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Severity, Course, and Predictors of Sleep Disruption Following Hematopoietic Cell Transplantation: A Secondary Data Analysis from the BMT CTN 0902 Trial

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Abstract

Sleep disruption has received little attention in hematopoietic cell transplantation (HCT). The goal of this study was to describe severity, course, and predictors of sleep disruption following HCT. A secondary data analysis was conducted of the Blood and Marrow Transplantation Clinical Trials Network (BMT CTN) 0902 study. Participants completed a modified version of the Pittsburgh Sleep Quality Index prior to transplant and 100 and 180 days post-transplant. Growth mixture

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models were used to characterize subgroups of patients based on baseline sleep disruption and change over time. A total of 570 patients (mean age 55, 42% female) were included in the current analyses. Patients could be grouped into four distinct classes based on sleep disruption: 1) clinically significant sleep disruption at baseline that did not improve over time (20%); 2) clinically significant sleep disruption at baseline that improved over time (22%); 3) sleep disruption that did not reach clinical significance at baseline and did not improve over time (45%); and 4) no sleep disruption at baseline or over time (13%). These data provide a more comprehensive understanding of sleep disruption that can be used to develop interventions to improve sleep in HCT recipients.

Despite significant advances in supportive care, morbidity following hematopoietic cell transplantation (HCT) remains high. Transplant related-complications and the medications used to manage them have the potential to significantly disrupt sleep. Sleep disruption can include difficulty falling asleep, staying asleep, awakening earlier than intended, and/or non-restorative sleep.(1) Although sleep disruption is a significant concern of HCT patients (2, 3), it has received little clinical or research attention (4, 5).

Previous research has primarily assessed sleep disruption in HCT patients in the context of quality of life. Several quality of life measures include single items assessing sleep disruption such as “I am sleeping well” (6) and “Have you had trouble sleeping?” (7). Studies using these measures have documented that sleep disruption is more severe in HCT recipients than in the general population (8). Studies using single-item measures also suggest that sleep disruption tends to peak during hospitalization and returns to pre-transplant levels within 6 months after HCT (9). Few studies (10–12) have used longer, well-validated measures of sleep disruption that provide detailed information about sleep latency (i.e., time required to fall asleep), sleep duration (i.e., total time spent sleeping), sleep efficiency (i.e., percentage of time in bed spent sleeping), and sleep medication usage. Available data suggest that 32% of patients report significant sleep disruption prior to HCT and 23% meet criteria for a clinical diagnosis of insomnia 1–10 years post-transplant (10, 12). Nevertheless, previous studies have primarily reported mean changes, which can obscure significant patient variability in change over time in the severity and course of sleep disruption. Moreover, many existing studies have been limited by small sample sizes and short follow-up times. In addition, data are scarce regarding sociodemographic, clinical, and behavioral risk factors for sleep disruption after transplant, although existing research suggests that older age, female gender, comorbidities, and high distress are risk factors (5).

Sleep disruption is associated with a variety of negative outcomes. Sleep disruption is associated with worse all-cause mortality in general as well as increased incidence of cancer progression (13, 14). Clinical and preclinical studies indicate that sleep disruption negatively impacts immune response and reconstitution (15–17). Among HCT recipients, sleep disruption is associated with worse quality of life and higher levels of systemic inflammation (2, 12, 18). Thus, sleep disruption is highly relevant to HCT outcomes. Greater attention to sleep disruption in HCT patients is warranted.

The goal of the current study was to examine the severity, course, and predictors of sleep disruption in a large sample of HCT patients prospectively enrolled on a randomized trial of

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exercise and stress management. Growth mixture modeling (GMM) (19, 20) was used to address two aims. The first aim was to determine whether the severity and course of sleep disruption varies across patients. We hypothesized that at least two subgroups of patients with different patterns of change in sleep disruption would be identified (e.g., patients with post-transplant improvement in sleep versus no change or worsening sleep disruption). The second aim was to examine whether subgroups can be distinguished based on baseline sociodemographic, clinical, and psychological characteristics. Based on prior literature (5), we hypothesized that older age, female gender, comorbidities, pain, and distress would predict greater sleep disruption at baseline and less improvement over time.

