrals to supportive care as appropriate.

INTRODUCTION

Success rates for hematopoietic cell transplantation (HCT) have continued to improve as the procedure has been increasingly refined [1,2]. Despite this significant progress, HCT remains an extraordinarily stressful procedure physically, mentally, and emotionally [3,4]. One significant, and potentially limiting, symptom associated with HCT is depression. Depression is one of the most common psychiatric conditions occurring during and after cancer treatment. The estimated prevalence of depression across cancer patients ranges from 3% to >50%, depending on the timing and method used to measure the symptoms [5]. Studies have indicated that depression is prevalent in patients undergoing HCT, with an estimated one-quarter to one-third of HCT recipients experiencing depression during the first 100 days post-transplantation or during recovery from transplantation [3,6-9].

Depression has many potential negative psychosocial and physical consequences in HCT recipients. It can interfere significantly with quality of life; physical, social, and recreational activities; and overall health, and can be comorbid with other significant concerns, such as post-traumatic stress disorder and suicidal ideation in HCT survivors [3,10,11]. Depression also can interfere with cancer treatment adherence and is associated with negative health behaviors, such as tobacco and alcohol use [12,13]. Depression is well known to be associated with increased mortality in the general population [14-16], as well as in cancer patients [17]. Depression may be an independent risk factor for survival after HCT over and above its status as a potential indicator of poorer health status [7,18].

National accreditation bodies, including the National Comprehensive Cancer Network [19] and the Commission on Cancer [20], have mandated that distress screening be completed during treatment. For patients with clinical evidence of moderate or severe distress, the oncology team must "assess the psychological, behavioral, and social problems…that may interfere with their ability to participate fully in their health care and manage their illness and its consequences" [20]. Patients must then be referred for appropriate supportive care and creation of a follow-up plan. Thus, for HCT clinicians, early identification of depression is a critical element of comprehensive HCT care, along with appropriate referrals and interventions to address symptoms. Understanding the risk factors and clinical course of

Financial disclosure: See Acknowledgments on page 949.

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1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.03.010

depressive symptoms after HCT will help inform with whom and at what time points screening should occur [11].

The time course of depressive symptoms may vary significantly among HCT recipients. In some, depression may occur before HCT and persist (or even worsen) throughout the course of treatment, whereas in others, depression may not appear until weeks or months after HCT, remaining a long-term concern for patients undergoing HCT. In one study of HCT survivors at 1 to 3 years post-transplantation, 15% reported moderate to severe depressive symptoms, with recipients of allogeneic HCT (versus recipients of autologous HCT) and those with poorer functional status reporting higher levels of depression [10]. Another long-term study of recovery post-HCT found that 19% of patients continued to experience depressive symptoms at 5 years post-HCT [6].

Despite the prevalence and known adverse impacts of depression after HCT, little is known about the trajectory of depression immediately after HCT, or which pretransplantation risk factors might help predict new or worsening depression post-HCT. We conducted the present analysis to evaluate the relationships between pre-HCT patient-reported outcomes and demographic characteristics and post-HCT depression. Variables of interest included symptom distress, quality of life, demographic data, and social roles (eg, vocational status, relationship status). The purpose of the analysis is to aid clinicians in identifying patients who might be at high risk for depression in the early post-HCT period, facilitating early detection and thus more effective intervention for those patients.

PATIENTS AND METHODS

Sample

Research participants in the larger Electronic Self-Report Assessment–Cancer (ESRA-C) study [21], from which these data were collected, were recruited from the Seattle Cancer Care Alliance (SCCA), a consortium of the University of Washington Medical Center, Fred Hutchinson Cancer Research Center, and Seattle Children's Hospital. The SCCA cared for 3609 new patients in 2006, when these data were collected, the majority of whom (85%) were from Washington state. Eligibility criteria for the analytic sample included the following: new patients being evaluated for HCT, at least 18 years of age, able to communicate in English, and able to understand the study information and provide informed consent. Participants were included irrespective of the presence of diagnosis or treatment of psychiatric conditions, as long as they met the criteria for HCT. Between April 2005 and November 2006, a total of 228 eligible HCT patients were enrolled in the study.

