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Rates and Risk Factors for Post-Traumatic Stress Disorder Symptomatology among Adult Hematopoietic Cell Transplant Recipients and Their Informal Caregivers

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Hematopoietic cell transplant (HCT) can cause significant distress in patients and their informal caregivers. Despite advances in reduced-intensity conditioning and supportive care, few recent studies have reported rates of clinically significant post-traumatic stress disorder (PTSD) symptomatology. Goals of the current study were to examine rates of PTSD and distress in patients and caregivers and to identify sociodemographic and clinical risk factors for PTSD. As part of an annual survivorship survey, 2157 HCT recipients and their caregivers were mailed self-report measures of PTSD and distress. Patients also completed self-report measures of sociodemographic information (eg, age, sex, employment status). Clinical variables (eg, time since transplant, transplant type) were captured in the transplant database. A total of 691 recipients (56% age 60 or above at the time of survey, 47% women, median 10.1 years post-HCT) and 333 caregivers provided PTSD data and were included in the current analyses. More caregivers reported PTSD (6.6%) than patients (3.3%; $P = .02$). Patients or caregivers who had PTSD reported significantly higher distress related to uncertainty, family strain, medical demands, finances, identity, and health burden ($P < .0001$) compared with those without PTSD. Patient but not caregiver PTSD was associated with more recent transplant ($P = .01$ and $P = .16$, respectively). Rates of PTSD are relatively low in long-term survivors of HCT and their caregivers. Nevertheless, results are consistent with other studies of cancer caregiving suggesting that caregivers often experience greater distress than patients. Timely referral to psychosocial services should be offered to both HCT recipients and caregivers reporting symptoms of PTSD.

INTRODUCTION

Hematopoietic cell transplant (HCT) is known to engender significant psychological distress in patients and their informal family caregivers due to the threat of mortality as well as short- and long-term side effects of treatment. HCT can be considered a traumatic event, which is defined as exposure to "death, threatened death, or actual or threatened serious injury" and can encompass "a sudden, catastrophic event" due to a medical incident according to the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [1,2]. The presence of a traumatic event, together with symptoms of re-experiencing (eg, intrusive thoughts, nightmares), avoidance of thoughts and reminders of the event, negative affect, and hyperarousal (eg, irritability, hypervigilance) are indicative of a post-traumatic stress disorder (PTSD) diagnosis if they occur for at least a month and are associated with impairment in daily functioning. Consistent with these criteria, HCT has the potential to lead to a PTSD diagnosis in patients and their informal family caregivers.

PTSD symptoms are commonly reported by adult HCT recipients. For example, El-Jawahri et al. [3] recently found that 6 months after allogeneic or autologous HCT, 39% of recipients reported moderate to severe re-experiencing, 33% moderate to severe avoidance, and 48% moderate to severe hyperarousal. These estimates of PTSD symptomatology are consistent with other studies in HCT recipients [4]. A smaller yet meaningful number of patients (ie, 5% to 28%) meet criteria for clinically significant PTSD symptomatology [3-8]. Interestingly, rates of PTSD appear to be relatively consistent

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independent of time since transplant, suggesting that PTSD may be chronic in some patients [4-7,9,,10]. Estimates of PTSD in HCT recipients have also remained relatively constant since the first studies conducted in the late 1990s, despite advances in transplant and supportive care [8]. Risk factors for PTSD have included longer length of hospital stay, pain, distress, more negative appraisals of the transplant, and lack of social support [4,11-13]. Data are mixed regarding associations with age, gender, marital status, transplant type, and history of acute graft-versus-host disease (GVHD) [3,,4,,6,,7]. The presence of comorbidities and disease relapse have not been found to be associated with PTSD [3]. Nevertheless, previous studies have tended to be relatively small, limiting statistical power to detect associations, and conducted relatively soon after transplant.

