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Worsening cognitive performance is associated with increases in systemic inflammation following hematopoietic cell transplantation

Aasha I. Hoogland[a], **Ashley M. Nelson**[a,b], **Brian D. Gonzalez**[a], **Brent J. Small**[b], **Elizabeth C. Breen**[c], **Steve K. Sutton**[b], **Karen L. Syrjala**[d], **Julienne E. Bower**[e], **Joseph Pidala**[a], **Margaret Booth-Jones**[a], **Paul B. Jacobsen**[f], **Heather S.L. Jim**[a]

[a]Moffitt Cancer Center, Tampa, FL

[b]University of South Florida, Tampa, FL

[c]University of California-Los Angeles, Los Angeles, CA

[d]Fred Hutchinson Cancer Research Center, Seattle, WA

[e]University of California-Los Angeles, Los Angeles, CA

[f]National Cancer Institute, Bethesda, MD

Abstract

Background: Cognitive decline is a frequently cited concern among patients receiving hematopoietic cell transplantation (HCT), and patients often experience neurocognitive deficits (i.e., stable or worsening neurocognitive performance) throughout the transplant course. Deficits can be most severe during the acute transplant period (i.e., 90 days after transplantation), when patients also typically experience elevated systemic levels of inflammation. Previous studies have identified inflammation as a likely mechanism underlying neurocognitive deficits, primarily in women with breast cancer; however, longitudinal studies have been limited. In this study, our aim was to evaluate the relationship between changes in systemic inflammation and changes in cognition from pre-to post-transplant in patients receiving allogeneic HCT.

Methods: Patients scheduled for allogeneic HCT (n=85) were assessed prior to HCT and 90 days after HCT. Biomarkers of inflammation included IL-6, sTNF-RII, CRP, and IL-1ra, which have been previously associated with neurocognitive deficits in cancer patients. Patients completed neuropsychological testing and self-report questionnaires.

Results: Mixed models demonstrated that from pre-to post-HCT, increases in IL-6 and sTNF-RII were associated with neurocognitive deficits, and decreases in CRP were associated with better

Corresponding author: Dr. Heather S. L. Jim, Department of Health Outcomes and Behavior, Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL 33612, USA. Telephone: 813-745-6369., heather.jim@moffitt.org.

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neurocognitive performance. There were no significant associations between changes in inflammation and self-reported cognitive performance.

Conclusions: Our findings are the first to our knowledge to report a robust relationship between increasing inflammation and neurocognitive deficits from pre-to post-HCT. Additional studies are needed to confirm these findings in a larger sample.

1. Introduction

Patients receiving hematopoietic cell transplant (HCT) often experience neurocognitive deficits compared to non-transplant patients with hematologic cancers,[1] non-cancer controls,[2] and population norms.[3–5] Neurocognitive deficits can take the form of worsening or stable performance (i.e., lack of expected improvements in performance due to practice effects).[6] Deficits are often observed prior to transplantation[3,5,7] and are most severe during the acute transplant period.[4,7–9] By one year after transplantation, neurocognition in many patients recovers to pre-HCT levels,[7,10] but deficits are evident in up to 40% of patients, and up to 60% self-report cognitive problems.[11] Further, certain subgroups of patients (e.g., older adults, patients receiving myeloablative allogeneic HCT) are particularly susceptible to worse cognitive outcomes after HCT.[2,12] Cognitive deficits can have profound detrimental consequences on quality of life and are a commonly-cited concern of patients treated with HCT.[13,14]

Experimental studies suggest that systemic inflammation may contribute to neurocognitive function,[15] whereby higher levels of biomarkers of inflammation such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF) impair neurocognitive processes. For example, research with animal models has shown that administration of IL-1 impairs spatial learning,[16] long-term memory,[17] and working memory.[18] Further, age-related memory loss co-occurs with increases in IL-6,[19] and is worse among older mice who over-express TNF.[20] Research has also shown that prolonged elevations in inflammation are associated with impaired cognition.[21]

Relationships between inflammation and neurocognitive function have not been investigated in HCT recipients. This state of affairs is surprising considering that elevated inflammation is a hallmark of allogeneic HCT.[22] Nevertheless, a significant body of research has reported associations between elevated inflammation and neurocognitive deficits in cancer patients who have not received transplantation. In cancer patients, subjective and neurocognitive performance have been consistently associated with higher concurrent levels of TNF[23–28] and IL-6,[27–30] with less consistent evidence for higher levels of concurrent IL-1[28] and C-reactive protein (CRP).[31–33] Longitudinal studies evaluating these associations have found that increasing inflammation (i.e., sTNF-RII, IL-6) is significantly associated with worsening neurocognition[23,28] and subjective cognition[34] over time in patients with breast cancer. Additional research is needed in patients with other cancer types.