Methods

Participants

Participants were recruited as part of a larger, multicenter randomized controlled trial of stress management and exercise among HCT recipients (BMT CTN 0902) (21). Patients were eligible for the study if they were: a) at least 18 years of age, b) able to speak and read English, c) able to exercise at low to moderate intensity as judged by physician judgment and self-reported ability to walk up one flight of stairs without supplementary oxygen, d) willing and able to provide informed consent, e) willing to comply with study procedures and reporting requirements, and f) planning to undergo autologous or allogeneic transplant within six weeks. Patients were excluded from the study if they: a) had orthopedic, neurologic, or other problems which prevented safe ambulation and protocol adherence, b) were participating in another clinical trial with quality of life or functional status as a primary endpoint, c) were planning to receive anti-cytotoxic therapies other than tyrosine kinase inhibitors, d) were planning to receive donor lymphocyte infusion within 100 days of transplant, e) were planning to receive a tandem transplant.

Procedure

The research protocol was approved by a protocol review committee appointed by the National Heart, Lung and Blood Institute (NHLBI), and by local institutional review boards or ethics committees. This study is registered with ClinicalTrials.gov, number NCT01278927. All participants provided written informed consent. Study eligibility was determined with chart review and in consultation with clinical staff. Patients deemed eligible for the study were recruited and informed consent was obtained prior to the day of graft infusion (day 0). Participants completed a packet of questionnaires prior to transplant and received audiovisual materials on exercise, stress management, both sets of materials, or usual care. Participants completed follow-up assessments of sleep disruption at 3 months and 6 months post-transplant.

Measures

Demographic and Clinical Data—Demographic data obtained prior to HCT included age, sex, race/ethnicity, marital status, education, and income. Pre-transplant co-morbid medical conditions were measured using the Sorror scale (22). Clinical data collected via Center for International Blood and Marrow Transplant Research (CIBMTR) reporting include pre-HCT Karnofsky score, disease type, transplant type (allogeneic vs. autologous),

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and conditioning regimen (i.e., myeloablative allogeneic vs. reduced intensity/non-myeloablative allogeneic).

Sleep Disruption—Participants completed an abbreviated, 7-item version of the Pittsburgh Sleep Quality Inventory (PSQI) (23) prior to transplant and at 3 months and 6 months post-HCT. Five dimensions of sleep were assessed including subjective sleep quality, latency, duration, efficiency, and sleep medication use.(24) The five sleep domains were summed to calculate a summary score ranging from 0 to 15 in which higher scores indicate greater sleep disruption. Clinically significant sleep disruption was categorized as a total score of 4 or above (i.e., prorated based on a cutoff of 5 or above for the full PSQI total score of 0 to 21) (23).

Treatment-Related Distress—Participants completed the Cancer and Treatment Distress CTXD scale prior to transplant (25). The CTX-D is a 22-item measure assessing treatment-related distress and consists of several subscales including uncertainty, health burden, family strain, identity, managing the medical system, and distress interference. Questions are rated on a 4-point Likert scale ranging from 0 to 3 with higher scores indicating more severe distress. A mean score is obtained by averaging the 22 items. The CTXD has demonstrated good internal consistency (26).

Pain—Participants completed the bodily pain subscale of the Medical Outcomes Survey Short Form (SF-36) (27) prior to transplant. The pain subscale ranges from 0 to 100 with higher scores reflecting less pain.(27) The SF-36 has demonstrated adequate internal consistency and has been widely used in cancer patients.(28, 29)

Statistical Analyses

In Aim 1, growth mixture modeling (GMM) was used to evaluate whether there are classes of individuals who vary in terms of their pre-HCT sleep disruption and/or changes in trajectories of sleep disruption over time. GMM is ideal for clinical trials such as BMT CTN 0902, which consists of a large, heterogeneous sample in which smaller, more homogenous subsamples are thought to exist. GMM is an iterative process in which the analyses began with a one-class model, and then successive models were extracted incrementally with more classes and compared using fit indices and other criteria (e.g., class size larger than 25 patients) to determine the optimal number of classes. Because there were no differences between study arms in sleep at baseline or follow-up, study arms were collapsed in the current analyses. Because change was the outcome of interest, these analyses focused on patients who had PSQI data at baseline and at least one additional time point. Autologous and allogeneic recipients were analyzed in the same model due to the large sample size required to conduct analyses.