Although several studies have examined PTSD symptomatology among adult HCT recipients, few have focused on their informal caregivers [14]. Limited research on caregivers is surprising in light of a previous study reporting that during the peritransplant period 91% of caregivers reported cancer-related distress [15]. Spousal caregivers of HCT patients report less social support, greater marital dissatisfaction, greater loneliness, and less spiritual well-being than their peers [16]. In qualitative interviews of HCT recipients and their spouses, spouses were more likely than patients to report negative life changes as the result of transplant [17]. These findings are consistent with studies of advanced cancer patients suggesting that depression and anxiety are often greater in caregivers than in the patients themselves [18-21]. There is more information about parent caregivers of children undergoing HCT or solid organ transplantation; in 1 such study 14% of caregivers and 15% of children self-reported PTSD [22].

The goal of the current study was to examine rates and risk factors for PTSD in a large sample of adult HCT recipients and their informal caregivers surveyed through the annual Fred Hutchinson Cancer Research Center HCT survivorship survey. We also evaluated comorbidity burden association with PTSD. We hypothesized that younger age, allogeneic HCT, longer hospital stay, presence of acute or chronic GVHD (among allogeneic recipients), and patient distress would be associated with clinically significant patient and caregiver PTSD symptomatology. We also hypothesized that caregivers of patients with PTSD would be more likely to report PTSD than the patients themselves.

METHODS

Participants

Patients treated with HCT at the Fred Hutchinson Cancer Research Center are mailed an annual survivorship survey to evaluate their self-reported health status. After approval by the Fred Hutchinson Cancer Research Center Institutional Review Board, measures of PTSD symptomatology and distress were included in surveys mailed between July 1, 2016 and December 31, 2016 to all consenting survivors who were at least 18 years of age, transplanted in the second half of their respective years, and at least 6 months after transplant. Surveys were mailed once with a self-addressed stamped return envelope. Patients who did not return their completed surveys within 1 month were sent a reminder letter. Included with the first patient mailing was a separate survey for caregivers with a stamped self-addressed envelope and instructions to give the survey to the person who was their caregiver during transplant. Thus, caregiver surveys were distributed by patients but were completed and returned independently of the patient surveys. Patient and caregiver surveys were linked by patient identification. Completed surveys were accepted through June 30, 2017.

Measures

The PTSD Checklist for the DSM-5 (PCL-5) [23] was used to assess PTSD symptomatology in the past month in patients and caregivers. The measure was administered without Criterion A (ie, evaluation of stressful life events) and was keyed to stem cell transplantation. Items correspond to the criteria required for a DSM-5 diagnosis of PTSD. Items are evaluated on a 5-point Likert scale (0 = not at all, 4 = extremely), and responses are summed to produce a total score. Ratings of "moderately" or worse (≥2) on at least 1 intrusion symptom, 3 avoidance symptoms, and 2 arousal symptoms were considered to be diagnostic of PTSD.

Cancer-related distress was assessed in patients and caregivers with the Cancer and Treatment Distress (CTXD) scale [24]. The CTXD 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 (0 = none, 3 = severe). A mean score is obtained by averaging the 22 items; higher scores indicate more severe distress. The CTXD has demonstrated validity and internal consistency in HCT recipients [25].

Data were not collected regarding caregiver characteristics such as age, sex, and relationship with the patient. However, patient and caregiver self-reports were paired with a linked identifier. The patient survey collected self-reported information about comorbidities, work/school status, and treatment for PTSD, anxiety, depression, and sleep disorders.

