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Coping strategies modify risk of depression associated with hematopoietic cell transplant symptomatology

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Abstract

To determine whether coping strategies modify the risk of depression among allogeneic recipients experiencing post-transplant-related symptomatology, 105 participants (mean age = 52 years, 42% female) completed questionnaires 90 days post-transplant. A total of 28 percent reported depressive symptoms. Univariate correlations indicated that depression was associated with greater transplant-related symptomatology and avoidance, acceptance/resignation, and emotional discharge coping. Depression was negatively associated with problem-solving coping. Moderator analyses indicated that transplant-related symptomatology was significantly associated with depression among patients who frequently used maladaptive coping and rarely used adaptive coping. These data suggest that transplant-related symptomatology, combined with maladaptive coping, place patients at risk of depression.

Keywords

cancer; coping; depression; hematopoietic stem cell transplantation; oncology

Allogeneic hematopoietic cell transplantation (HCT) improves long-term survival rates among patients diagnosed with malignant hematologic diseases (Pasquini and Wang, 2011). Allogeneic HCT is increasingly performed worldwide, resulting in a large number of survivors for whom HCT-related morbidities are an important outcome. Morbidities among HCT recipients are common due to high-dose chemotherapy, opportunistic infections, and acute and chronic graft-versus-host disease (GVHD). Morbidities can affect multiple organs and be life-threatening; the cardiovascular, gastrointestinal, musculoskeletal, and auditory or visual systems are particularly vulnerable (Sun et al., 2013). Consequently, patients often report a high degree of HCT-related symptomatology which is associated with reduced quality of life (Bevans et al., 2008; Cohen et al., 2012) and worse mental health (Bevans et

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al., 2008). For example, 12–29 percent of HCT recipients report posttraumatic stress disorder (El-Jawahri et al., 2015b; Hefner et al., 2014), 13–20 percent anxiety (El-Jawahri et al., 2015a; Pillay et al., 2015), and 6–44 percent depression (Artherholt et al., 2014; El-Jawahri et al., 2015a, 2015b; Pillay et al., 2015).

Depression is a cause for concern among HCT recipients due to its association with adverse health outcomes. For example, pre-transplant depression prospectively predicted slower white blood cell recovery in the first 3 weeks after transplant (McGregor et al., 2012), while post-transplant depression has been found to be associated with non-adherence to treatment (Mumby et al., 2011), increased hospital length of stay (Prieto et al., 2002), and greater mortality (Loberiza et al., 2002; Prieto et al., 2002). Moreover, HCT recipients with depression are 13 times more likely to report suicidal ideation as recipients without depression (Sun et al., 2013).

An important question is the extent to which risk of depression is modifiable among HCT recipients, such as through adaptive patient coping. Coping can be defined as dynamic cognitive and behavioral efforts to manage stress (Lazarus and Folkman, 1984). Coping strategies can be broadly conceptualized as adaptive (e.g. engaging with the problem in a constructive manner) or maladaptive (e.g. evading the problem or blaming others) (Moos, 1993; Wenzel et al., 2002). To our knowledge, only three studies have examined coping and depression in HCT recipients. They suggest that prior to HCT, problem solving was associated with less depression, while acceptance/resignation and avoidant coping were associated with greater depression (Fife et al., 2000; Rodrigue et al., 1993; Wells et al., 2009). However, coping was not associated with depression at 2 weeks or at 6-months post-HCT (Fife et al., 2000; Wells et al., 2009). All three studies included both allogeneic and autologous HCT recipients; thus, differences in recovery post-HCT based on transplant type (e.g. GVHD) may have obscured relationships between coping and depression. In summary, existing data suggest that HCT recipients who cope with maladaptive coping strategies rather than adaptive coping strategies may be at higher risk for depression; however, the degree to which these relationships persist beyond the pre-HCT period remains to be clarified.

