HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2021 March 17.

Published in final edited form as:

Bone Marrow Transplant. 2020 September ; 55(9): 1868–1871. doi:10.1038/s41409-020-0937-y.

Associations among Depression, Antidepressants, Survival and Quality of Life in Hematopoietic Cell Transplant Recipients

Anna Barata[1,2], **Brian D. Gonzalez**[2], **Jun-Min Zhou**[3], **Jongphil Kim**[3], **Aasha I. Hoogland**[2], **Areej El-Jawahri**[4], **Margaret Booth-Jones**[2], **Heather S.L. Jim**[2]

[1]II-B & José Carreras Leukemia Research Institute, Barcelona, Spain

[2]Department of Health Outcomes and Behavior, Moffitt Cancer Center, Tampa, FL, USA

[3]Department of Biostatistics and Bioinformatics, Moffitt Cancer Center, Tampa, FL, USA

[4]Department of Hematology/Oncology Massachusetts General Hospital, Boston, MA, USA

Introduction

Depression is a significant problem among hematopoietic cell transplant (HCT) recipients. Approximately 15% of patients meet criteria for clinically-significant depressive symptomatology before transplant, 37% in the week after transplant, and 13% during long-term survivorship.[1, 2] In contrast, the prevalence of current depression in the general U.S. population is 9%.[3] Depression is associated with worse concurrent quality of life (QOL)[1] and is inconsistently associated with worse overall survival (OS).[4–6] Mixed evidence may be due to the fact that previous literature has not taken antidepressant usage into consideration. Thus, this study examined the association of pre-transplant depression and antidepressant usage with HCT outcomes, specifically concurrent physical function and OS. Four groups of HCT recipients were examined: 1) not depressed/taking antidepressants (treated depression), 2) depressed/taking antidepressants (undertreated depression), 3) depressed/not taking antidepressants (untreated depression), and 4) not depressed/not taking antidepressants (control). We hypothesized that patients with untreated and undertreated depression would demonstrate worse concurrent physical functioning and OS.

Methods

This retrospective study identified all adult English-speaking patients (≥18 years old) diagnosed with hematologic cancer who received an HCT at Moffitt Cancer Center and completed pre-transplant questionnaires between 2011 and 2015. All participants provided

Corresponding author: Dr Heather S. L. Jim Ph. D., Department of Health Outcomes and Behavior, Moffitt Cancer Center, MRC-PSY, 12902 Magnolia Drive, Tampa FL 33612, USA; Heather.Jim@moffitt.org; Phone: 813-745-6369, Fax: 813-745-3906.

Disclosure of Conflicts of Interest

HSLJ: has served as a consultant for RedHill BioPharma, Janssen Scientific Affairs and Merck. AB, BDG, JMZ, JK, AIH, AEJ and MBJ declare no competing financial interests.

informed consent. The study was approved by the University of South Florida Institutional Review Board.

Demographic and clinical data were abstracted from medical charts. The European Bone Marrow Transplant (EBMT) risk score was calculated from abstracted variables.[7] Antidepressant usage between pre-transplant vital organ testing (VOT) and three weeks post-transplant included: citalopram, escitalopram, sertraline, bupropion, venlafaxine, duloxetine, paroxetine, fluoxetine, trazodone, phenelzine, amitriptyline, nortriptyline, mirtazapine, and desvenlafaxine. Reasons for antidepressant usage were not available. Depression and QOL were assessed during VOT using the Patient Health Questionnaire-8 (PHQ-8)[3] and the Medical Outcomes Study Short Form (SF-12),[8] respectively. The PHQ-8 has been adapted to the criteria required for a DSM-V diagnosis of major depressive disorder;[3] scores≥10 indicated depression. The SF-12 examines QOL using the Physical Component Score and the Mental Component Score; analyses focused on the Physical Component Score to avoid overlap with depression. A half a standard deviation (SD) in physical functioning indicated a clinically meaningful difference.[9] Higher scores indicated better functioning.

Statistical Analyses

Allogeneic and autologous recipients were analyzed separately. Univariate linear regressions examined associations among sociodemographic and clinical characteristics, depression/antidepressant usage, and pre-transplant physical functioning. Univariate Cox proportional models examined the above-mentioned predictors of OS (i.e., death from any cause). Time to event was time from transplant to death or last follow-up. We decided a priori that sociodemographic and clinical characteristics significant at $p \leq 0.25$ in univariate models as well as depression/anti-depressant usage would be forced into multivariable analyses using backward elimination to determine whether depression/anti-depressant use was associated with OS and physical functioning over and above other factors. Variables with $p \leq 0.10$ were removed from multivariable models. Values at $p \leq 0.05$ (two-sided) were considered statistically significant. Analyses were performed using SAS 9.4 (Cary, NC).