Statistical Analyses

Patient characteristics of responders and nonresponders were compared using chi-square tests. Rates of clinically significant PTSD symptomatology were compared between patients and caregivers using the McNemar test in the subset of cases where both patient and caregiver responses were available. Univariate associations of PTSD with sociodemographic, clinical, and distress variables in patients and caregivers were examined using 2-sample *t*-tests for continuous factors and chi-squared tests for categorical factors. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Surveys were mailed to 2157 patients. A total of 691 patients (32%) and 333 caregivers (15%) (with 274 patient–caregiver pairs) had evaluable PCL-5 scores and were included in the current analyses (Table 1). Most patients who responded were men (53%), over age 60 at the time of the survey (56%), at least 5 years from HCT (71%), and had received allogeneic HCT (67%). Most caregivers who responded were caring for male patients (56%), under age 60 at the time of the survey (53%), less than 5 years from HCT (51%), and had received allogeneic HCT (65%). The median time since HCT was 10.1 years (interquartile range, 4.0 to 19.1) for patients and 7.0 years (interquartile range, 3.0 to 14.1) for caregivers. Caregivers (22/333; 6.6%; 95% confidence interval, 3.9% to 9.3%) had a significantly higher rate of PTSD than patients (23/691; 3.3%; 95% confidence interval, 2.0% to 4.7%; $P = .02$). As shown in Table 2, clinically significant PTSD was observed in 21 of 274 patient–caregiver pairs. Caregivers with PTSD were more likely to be caring for a patient with PTSD ($P = .004$).

Patient sociodemographic and clinical risk factors for PTSD are shown in Table 3. Shorter time since transplant was associated with greater likelihood of reporting PTSD in both patients ($P = .01$) and caregivers ($P = .05$). There was no significant correlation between PTSD and other factors analyzed, including age at survey, sex, type of transplant, type of disease, graft source, conditioning, acute or chronic GVHD, relapse, and inpatient days within the first 100 days. Data were not available regarding hospital days spent in the intensive care unit.

Differences in cancer-related distress for patients and caregivers with and without PTSD are shown in Table 4. Distress due to uncertainty, family strain, medical demands, finances, identity, and health burden was significantly higher among patients with PTSD versus those without ($P < .0001$); similar differences were seen among caregivers with PTSD versus those without ($P < .0001$).

Table 5 shows the correlation of patient self-reported health with PTSD. Patients with PTSD were more likely to be disabled or unable to work, have had treatment for PTSD, and to be taking medications for anxiety, depression, and sleep.

Table 1
Patient Characteristics of Respondents and Nonrespondents

	Patients			Caregivers		
	Respondents (n = 691)	Nonrespondents (n = 1466)	*P*	Respondents (n = 333)	Nonrespondents (n = 1824)	*P*
Patient age at survey						
<60 yr	302 (44)	934 (64)	<.0001	176 (53)	1326 (73)	<.0001
≥60 yr	389 (56)	532 (36)		157 (47)	498 (27)	
Patient sex						
Female	322 (47)	642 (44)	.22	146 (44)	818 (45)	.74
Male	369 (53)	824 (56)		187 (56)	1006 (55)	
Patient age at HCT						
<18 yr	30 (4)	217 (15)	<.0001	10 (3)	237 (13)	<.0001
≥18 yr	661 (96)	1249 (85)		323 (97)	1587 (87)	
Time since HCT*						
≤5 yr	203 (29)	407 (28)	.44	171 (51)	801 (44)	.01
>5 yr	488 (71)	1059 (72)		162 (49)	1023 (56)	
Type of transplant						
Autologous	230 (33)	463 (32)	.19	118 (35)	575 (32)	.009
Related allogeneic	253 (37)	596 (41)		106 (32)	743 (41)	
Unrelated allogeneic	208 (30)	407 (28)		109 (33)	506 (28)	
Disease						
Acute myeloid leukemia	133 (19)	273 (19)	.0001	66 (20)	340 (19)	<.0001
Chronic myeloid leukemia	112 (16)	254 (17)		35 (11)	331 (18)	
Myelodysplastic syndrome	93 (13)	127 (9)		47 (14)	173 (9)	
Multiple myeloma	109 (16)	173 (12)		67 (20)	215 (12)	
Lymphoma	132 (19)	315 (21)		72 (22)	375 (21)	
All others	112 (16)	324 (22)		46 (14)	390 (21)	
Graft source						
Bone marrow	220 (32)	597 (41)	<.0001	72 (22)	745 (41)	<.0001
Peripheral blood stem cells	457 (66)	827 (56)		252 (76)	1032 (57)	
Cord blood	14 (2)	42 (3)		9 (3)	47 (3)	
Conditioning						
Myeloablative	594 (86)	1332 (91)	.0006	270 (81)	1656 (91)	<.0001
Nonmyeloablative	97 (14)	134 (9)		63 (19)	168 (9)	
Acute GVHD (allogeneic only)						
0-1	174 (38)	360 (37)	.17	75 (35)	459 (37)	.40
2	244 (53)	509 (52)		120 (56)	633 (52)	
3	39 (9)	117 (12)		19 (9)	137 (11)	
Chronic GVHD* (allogeneic only)						
Never	169 (37)	433 (43)	.0008	67 (31)	535 (43)	.0002
≤5 yr ago	92 (20)	128 (13)		76 (35)	289 (23)	
>5 yr ago	200 (43)	442 (44)		72 (33)	425 (34)	
Relapse*						
Never	641 (93)	1323 (90)	.14	309 (93)	1655 (91)	.34
≤5 yr ago	16 (2)	52 (4)		14 (4)	82 (5)	
>5 yr ago	34 (5)	91 (6)		10 (3)	87 (5)	
Inpatient days						
≤35 d	523 (78)	952 (67)	<.0001	274 (84)	1201 (68)	<.0001
>35 d	151 (22)	474 (33)		52 (16)	573 (32)	