The goal of the current study was to investigate the relationship between changes in inflammation and changes in subjective and neurocognitive performance in adult allogeneic HCT recipients during the acute transplant period (i.e., 90 days). We hypothesized that: 1) inflammation would increase from pre-to post-HCT, 2) subjective and objective

neurocognitive performance would worsen or remain stable from pre-to post-HCT, and 3) increasing inflammation would be associated with worsening subjective and objective neurocognitive performance over time.

2. Methods

2.1. Participants

Eligible participants: were at least 18 years of age; were diagnosed with a hematologic cancer; were scheduled to receive allogeneic HCT with peripheral blood stem cells; had not previously been treated with HCT; had no history of cerebrovascular accident, head trauma with loss of consciousness within the past five years, or brain damage/injury; had completed at least six years of formal education; were willing and able to provide written informed consent; and were able to read and speak English. Participants were part of a larger IRB-approved study evaluating quality of life in patients receiving allogeneic HCT. Participants were paid $20 at each evaluation. The study was approved by the University of South Florida Institutional Review Board.

2.2. Procedure

Participants were recruited during an outpatient appointment at Moffitt Cancer Center. Written informed consent was obtained prior to initiation of study procedures. Participants completed baseline self-report questionnaires and neurocognitive testing prior to hospital admission for transplantation. Neurocognitive testing was administered by a trained research coordinator or a doctoral student in clinical psychology at the University of South Florida. All neurocognitive testing was supervised by a clinical neuropsychologist with extensive experience working with individuals receiving HCT. Participants were asked to return at 90 days after transplant (i.e., a time when acute graft-versus-host disease (GVHD) had largely resolved, and chronic GVHD had yet to emerge), to complete the same assessments. A blood sample was drawn from participants at each assessment to measure circulating biomarkers of inflammation. Data were collected between September 2010 and April 2014. Neurocognitive findings for the full sample have been reported previously.[12] Participants were included in the current analyses if they had biomarker data at baseline and 90 days after HCT.

2.3. Measures

2.3.1. Demographic and Clinical Information—Prior to transplantation, participants completed a sociodemographic questionnaire assessing age, sex, ethnicity, race, marital status, education, and annual household income. Comorbidities were assessed via medical chart review using the Hematopoietic Cell Transplantation Comorbidities Index (HCT-CI).[35] Additional clinical information (i.e., disease type, full vs. reduced intensity conditioning, pre-HCT disease status, length of hospital stay, donor status, body mass index or BMI, history of total body irradiation, history of prophylactic cranial irradiation) was obtained via the Moffitt Department of Blood and Marrow Transplantation database and medical chart review.

2.3.2. Neurocognitive Performance—Neurocognitive tests were selected based on published recommendations from the International Cognition and Cancer Task Force.[36] Premorbid intellectual ability was evaluated using the Wechsler Test of Adult Reading.[37] Neurocognitive domains included verbal memory (Hopkins Verbal Learning Test-Revised[38] Immediate and Delayed Recall), verbal fluency (Controlled Oral Word Association Test[39]), visuospatial memory (Brief Visuospatial Memory Test-Revised[40] Immediate and Delayed Recall), attention (Wechsler Adult Intelligence Scale Digit Span[41] and Color Trails Test Part 1[42]), and executive functioning (Color Trails Test Part 2[42] and Stroop Neuropsychological Screening Test[43]). Participants' scores on each test were standardized as t-scores based on age-adjusted population norms and averaged to create a domain score. Scores across each of the neurocognitive domains were averaged to derive a total neuropsychological performance (TNP) score. For each domain and TNP, higher scores indicate better neurocognitive performance. These measures are not intended to be pure tests of each domain; instead they provide a useful heuristic for characterizing neurocognitive functioning in individuals treated with HCT.

2.3.3. Self-Reported Cognitive Performance—Subjective cognition was evaluated using the Everyday Cognition (ECog) scale.[44] The ECog yields a global cognition score and subscale scores for divided attention, language, memory, planning, organization, and visuospatial abilities. In this study, the global score (i.e., average of the six subscales) was used in analyses. Higher scores indicate worse cognitive performance.

2.3.4. Biomarkers of Inflammation—Blood was processed for serum, which was stored at −80 degrees C and shipped frozen to the UCLA Cousins Center for Psychoneuroimmunology Inflammatory Biology Laboratory for immunoassays. Consistent with previous studies examining inflammation and cognition in cancer patients, biomarkers included IL-6, interleukin-1 receptor antagonist (IL-1ra), soluble tumor necrosis factor receptor 2 (sTNF-RII), and CRP.[23,24] High sensitivity (IL-6) and regular sensitivity (IL-1ra, sTNF-RII, CRP) enzyme-linked immunosorbent assays (R&D Systems Human Quantikine ELISA; Minneapolis, MN) were performed according to the manufacturer's instructions with the following modifications. CRP assays were performed with a sample dilution of 1:500 and an extended standard curve, to yield a lower limit of detection of 0.2 mg/L. sTNF-RII assays were performed with a sample dilution of 1:30, yielding a lower limit of detection of 234 pg/mL. The lower limits of detection of the IL-6 and IL-1ra assays were 0.2 and 31.2 pg/mL, respectively. All samples were assayed in duplicate, with both samples from each participant tested on the same immunoassay plate. An internal control sample was included on every plate to monitor inter-assay (<10%) and mean intra-assay (<5%) variability.