In Aim 2, differences in class membership as a function of sociodemographic (i.e., age, gender, race, ethnicity, marital status, education, income), clinical (i.e., pre-HCT comorbidities, pre-HCT Karnofsky score, baseline pain, transplant type, degree of myeloablation), and psychological (i.e., baseline distress) factors were examined using ANOVA and chi square analyses. PSQI class membership was the outcome of interest.

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GMM was conducted using Mplus v. 7 (30) and all other analyses were conducted using SAS 9.4. (31).

Results

Of the 711 patients recruited to the randomized trial, 570 patients completed the baseline PSQI and at least one follow-up assessment and were included in the current analyses. Participant characteristics are shown in Table 1. The majority of patients were male, non-Hispanic, white, married, had an annual household income of $50,000 or more, and had been treated with autologous transplant. The most common diagnosis was myeloma (30%), followed by non-Hodgkin's lymphoma (26%) and acute leukemia (23%).

Participants could be grouped into four distinct classes based on PSQI scores with GMM analysis. As shown in Figure 1, members of class 1 (n=257) reported sleep disruption pre-HCT that did not meet criteria for clinical significance and remained stable across time. Members of class 2 (n=126) reported clinically significant sleep disruption at pre-HCT that improved at 3 months post-HCT, then worsened slightly at 6 months post-HCT but remained better than baseline. Members of class 3 (n=112) reported clinically significant sleep disruption pre-HCT that remained stable across time. Members of class 4 (n=75) reported no sleep problems pre-HCT or across time.

Comparing sociodemographic and clinical variables between classes, older patients tended to be members of class 4 (i.e., none/stable) and class 1 (i.e., non-significant/stable) rather than class 3 (i.e., significant/stable) (p values <.05). Married patients were more likely to be members of class 4 (i.e., none/stable) than members of the other classes (p values≤.006). Married patients were also more likely to be members of class 1 (i.e., non-significant/stable) than class 2 (i.e., significant/improving) (p=.04). Allogeneic transplant recipients were more likely to be members of class 3 (i.e., significant/stable) than class 1 (i.e., non-significant/stable) and class 2 (i.e., significant/improving). Patients with greater pain at baseline were more likely to be members of class 2 (i.e., significant/improving) and class 3 (i.e., significant/stable) than class 1 (i.e., non-significant/stable) and class 4 (i.e., none/stable) (p values<.05). Patients with greater distress at baseline were more likely to be members of class 2 (i.e., significant/improving) and class 3 (i.e., significant/stable) than class 1 (i.e., non-significant/stable) and class 4 (i.e., none/stable) (p values<.05). Patients with greater distress at baseline were also more likely to be members of class 3 (i.e., significant/stable) than class 2 (i.e., significant/improving) (p<.05). There were no class differences in sleep disruption by sex, race/ethnicity, education, income, comorbidities, pre-HCT Karnofsky score, and degree of myeloablation (i.e., for allogeneic HCT).

Discussion

The current study examined change in sleep disruption over time in large sample of HCT recipients. Specifically, we found that HCT recipients could be grouped into one of four classes based on the severity of pre- HCT sleep disruption and changes in sleep over time. A majority of patients (58%) reported non-clinically significant or no sleep disruption that remained stable over time (classes 1 and 4). Another class of patients (22%) reported

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clinically significant sleep disruption that improved at three months post-HCT, then worsened somewhat at six months post-HCT but remained better than baseline (class 2). The remaining patients (20%) experienced clinically significant sleep disruption that remained stable over time (class 3). The presence of clinically-significant sleep disruption in 42% of our sample is consistent with previous estimates of the prevalence of insomnia in cancer patients not treated with HCT (32). Risk factors for greater sleep disruption in the current sample were younger age, non-married status, allogeneic HCT, baseline pain, and baseline distress. No other sociodemographic or clinical variables were associated with sleep disruption.