Values are n (%).
*Based on date returned for respondents and date sent for nonrespondents.

DISCUSSION

The current study investigated rates of clinically significant PTSD symptomatology among HCT recipients and their caregivers. Notably, caregivers were more likely to report PTSD than patients. Notably, most caregivers with PTSD were not caring for a patient who reported PTSD. These data are striking yet consistent with previous studies of cancer patients not treated with HCT, suggesting that distress is often higher among caregivers than patients [18-21]. Taken together with previous research, our data suggest that screening and treatment of PTSD in caregivers should be given equal consideration to that in patients. It would also be noteworthy to examine the barriers to mental health service use among caregivers to maximize the resources available to mitigate distress. Many symptoms of PTSD are treatable and can be improved through therapeutic support care measures; a randomized study showed that cognitive-behavioral therapy, delivered over the phone, can decrease the symptoms of PTSD in HCT patients [26]. However, further research is necessary to identify the most effective intervention methods for caregivers.

Table 2
Patient–Caregiver Pairs with Definable PTSD (n = 274)

Patient PTSD	Caregiver PTSD	
	No	Yes
No	253	16
Yes	3	2

P = .004 by the McNemar test.

The prevalence of PTSD among HCT patients (3.3%) was lower in the current study compared with that reported in prior studies (10% to 28.4%) [3,,4,,22,,27]. Similarly, 7.1% of caregivers reported PTSD, consistent with that of other illness populations [28,,29]. In regards to risk factors, a significant correlation was found between PTSD and shorter time since HCT among both patients and caregivers, in contrast to some previous studies that have found stable or worsening PTSD symptomatology over time [4-7,9,,10,,14]. Both patients and caregivers reported