The goal of this study was to examine the relationship between HCT-related symptomatology, coping, and depression in a sample of allogeneic HCT recipients. Moreover, we sought to examine the extent to which coping modifies risk of depression associated with HCT-related symptom severity. Significant results would suggest that depression risk may be mutable among patients experiencing HCT-related symptoms, perhaps via intervention to improve coping skills. We hypothesized that (1) severity of HCT-related symptomatology would be significantly associated with depression, (2) adaptive coping strategies would be associated with less depression and maladaptive coping would be associated with more depression, and (3) risk of depression associated with HCT-related symptom severity would be greatest in patients who exhibited poor coping.

Methods

Participants

Participants were recruited as part of a larger study of quality of life in allogeneic HCT recipients. Eligible patients were at least 18 years old, were diagnosed with hematologic cancer, were scheduled to receive allogeneic HCT with peripheral blood stem cells at Moffitt Cancer Center, had no history of cerebrovascular accident or head trauma with loss of consciousness, had completed 6 or more years of formal education, were able to speak and read standard English, and signed the written informed consent. The study was approved by the University of South Florida Institutional Review Board.

Procedures

Potential participants were identified using clinical information systems in consultation with the attending physician. Participants were approached at an outpatient visit approximately 1 month prior to transplant. Eligible patients who wished to participate signed informed consent prior to participation and completed baseline demographic information at this time. Participants were contacted again 90 days after transplant to complete follow-up questionnaires regarding HCT-related symptomatology, depression, and coping. Participants for the current analyses were recruited between December 2010 and January 2013. At the time the analyses were conducted, 217 patients were approached, 34 refused (e.g. not interested, overwhelmed or no reason given), 183 signed consent, and 105 had data at baseline and 90 days post-HCT.

Measures

Demographic and clinical data—Self-reported sociodemographic characteristics were assessed prior to transplant (i.e. age, gender, race, ethnicity, marital status, education, and annual household income). A medical record review was performed at study entry in order to obtain clinical information (i.e. cancer type and date of HCT).

HCT-related symptomatology—The 30-item HCT Symptom Scale (Lee et al., 2002) assesses self-reported severity of HCT symptomatology across multiple organ systems in the previous month. Items are evaluated on a five-point Likert scale, (0 = not at all, 4 = extremely), with higher scores indicating more severe symptoms. The scale yields a total score and subscales for seven categories of symptomatology: skin, eyes and mouth, lung, digestive, muscles and joints, energy, and psychological symptoms. A modified version of the total summary score was used in the current analyses; this version did not include the psychological symptoms subscale to avoid inflated relationships with coping and depression. The scale has excellent reliability and validity (Lee et al., 2002).

Coping—Coping was assessed using the 48-item Coping Response Inventory (CRI) (Moos, 1993). Items are assessed on a four-point Likert scale (0 = not at all, 3 = fairly often). The scale yields eight subscales: Logical Analysis, Positive Reappraisal, Seeking Guidance, Problem Solving, Cognitive Avoidance, Acceptance/Resignation, Seeking Alternative Rewards, and Emotional Discharge. Subscale scores range from 0 to 18 with higher scores indicating more frequent use of the strategy. The CRI has demonstrated reliability and

validity (Moos, 1993) and has previously been used in HCT recipients (Jacobsen et al., 2002; Wells et al., 2009).

Depression—Depression was assessed using the 20-item Center for Epidemiological Studies—Depression Scale (CES-D) (Radloff, 1977). Items assess the frequency of depressive symptoms in the past week according to a four-point scale (0 = rarely or none of the time, 3 = most or all of the time). A total score is obtained by summing item responses. Scores range from 0 to 60 with higher scores indicating greater depressive symptomatology. A score of 16 or higher indicates clinically significant depressive symptomatology (Radloff, 1977). The CES-D is commonly used for assessing depression in patients with cancer due to the absence of items related to cancer-related physical symptoms that could overlap with depression (e.g. weight loss, appetite, fatigue, and health concerns) (Andrykowski, 1994). The CES-D has high internal consistency (Radloff, 1977) and validity in cancer populations (Hann et al., 1999).