These findings add new knowledge to existing literature regarding sleep disruption in HCT recipients. Mean levels of sleep disruption reported in previous studies obscure significant inter-individual variation in sleep disruption. While patients reporting no or non-clinically significant sleep disruption at baseline can expect to experience continued good sleep across time, patients with clinically significant sleep disruption at baseline fell into two groups. In one group, sleep improved by day 100, whereas in the other group sleep disruption continued to be a problem throughout the first six months following transplant. A relevant question is whether it is possible to distinguish between the two groups at baseline to target interventions to the patients with clinically significant sleep disruption that is unlikely to improve on its own. Patients demonstrating improved sleep were more likely to have received an autologous transplant and less likely to experience baseline distress. Therefore, our results suggest that most patients can expect sleep disruption at 100 days and six months post-transplant to be similar to that pre-transplant. However, autologous patients with clinically significant sleep disruption and low levels of distress at baseline can expect some improvement in sleep.

Younger age and allogeneic transplant were risk factors for worse sleep disruption in this population. These findings can be contrasted with previous studies showing that older age and autologous transplant are associated with worse sleep disruption (31, 33). Nevertheless, evidence of a relationship between younger age and greater sleep disruption comes from a study of cancer patients not treated with HCT (33). The study demonstrating autologous transplant to be a risk factor for worse sleep disruption assessed long-term survivors (34). Other studies have suggested that allogeneic recipients experience worse sleep disruption than autologous recipients during the acute transplant period (11, 12, 35). Thus, it may be that risk factors change over time.

The current study is characterized by several strengths, including a clinically-important research question, a large sample size, a prospective longitudinal design, a well-validated multi-item measure of sleep, and sophisticated statistical analyses. Study limitations should also be noted. It was a multicenter study with the potential for significant variability in transplant care and practices across centers (e.g., inpatient vs. outpatient transplant, whether patients are discharged home or to local lodging). The sample was relatively homogenous in terms of race and ethnicity; therefore results may not generalize to HCT recipients who are non-white and non-Hispanic. We did not collect data regarding use of medication or behavioral therapy for sleep disruption; thus, it is unknown the extent to which patients were receiving care for their sleep disruption and whether the care was effective. Additionally, the

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data came from a randomized trial of a stress management and exercise intervention. Consistent with previous secondary analyses of this dataset (36, 37), study arms were collapsed in the current analyses because no effects of the intervention were found on study outcomes, including sleep (21). Nevertheless, results may not generalize to HCT recipients who are unable or unwilling to participate in such a study.

In summary, the current paper suggests that a significant proportion of patients experience sleep disruption prior to transplant and through the first six months after transplant. Intervention should be considered for patients reporting clinically-significant sleep disruption at baseline, as these patients tend to experience transient or no improvement in sleep over time. The National Comprehensive Cancer Network (NCCN) Survivorship guidelines recommend screening for sleep disruption at regular intervals (38). Following evaluation and treatment of contributing factors (e.g., comorbidities, medications, pain), NCCN guidelines recommend sleep hygiene education, cognitive-behavioral therapy for insomnia (CBT-I), and pharmacologic management for insomnia (38). Although there is high-quality evidence demonstrating the efficacy of these interventions in cancer patients not treated with HCT, to date we are unaware of studies evaluating their efficacy in HCT recipients. Randomized trials of interventions for sleep disruption in HCT recipients are critical. Results from our study suggest that distress and pain should also be managed, as they may contribute to sleep disruption. In the meantime, strategies to manage sleep should be adapted from current evidence in cancer patients and individuals without cancer (5).