Table 3
Risk Factors for PTSD among Survey Respondents*

	Patient (n = 691)			Caregiver(n = 333)		
	N	PTSD (%)	*P*	N	PTSD (%)	*P*
Patient age at survey						
<60 yr	302	14 (4.6)	0.09	142	12 (8.5)	0.24
≥60 yr	389	9 (2.3)		191	10 (5.2)	
Patient age at HCT						
<18 yr	30	1 (3)		10	20 (6.2)	0.08
≥18 yr	661	22 (3)		323	2 (20.0)	
Patient sex						
Female	322	9 (2.8)	0.47	146	9 (6.2)	0.77
Male	369	14 (3.8)		187	13 (7.0)	
Time since HCT†						
≤5 yr	203	12 (5.9)	0.01	134	12 (9.0)	0.16
>5 yr	488	11 (2.3)		199	10 (5.0)	
Type of transplant						
Autologous	230	8 (3.5)	0.98	118	4 (3.4)	0.13
Related allogeneic	253	8 (3.2)		106	7 (6.6)	
Unrelated allogeneic	208	7 (3.4)		109	11 (10.1)	
Disease						
Acute myeloid leukemia	133	8 (6.0)	0.14	66	5 (7.6)	0.67
Chronic myeloid leukemia	112	0		35	3 (8.6)	
Myelodysplastic syndrome	93	3 (3.2)		47	5 (10.6)	
Multiple myeloma	109	5 (4.6)		67	4 (6.0)	
Lymphoma	132	5 (3.8)		72	4 (5.6)	
All others	112	2 (1.8)		46	1 (2.2)	
Graft source						
Bone marrow	220	4 (1.8)	0.26	72	5 (6.9)	0.72
Peripheral blood stem cells	457	18 (3.9)		252	17 (6.8)	
Cord blood	14	1 (7.1)		9	0	
Conditioning						
Myeloablative	594	20 (3.4)	0.89	270	15 (5.6)	0.11
Non-myeloablative	97	3 (3.1)		63	7 (11.1)	
Acute GVHD (allogeneic only)						
0-1	179	4 (2.2)	0.34	75	5 (6.7)	0.50
2-4	285	11 (3.9)		139	13 (9.4)	
Chronic GVHD† (allogeneic only)						
Never	169	5 (3.0)	0.80	67	9 (13.4)	0.14
≤5 yr ago	92	4 (4.4)		59	5 (8.5)	
>5 yr ago	200	6 (3.0)		89	4 (4.5)	
Relapse†						
Never	641	23 (3.6)	0.40	309	18 (5.8)	0.10
≤5 yr ago	16	0		10	2 (20.0)	
>5 yr ago	34	0		14	2 (14.3)	
Inpatient days‡						
≤35 d	523	20 (3.8)	0.27	274	18 (6.6)	0.77
>35 d	151	3 (2.0)		52	4 (7.7)	

Values are n (%).
* All factors defined by patient *except* "time since" factors.
† Based on date returned for respondents and date sent for nonrespondents.
‡ Divided on 75th percentile.

higher proportions of PTSD (5.9% and 10.2% versus 2.3% and 4.8%, respectively) when within 5 or less years of their transplant compared with a longer duration; the current study may have been able to detect this association because of the wide range of time since transplant compared with other studies. Thus, the lower rate of PTSD in our population may be due to a longer time since transplant compared with previous studies or due to use of different PCL-5 scoring definitions for PTSD [13]. Nevertheless, mixed findings on rates of PTSD over time indicate that screening should occur in all survivors and caregivers regardless of time since HCT. The addition of PTSD screening to survivorship care plans should be considered.

Table 4
Cancer-Related Distress among Survey Participants with and without PTSD*

	Patient		Caregiver	
	No PTSD (n = 668) Mean (SD)	PTSD (n = 23) Means (SD)	No PTSD (n = 256) Mean (SD)	PTSD (n = 18) Mean (SD)
Uncertainty	.66 (.60)	2.22 (.60)	.84 (.66)	1.88 (.68)
Family strain	.51 (.66)	1.74 (.88)	.44 (.52)	1.48 (.70)
Medical demands	.37 (.55)	1.62 (.79)	.42 (.57)	1.18 (.75)
Finances	.47 (.65)	1.61 (.84)	.55 (.69)	1.38 (.84)
Identity	.47 (.57)	1.56 (.80)	.40 (.53)	1.46 (.77)
Health burden	.96 (.85)	2.35 (.67)	.77 (.76)	2.12 (.72)

* All comparisons between No PTSD versus PTSD significant at $P < .0001$ (2-sample *t*-test).

Interestingly, the remaining demographic and medical risk factors (ie, age at survey, sex, type of transplant, type of disease, graft source, conditioning, acute versus chronic GVHD, inpatient days, relapse) were not significant correlates. Because of our large sample size, an absence of significant associations is not due to lack of statistical power. These findings did not align with our hypotheses [4,13] and suggests that it may be difficult to predict patients and caregivers at higher risk for PTSD. Instead, all patients and accompanying caregivers could be easily screened for PTSD symptoms and referred if necessary. Brief screening tools are available that are appropriate for both patients and caregivers [30].