Statistical analyses

Means and frequencies were calculated to describe sample sociodemographic and clinical characteristics. Spearman's correlations were performed to assess the magnitude of univariate relationships among depression, HCT-related symptomatology, and coping strategies. Linear regression analyses were conducted to examine the relationship between HCT-related symptomatology and depressive symptomatology. Because younger age and female gender have been found to be risk factors for depression in HCT recipients (Kuehner, 2003), these variables were identified *a priori* as covariates to be included in multivariate analyses. Analyses examining coping strategies as moderators of the relationship between HCT-related symptomatology and depression were conducted using bootstrapping (Hayes and Matthes, 2009). Interactions significant at $p < .05$ were decomposed using the Johnson–Neyman technique to plot changes in beta weights regressing depression on HCT-related symptomatology at various levels of the coping strategy examined.

Results

A total of 105 participants contributed data to the current analyses. Sample demographic and clinical descriptives are reported in Table 1. At 90 days post-HCT, 30 (28%) patients met criteria for clinically significant depressive symptoms. Self-reported HCT symptomatology at this time was widespread. A total of 88 (83%) patients reported symptoms of the skin, 73 (71%) eye or mouth symptoms, 65 (62%) pulmonary symptoms, 43 (41%) digestive symptoms, 86 (82%) muscle and joint symptoms, and 91 (87%) reported reduced energy.

Frequency of coping strategy use and correlations between coping, HCT-related symptomatology, and depression are shown in Table 2. Problem-solving coping was associated with significantly less depressive symptomatology ($p = .04$), while avoidance, acceptance/resignation, and emotional discharge were associated with greater depressive symptomatology (p values $< .002$). HCT-related symptomatology was not associated with any coping strategy (p s $> .13$) but was significantly associated with depressive symptomatology ($p < .0001$). The relationship between HCT-related symptomatology and

depressive symptomatology remained significant in regression analyses controlling for age and gender (see Table 3).

Moderation analyses indicated that coping significantly modified the risk of depression associated with HCT-related symptomatology (see Table 4). Specifically, the relationship between HCT-related symptomatology and depression was stronger among patients who frequently used maladaptive coping strategies (i.e. cognitive avoidance and emotional discharge) and rarely used adaptive coping strategies (i.e. positive reappraisal and problem solving) (p values $< .05$). The relationship between HCT-related symptomatology and depression was not modified by patients' use of logical analysis, seeking guidance and support, acceptance or resignation, or seeking alternative rewards (p values $> .11$). Figure 1 shows the risk of depression associated with HCT-related symptomatology according to the use of the four coping strategies found significant in the moderation analyses.

Conclusion

This study examined relationships among self-reported HCT symptomatology, depressive symptoms, and coping strategies in hematologic cancer patients treated with allogeneic HCT. Hypotheses were largely confirmed. Greater depressive symptomatology was associated with greater HCT-related symptomatology, less use of problem-solving coping, and greater use of avoidance, acceptance/resignation, and emotional discharge coping. Coping moderated the risk of depression associated with HCT-related symptomatology such that patients with greater HCT-related symptomatology who used more maladaptive coping strategies (i.e. cognitive avoidance and emotional discharge) and less adaptive strategies (i.e. reappraisal and problem solving) were more likely to be depressed.

The significant relationship between HCT-related symptomatology and depressive symptomatology observed in this study is consistent with previous literature reporting that severity of HCT-related symptoms is a risk factor for depression (Lee et al., 2006; Mosher et al., 2011; Pidala et al., 2011; Syrjala et al., 2004). We observed significant relationships among post-HCT coping and depression, which has not been reported in previous studies (Rodrigue et al., 1993; Wells et al., 2009). In contrast to previous studies which analyzed data from mixed samples of autologous and allogeneic HCT recipients, this study focused exclusively on allogeneic HCT recipients. Greater homogeneity of our sample regarding treatment type may have enabled us to detect a signal that other studies missed. Interestingly, coping was not associated with HCT-related symptomatology, suggesting that patients do not cope with HCT-related symptoms in a consistent manner. This study adds significant new knowledge regarding coping as a moderator of the risk of depression associated with HCT-related symptomatology. Specifically, HCT recipients with good coping skills demonstrate psychological resilience even when experiencing greater HCT-related symptoms.