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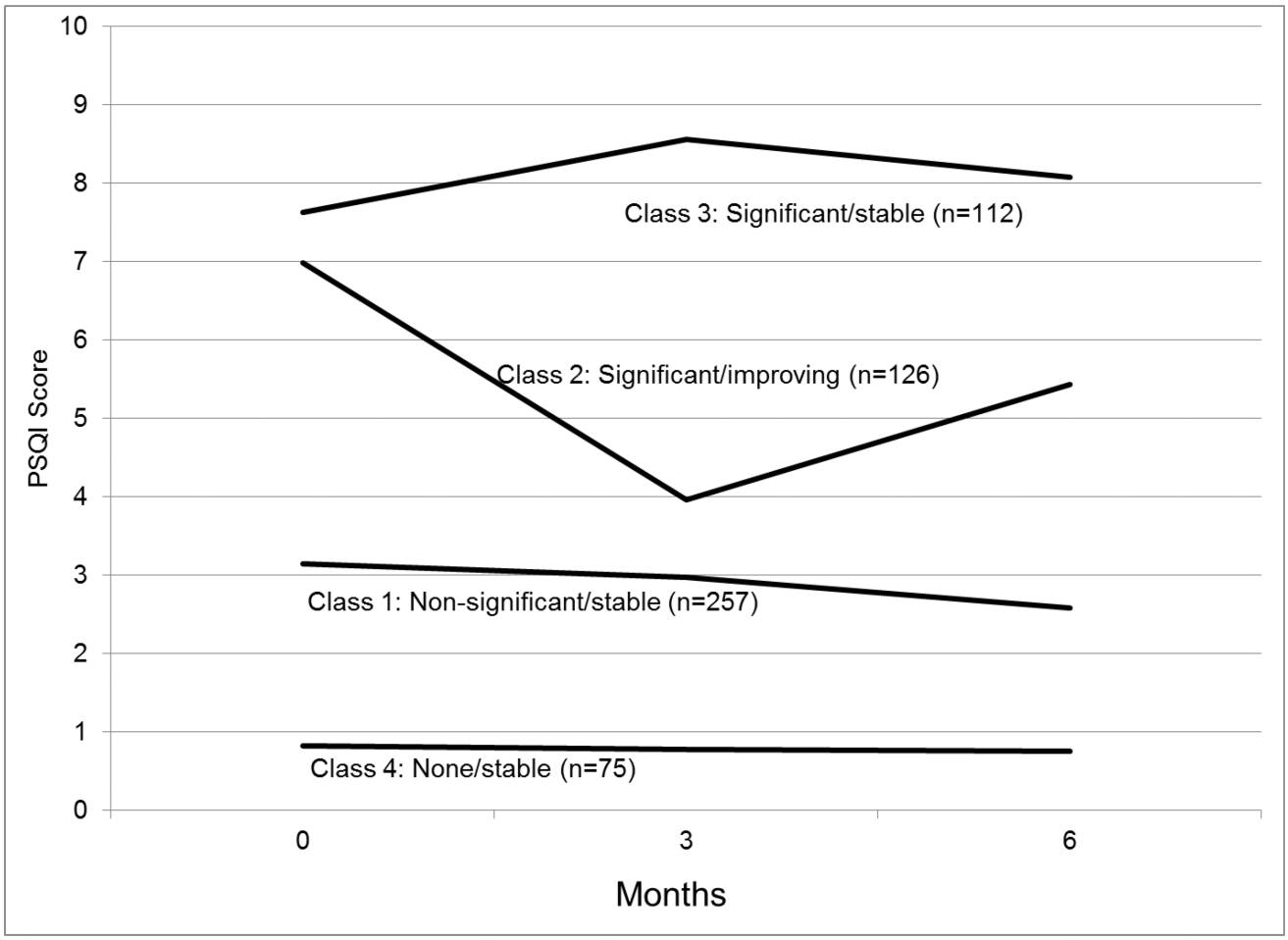

Figure 1.
Trajectories of Sleep Disruption in the First Six Months after Transplant.

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Table 1

Sociodemographic and Clinical Characteristics of the Sample (n=570).

Gender: n (%) female	241 (42)
Age: mean (SD)	54.85 (12.43)
Ethnicity: n (%) non-Hispanic	520 (91)
Race: n (%) White	490 (86)
Education	460 (70)
High school graduate or less	108 (19)
College graduate or some college	342 (60)
Postgraduate	118 (21)
Missing	2 (0)
Marital status: n (%) married/partnered	422 (74)
Annual household income: n (%) ≥ $75,000	252 (44)
Diagnosis	
Aplastic anemia	5 (1)
Acute leukemia	131 (23)
Chronic leukemia	9 (2)
Hodgkin's lymphoma	38 (7)
Myelodysplastic syndrome	46 (8)
Myeloma	169 (30)
Non-Hodgkin's lymphoma	147 (26)
Solid tumor	1 (<1)
Other	24 (4)
Transplant type	
Autologous	307 (54)
Allogeneic – myeloablative	136 (24)
Allogeneic – non-myeloablative	127 (22)
Baseline Karnofsky score	
100	104 (18)
90	228 (40)
80	133 (24)
≤70	92 (16)
Missing	13 (2)
Number of comorbidities: mean (SD)	1.76 (1.75)