It is important to note that all the CTXD subscales (uncertainty, family strain, medical demands, finances, identity, health burden) [25] were significantly correlated with PTSD. These findings are consistent with those of Kuba et al. [13], indicating that distress is evident in multiple domains and that CTXD subscales may be sensitive to the presence of PTSD in both patients and caregivers. Patients with PTSD were also more likely to be taking medications for anxiety, depression, and sleep, suggesting clinical recognition of some symptoms related to PTSD but perhaps not the syndrome itself.

Despite these novel findings, it is important to address limitations. This was a cross-sectional study of primarily long-term HCT survivors and did not examine the

Table 5
Correlation of PTSD with Selected Patient-Reported Responses

	Patient		
	No PTSD (n = 666)	PTSD (n = 23)	*P*
Work school status*			
Working or in school full or part time, homemaker, unemployed but looking for work	389 (58)	10 (43)	.15
Disabled, on medical leave, unemployed and not looking for work, retired because of health	187 (28)	14 (61)	.0007
Retired, for reasons not related to health	197 (30)	2 (9)	.03
No. of comorbidities			
0	491 (74)	15 (65)	.15
1	128 (19)	4 (17)	
2+	45 (7)	4 (17)	
Ever treated for PTSD			
No	621 (96)	16 (76)	<.0001
Yes	24 (4)	5 (24)	
Current medication for			
Anxiety	108 (16)	8 (35)	.02
Depression	100 (15)	8 (35)	.01
Sleep	144 (22)	13 (57)	.0001

* Patients could respond in more than 1 category.

prevalence of PTSD and risk factors over time. In addition, only 32% of eligible patients completed the PTSD questions. Fewer caregivers (16%) responded, although this may reflect the possibility that some caregivers no longer identified with that role years after the transplant, had died, were no longer associated with the patient, or were not given the survey by the patients. The low patient and caregiver participation rate may have biased results. Patients and caregivers with high levels of distress may have been less likely to respond, leading to underestimates of PTSD. Conversely, perhaps highly distressed patients and caregivers may have been more likely to complete the survey because it asked questions relevant to their experience. We did not collect sociodemographic information about caregivers, which limits our ability to describe caregiver risk factors for PTSD. Also, all patients were all drawn from a single transplant center. Thus, our findings may not be generalizable to populations in other geographic areas or transplant centers with different clinical practices.

Despite limitations, the current study offers valuable information about the prevalence of PTSD and associated distress among both patients and caregivers of patients after undergoing HCT. Although rates of PTSD are relatively low, both patient and caregiver distress should be evaluated regardless of time since transplant. We have previously demonstrated the feasibility of screening for distress in HCT recipients [5].

In light of the high associations between PTSD and distress reported in this study, high levels of distress should trigger an evaluation of possible PTSD. It is especially important for transplant centers to offer caregivers with PTSD lists of resources in the community. Transplant centers may consider dedicated classes and support groups for caregivers, if they do not already offer those services. Caregiver respite services or periodic rotation of caregivers could also be considered for those who are deemed at high risk of PTSD or who seem to be overwhelmed. The increasing use of telehealth in mental healthcare may increase the likelihood that caregivers will seek help, particularly those who live in rural areas or are reluctant to leave the patient. A randomized study showed that cognitive-behavioral therapy, delivered over the phone, can decrease the symptoms of PTSD in patients who were 1 to 3 years post-HCT [26]. One multicenter study of survivors 1 to 3 years post-HCT found that 50% of survivors with PTSD received mental health treatment [31], which is higher than the 24% we observed. Given the high burden of symptoms and associated quality of life deficits, attention to PTSD symptomatology and appropriate treatment may help survivors and caregivers to manage a different but equally devastating form of ongoing damage from the transplant procedures.

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