This study is characterized by several strengths, including a focus on allogeneic HCT recipients who face significant challenges post-transplant but for whom little about their coping is known. The study also used validated measures of coping, depression, and self-

reported HCT-related symptomatology. In addition, participants were assessed at a uniform time since transplant when many were experiencing HCT-related morbidities. Nevertheless, study limitations should also be noted. The cross-sectional design of the study does not allow for determination of directionality of findings. For example, it may be that depression alters patients' coping repertoire such that they cope less adaptively after onset of depression. However, studies in other cancer populations have demonstrated that maladaptive coping strategies often precede depressive symptoms (Hack and Degner, 2004; Kraemer et al., 2011). In addition, the study was performed at a single site in the United States and included a sample of mainly white, Caucasian, married, and well-educated participants. Both of these factors may limit the generalizability of findings.

In conclusion, results highlight the fact that patients with poor coping skills are more vulnerable to depression when faced with HCT-related symptomatology. These patients may benefit from proactive clinical care to reduce or prevent depression when experiencing HCT-related symptoms, such as antidepressant medication or referral to a mental health professional. Future studies should examine whether interventions to improve coping skills reduce risk of depression among patients who cope poorly with HCT-related symptoms. Previous research in breast cancer patients has demonstrated benefits of group psychological interventions aimed at helping patients cope with their illness and treatment side effects (Andersen et al., 2004, 2008; Antoni, 2013; Antoni et al., 2006; Carver et al., 2005). These benefits include decreased symptoms of depression and anxiety, less intrusive thoughts, less social disruption, greater positive emotions, and better quality of life. Moreover, benefits persisted up to 13 years after treatment (Carver et al., 2005). Only two studies have aimed to adapt such interventions to the unique needs of HCT survivors. DuHamel et al. (2010) developed a 10-week telephone-delivered psychological intervention to address posttraumatic stress and social support in patients who were 1 to 3 years post-HCT (DuHamel et al., 2010). Participants receiving this intervention reported significant improvement in posttraumatic stress symptoms, distress, and depression relative to controls (DuHamel et al., 2010). Syrjala et al. (2011) reported on the development of an Internet-delivered intervention to address survivorship care needs in HCT survivors who were 3 to 18 years post-HCT; a large clinical trial is currently underway (Syrjala et al., 2011). Therefore, additional studies are needed to adapt psychosocial interventions for HCT recipients. Such studies have the potential to significantly improve patient outcomes after HCT.

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Figure 1.

Associations between HCT-related symptomatology and depression at high, medium, and low levels of coping: (a) avoidance, (b) emotional discharge, (c) problem solving, and (d) positive reappraisal. As a guide to interpretation, relationships between HCT-related symptomatology and depression are shown for the 25 percent of the sample reporting the greatest use of the coping strategy (solid line, Xs), the 50 percent of the sample reporting moderate use of the symptom (short dashed line, Os), and the 25 percent of the sample reporting the least use of the coping strategy (long dashed line, diamonds). Beta weights and p values for the relationship between HCT-related symptomatology and depression within each group are provided in the legends.

Table 1Demographic and clinical characteristics of the sample ($n = 105$).

Age: mean, SD	51.85	12.90
Gender: n , % female	44	42
Ethnicity: n , % non-Hispanic	98	93
Race: n , % Caucasian	90	86
Marital status: n , % married	70	67
Education: n , % college graduate	44	42
Annual household income: n , % US\$ 40,000 or greater	56	53
Diagnosis: n , %		
AML	32	30
MDS	20	19
NHL	17	16
ALL	13	12
CLL	8	8
CML	7	7
MM	4	4
MPD	2	2
Other leukemia	2	2
Mean (SD) CES-D score	12.03	8.70
Mean (SD) HCT Symptom	15.40	10.89
Scale score ^a		

ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; CES-D: Center for Epidemiological Studies—Depression Scale CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; MM: multiple myeloma; MPD: myeloproliferative syndrome; NHL: non-Hodgkin lymphoma; SD: standard deviation;.

^aHCT Symptom Scale score calculated as a mean of all subscales except mental distress.

Frequency of use of coping strategies and correlations with HCT-related symptomatology and depression.