Procedures

The methods and procedures of the ESRA-C study have been described in detail elsewhere [21]. In brief, baseline assessments (T1) were administered via touch-screen computer at a clinic visit before the start of HCT conditioning. At the first ambulatory visit post-HCT (at 6 to 7 weeks), patients were surveyed a second time (T2) using the same methodology. The technical aspects and navigability of the ESRA-C program have been described previously [22-24]. The ESRA-C has been well received by patients [21,25]. During the T1 session, patients were presented with an introductory screen, followed by demographic questions. They were then presented with 4 validated questionnaires during both the T1 and T2 survey sessions:

- Symptom Distress Scale (SDS) [26]. The 13-item SDS assesses the level of symptom distress for 11 symptoms, including nausea, appetite, insomnia, pain, fatigue, concentration, and others. Each item is scored on a scale of 1 to 5 with descriptive options. The SDS score is the sum of all item scores.
- The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30, version 3 [27]. The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients, including those undergoing HCT [28]. The QLQ-C30 incorporates 9 multi-item scales, including 5 functional scales (physical, role, cognitive, emotional and social), 3 symptom scales (fatigue, pain, nausea and vomiting), and a global health and quality of life scale. Each subscale is a multi-item index that yields a score of 0 to 100, with higher scores indicating better function for the functional scales (eg, emotional function) and more symptoms for the symptom scales (eg, fatigue). Emotional function questions cover such symptoms as irritability, worry, tension, and depression.
- A single-item numerical pain intensity scale of 0 to 10, with 0 indicating no pain and 10 indicating the worst pain imaginable.
- The 9-item Patient Health Questionnaire (PHQ-9) depression scale [29]. The PHQ-9 has been validated for in-person self-report or interviewer administration, as well as for administration over the telephone [30-33]. Standard PHQ-9 depression scores were categorized as follows: none ($\leq$4), mild (5 to 9), moderate (10 to 14), moderately severe (15 to 19), and severe ($\geq$20). A score of 10 has been identified as the optimal cutoff for identifying probable major depressive disorder (sensitivity, 0.88; specificity, 0.88) in primary care patients [29]. For analysis, we classified patients into 2 groups, "no/mild" depression (PHQ-9 total score $<$10) and "moderate or higher" depression (PHQ-9 total score $\geq$10). To minimize patient burden, we used the presence of at least 1 cardinal symptom of depression on at least half of the days in the previous 2 weeks, either anhedonia or depressed mood, as a trigger for completing the remaining 7 items of the PHQ-9. Initial screening in this manner, known as the PHQ-2, has been validated in medical populations [34-36]. Participants who did not trigger the full PHQ-9 were classified as having "no/mild" depression. To provide additional data for distressed subjects, the full PHQ-9 was also triggered in the case of specific responses on the QLQ-C30 (score of $\leq$50 on a possible 100 for the Emotional Function or Cognitive Function subscale) or SDS (score of $\geq$3 on the response range of 1 to 5 for the fear/worry, concentration, or sleep disturbance items).

Analysis

Baseline patient socioeconomic factors and quality of life measures were compared between dropouts and those completing the study using the *t*-test for continuous variables (age) or the Fisher exact/chi-square test for categorical variables. A generalized McNemar test was used to check for potential pattern changes in depression between T1 and T2. Logistic regression was used to predict moderate or higher depression at T2, with a list of preselected baseline variables, including minority (or not), income, education, working status, computer use, partnered (or not), transplant type, and baseline measures on the QLQ-C30, SDS, pain intensity scale, and the PHQ-9. The factors were first checked individually, adjusting for T1 depression status, and then factors with a P value $<$.20 were included in the multivariable model. Backward model selection was used for variable selection, and all variables with a P value $<$.10 were retained in the final model. Odds ratios and 2-sided P values were calculated. Analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC) and R version 2.15.0 (R Institute for Statistical Computing, Vienna, Austria).

RESULTS

A total of 228 HCT recipients were enrolled in the study. Thirty-six of the participants did not complete the assessment at both time points, with attrition due mainly to death or illness; thus, the final analytic sample comprised 192 participants. There were no significant differences in demographic characteristics between study completers and noncompleters, although there were trends toward older age ($P = .06$) and lower likelihood of working at T1 ($P = .07$) in noncompleters compared with completers. However, noncompleters did have significantly lower global quality of life scores (subscale of the QLQ-C30) at T1 compared with completers ($P = .04$).

Demographic and clinical characteristics of the 192 study participants are shown in Table 1. The sample was 59% male, and the majority were married, had 2 or more years of college education, and used computers at home and/or work. Participants were predominately Caucasian and non-Hispanic/Latino (91%). The majority of participants (59%) were working, on medical leave, or in school.

Changes in PHQ-9 depression categories from T1 to T2 are presented in Table 2. At T1, rates of depression were low, with only 11 participants (6%) reporting moderate or higher