Results

Sample characteristics and results of univariate analyses examining physical functioning and OS are shown in Table 1. Data was normally distributed. Regarding physical functioning, multivariable analyses in allogeneic patients indicated depression/antidepressant usage was independently associated with physical functioning after controlling for Karnofsky performance status (KPS), regimen intensity, and days from diagnosis to HCT. Allogeneic patients with treated depression (B=−2.75, 95% CI=−4.77, −0.74) reported better physical functioning than patients with undertreated (B=−7.10, 95% CI=−10.34, −3.85) and untreated (B=−7.60, 95% CI=−10.80, −4.39) depression but worse physical functioning than controls (p-values <0.05). Similarly, among autologous patients, depression/antidepressant usage was independently associated with physical functioning after controlling for KPS and disease status. Autologous patients with treated depression (B=−3.24, 95% CI=−4.94, −1.54) reported better physical functioning than patients with undertreated (B=−8.70, 95% CI=−11.26, −6.14) and untreated (B=−8.56, 95% CI=−11.07, −6.14) depression, but worse

physical functioning than controls (p-values <0.05). Regarding OS, multivariable analyses in allogeneic patients after controlling for EBMT risk, indicated depression/antidepressant usage was not significant (p-values ≥0.09). Among autologous patients, after controlling for KPS, disease status, and diagnosis, depression/antidepressant usage was not significant (p-values ≥0.18).

Discussion

Successful treatment with antidepressants was associated with better concurrent physical functioning than untreated and undertreated depression, although it did not completely mitigate the impact of depression on physical functioning. Depression/antidepressants usage was not associated with OS, however. This study is among the first to examine associations of depression and antidepressants on HCT outcomes in a large sample. To our knowledge, only one small, prospective study has examined the effects of antidepressants on HCT outcomes;[10] patients treated with sertraline (n=30) exhibited lower mortality and readmission rates than those treated with placebo (n=26). Overall results underscore the need to proactively screen and treat depression, particularly prior to transplant.[11] This study has several strengths such as a large sample size, the use of validated measures of depression and QOL, and appropriate statistical analyses. Limitations include a retrospective dataset, and small depression/antidepressants subgroups that may have limited our ability to detect differences in OS. We were unable to determine the indication for which patients were prescribed antidepressants (e.g., depression, pain), and whether patients were receiving psychosocial services. Depression was assessed at the time of VOT and did not capture depression during the peri-transplant period. In addition, it was possible that antidepressants were started recently and were not fully effective at time of assessment. Nevertheless, findings lend support for integrated psychosocial care in the allogeneic and autologous setting.

Acknowledgement

This work has been supported in part by the Biostatistics Core Facility at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292). Dr. El-Jawahri is a scholar in clinical research of the Leukemia and Lymphoma Society.

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Bone Marrow Transplant. Author manuscript; available in PMC 2021 March 17.

Table 1.