Table 2

Coping strategy	Definition (Moos, 1993)	Any use, <i>n</i> (%)	Use “sometimes” or “fairly often,” <i>n</i> (%)	Correlation: HCT-related symptomatology, <i>r</i>	Correlation: depression, <i>r</i>
Logical analysis	Cognitive attempts to prepare mentally for a stressor	102 (97)	26 (25)	0.09	0.11
Positive reappraisal	Cognitive attempts to construe and restructure a problem in a positive way while accepting the reality	103 (98)	63 (60)	0.00	-0.05
Seeking guidance and support	Behavioral attempts to seek information, guidance, and support	103 (98)	35 (33)	0.05	0.04
Problem solving	Behavioral attempts to take action to deal directly with the problem	104 (99)	54 (51)	-0.13	-0.20*
Cognitive avoidance	Cognitive attempts to avoid thinking realistically	99 (94)	14 (13)	0.08	0.37**
Acceptance/resignation	Cognitive attempts to react to the problem by resigning oneself to it	99 (94)	14 (13)	0.15	0.31**
Seeking alternative rewards	Behavioral attempts to get involved in substitute activities and create new sources of satisfaction	100 (95)	12 (11)	-0.03	-0.11
Emotional discharge	Behavioral attempts to reduce tension by expressing negative feelings	92 (88)	1 (1)	0.13	0.32**

* $p < .05$;

** $p < .01$.

Table 3

Linear regression analyses examining the effects of HCT-related symptomatology on depressive symptomatology controlling for age and gender.

	Statistics by predictor	
	<i>b</i>	<i>t</i>
Age	−0.26	−3.22**
Gender (female)	−0.01	−0.12
HCT-related symptomatology	0.51	6.25**

**
 $p < .01$.

Table 4

Results of analyses examining coping strategies as moderators of the relationship between HCT-related symptomatology and depression.

	Statistics by predictor	
	b	t
Moderator: logical analysis		
Age	-0.18	-3.39**
Gender (female)	-0.65	-0.45
HCT-related symptomatology	0.62	4.18***
Logical analysis	0.47	1.55
Interaction HCT-related symptomatology × logical analysis	-0.02	-1.61
Moderator: positive reappraisal		
Age	-0.19	-3.29**
Gender (female)	-0.52	-0.36
HCT-related symptomatology	0.74	4.25***
Positive reappraisal	0.45	1.53
Interaction HCT-related symptomatology × positive reappraisal	-0.03	-2.06*
Moderator: seeking guidance		
Age	-0.18	-3.34**
Gender (female)	-0.43	-0.29
HCT-related symptomatology	0.52	4.23***
Seeking guidance and support	0.26	0.84
Interaction HCT-related symptomatology × seeking guidance and support	-0.01	-1.13
Moderator: problem solving		
Age	-0.16	-2.92**
Gender (female)	-0.13	-0.09
HCT-related symptomatology	0.87	3.84***
Problem solving	0.27	0.79
Interaction HCT-related symptomatology × problem solving	-0.04	-2.18*
Moderator: cognitive avoidance		
Age	-0.12	-2.34*
Gender (female)	-0.95	-0.72
HCT-related symptomatology	0.02	0.10
Cognitive avoidance	-0.01	-0.03
Interaction HCT-related symptomatology × cognitive avoidance	0.04	2.62*
Moderator: acceptance or resignation		
Age	-0.16	-2.91**
Gender (female)	-0.17	-0.12
HCT-related symptomatology	0.39	2.28*

	Statistics by predictor	
	b	t
Acceptance or resignation	0.38	1.23
Interaction HCT-related symptomatology × acceptance or resignation	−0.01	−0.06
Moderator: seeking alternative rewards		
Age	−0.17	−3.01**
Gender (female)	0.37	0.25
HCT-related symptomatology	0.37	3.27**
Seeking alternative rewards	−0.33	−0.99
Interaction HCT-related symptomatology × seeking alternative rewards	<0.01	0.35
Moderator: emotional discharge		
Age	−0.13	−2.42*
Gender (female)	−1.04	−0.76
HCT-related symptomatology	0.13	1.05
Emotional discharge	0.09	0.19
Interaction HCT-related symptomatology × emotional discharge	0.04	2.08*

* $p < .05$;

** $p < .01$;

*** $p < .001$.