Sample characteristics and univariate analyses

				Physical Function		OS	
	Total	**Allogeneic**	**Autologous**	**Allogeneic**	**Autologous**	**Allogeneic**	**Autologous**
	n (%) / M (SD)	**n (%) / M (SD)**	**n (%) / M (SD)**	***B* (95% CI)**	***B* (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	N=1,797	**n=703**	**n=1,094**				
Sex							
Male	1,047 (58)	405 (58)	642 (59)	-	-	-	-
Female	750 (42)	298 (42)	452 (41)	−0.31 (−2.02–1.40)	**−2.24 (−3.64, −0.84)**	0.98 (0.78–1.24)	0.88 (0.66–1.19)
Age*	57 (12)	54(13)	59 (11)	−0.10 (−0.89–0.68)	−0.14(−0.90, 0.62)	**1.29 (1.14–1.45)**	1.05 (0.89–1.24)
PCS*	39.71 (11.24)	40.61 (10.95)	39.14 (11.30)			**0.85 (0.75–0.96)**	0.89 (0.76–1.03)
Depression	256 (14)	96 (14)	160 (15)	**−4.23 (−5.02, −3.45)**	**−4.65 (−5.30, −4.01)**	0.99 (0.89–1.11)	1.06 (0.92–1.22)
Depression & Antidepressants							
No Depression/ Antidepressant (treated)		146 (21)	195 (18)	**−3.60 (−5.64, −1.55)**	**−4.43 (−6.18, −2.68)**	1.27 (0.96–1.68)	**1.43 (1.00–2.04)**
Depression/ Antidepressant (undertreated)		49 (7)	77 (7)	**−7.78 (−11.02, −4.53)**	**−9.96 (−12.58, −7.34)**	0.86 (0.52–1.41)	0.80 (0.42–1.53)
Depression/ No Antidepressant (untreated)		47 (7)	83 (8)	**−8.28 (−11.56, −5.00)**	**−10.06 (−12.65, −7.47)**	1.18 (0.76–1.83)	1.37 (0.82–2.28)
No Depression/ No Antidepressant (control)		461 (65)	739 (67)	-	-	-	-
KPS**							
100	320 (18)	164 (23)	156 (14)	-	-	-	-
90	906 (50)	402 (57)	504 (46)	**−2.97 (−4.94, −1.00)**	**−4.84 (−6.82, −2.85)**	1.03 (0.77–1.37)	1.33 (0.83–2.14)
≤80	546 (30)	130 (18)	416 (38)	**−9.02 (−11.55, −6.49)**	**−10.14 (−12.17, −8.10)**	1.35 (0.95–1.91)	1.54 (0.95–2.51)
EBMT Risk Score**							
>5	61 (3)	61 (10)	0 (0)	0.35 (−2.71, 3.41)		**1.65 (1.11–2.44)**	
4–5	648 (36)	262 (40)	386 (40)	−0.45 (−2.26, 1.37)	−0.27 (−1.77, 1.23)	**1.49 (1.15–1.92)**	1.25 (0.92–1.69)
0–3	909 (51)	317 (50)	592 (60)	-	-	-	-
Diagnosis**							
Acute Leukemia	386 (22)	380 (54)	6 (1)	−2.26 (−4.72, 0.19)	−5.24 (−16.30, 5.81)	1.15 (0.82–1.62)	0.00 (0.00-)
Multiple Myeloma/ Amyloidosis	726 (40)	25 (3)	701 (64)	−0.68 (−5.47, 4.11)	**−3.83 (−5.28, −2.38)**	0.87 (0.43–1.73)	**0.72 (0.54–0.98)**
Myeloproliferative neoplasms/ Myelodisplasia	185 (10)	184 (26)	1 (<1)	−0.75 (−3.46, 1.96)	16.49 (−5.53, 38.51)	1.23 (0.85–1.79)	0.00 (0.00-)

				Physical Function		OS	
	Total	**Allogeneic**	**Autologous**	**Allogeneic**	**Autologous**	**Allogeneic**	**Autologous**
	n (%) / M (SD)	**n (%) / M (SD)**	**n (%) / M (SD)**	***B* (95% CI)**	***B* (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
	N=1,797	**n=703**	**n=1,094**				
Other***	22 (1)	11 (2)	11 (1)	−5.72 (−12.81, 1.37)	−0.56 (−7.61, 6.49)	0.25 (0.03–1.79)	2.04 (0.75–5.60)
Lymphoma	478 (27)	103 (15)	375 (34)	-	-	-	-
Disease Status**							
Partial Response	692 (39)	64 (9)	628 (57)	**3.03 (0.14–5.92)**	**−1.47 (−2.94–0.01)**	0.87 (0.57–1.33)	**1.61 (1.15–2.26)**
Refractory Disease	283 (16)	210 (30)	73 (7)	0.54 (−1.34–2.43)	**3.55 (0.68–6.42)**	1.27 (0.99–1.63)	1.73 (0.97–3.09)
Complete Remission	796 (44)	411 (58)	385 (35)	-	-	-	-
Other***	26 (1)	18 (3)	8 (<1)				
Donor Type							
Cord Blood		39 (6)		3.36 (−0.45–7.17)		**2.79 (1.86–4.26)**	
Mismatched Unrelated Donor		97 (14)		0.18 (−2.52–2.88)		1.39 (0.98–1.97)	
Matched Unrelated Donor		344 (48)		−0.37 (−2.27–1.53)		0.97 (0.74–1.28)	
Matched Related Donor		223 (32)		-		-	
Regimen Intensity							
Myeloablative	1,543 (86)	449 (64)	1,094 (100)	−1.14 (−2.90–0.62)		0.86 (0.67–1.09)	
Non-myeloablative	13 (<1)	13 (2)	0	**6.35 (0.27–12.44)**		0.20 (0.05–0.80)	
Reduced Intensity	241 (13)	241 (34)	0	-		-	
Days From Diagnosis To HCT*	578 (892)	539 (828)	604 (9230)	0.65 (−0.24–1.54)	0.28 (−0.37. 0.93)	1.03 (0.91–1.16)	1.00 (0.86–1.15)

Note. Percentages may not total 100% due to rounding.

*Analysis are for HR per 1 SD increase.

**Frequencies may not add to 100% due to excluding cases with unknown values.

***We did not include Other categories on multivariable analyses because of small cell sizes. OS: overall survival, HR: Hazard Ratio, CI: Confidence Interval, SD: Standard Deviation, KPS: Karnofsky Performance Status, EBMT: European Bone Marrow Transplant, PCS: Physical Component Score, HCT: Hematopoietic Cell Transplant.

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