2.4. Data Analyses

Means and standard deviations (continuous variables) and frequencies and percentages (categorical variables) were used to describe sociodemographic and clinical characteristics of the sample. Differences in sociodemographic and clinical characteristics between participants included in analyses and participants in the larger study were assessed using independent samples t-tests, chi-square tests, and fisher's tests. Associations among biomarkers of inflammation and neurocognitive domains at each time point were assessed

using Spearman's correlations. Associations between participant characteristics (i.e., age, gender, premorbid IQ, comorbidities) and TNP at baseline were assessed using Spearman's correlations, and variables significant at $p<.10$ were included as covariates in longitudinal analyses. Inflammatory biomarker levels were halved when below the limit of detection (e.g., if the lower limit of detection was <.2 mg/L, the datum was entered as .1 mg/L), and estimated when above the upper limit of detection (e.g., 25 mg/L). Biomarkers of inflammation were natural log-transformed to normalize their distributions. Changes in biomarkers of inflammation, neurocognitive performance, and subjective cognition over time were evaluated using Wilcoxon sign rank tests. Relationships between changes in biomarkers of inflammation and changes in global cognition and TNP over time were examined using mixed models, which included all available data at each time point.[45,46] Biomarkers of inflammation were mean-centered and included as time-varying covariates. The associations between biomarkers of inflammation and cognitive performance were examined by including the time x biomarkers of inflammation interaction while controlling for main effects and covariate x time interactions. To reduce the potential for Type 1 error, further probing of subjective and objective cognitive domains was conducted if the omnibus tests of global cognition and TNP were significant, respectively. Changes in biomarkers of inflammation are depicted as binary variables (above median change versus below median change) in figures for illustrative purposes, but were analyzed as continuous variables. All inferential statistical analyses were conducted with an alpha of 0.05. SAS version 9.4 (Cary, NC) was used for all statistical analyses.

3. Results

Of the 225 participants who provided informed consent, 89 provided both neurocognitive data and blood samples at both time points and were initially included in the current analyses (see Supplemental Figure 1 for a participant flow diagram). Compared to participants who did not provide blood samples in the larger study, participants included in the current analyses were more likely to be married (p=.03). There were no other significant differences between these groups on sociodemographic or clinical variables (i.e., age, premorbid IQ, comorbidities, sex, ethnicity, race, marital status, education, annual household income, disease type, conditioning regimen, pre-HCT disease status, length of hospital stay, donor type, BMI, total body irradiation, or prophylactic cranial irradiation) (see Supplemental Table 1) (ps>.05). Of the 89 participants initially included, three participants were removed for having two or more biomarkers of inflammation considered to be an outlier (i.e., ≥3 SD above the sample mean), and one for having both a documented infection and one biomarker of inflammation outlier. Patients taking steroids ($n=4$) or without documented infection who had one biomarker of inflammation outlier ($n=9$) were included in analyses. Thus, our final sample was comprised of 85 participants.

Demographic and clinical characteristics are displayed in Table 1. Participants were mostly male (58%), Caucasian (94%), married (75%), and reported a household income over $40,000/year (69%). Most had acute myeloid leukemia (31%), followed by myelodysplastic syndrome (18%), non-Hodgkin lymphoma (15%), and acute lymphocytic leukemia (12%). The majority were in complete or partial remission (71%) at the time of HCT. Gender and IQ were associated with TNP at baseline (ps<.01) and were included as covariates in

multivariate analyses. Additionally, consistent with previous literature, BMI[47] and age[12] were included as covariates.

Means for biomarkers of inflammation (absolute and natural log-transformed) and cognitive performance at both time points are shown in Table 2. Correlations among biomarkers of inflammation and among neurocognitive domains at each time point are in Supplemental Tables 2 and 3, respectively. Over time, there were significant increases in circulating levels of IL-6 and sTNF-RII and a significant decrease in CRP. There was no significant change in IL-1ra. For neurocognitive performance, TNP remained stable over time, in spite of the potential for repeat practice effects. Further probing of TNP revealed that all domains worsened (verbal fluency) or remained stable (verbal memory, visual memory, attention, and executive functioning). There was no significant change in self-reported (subjective) global cognition.

Results of the linear mixed models are shown in Table 3. Regarding TNP, while IL-6 increased on average for the entire sample, patients with greater increases in IL-6 demonstrated worse TNP that did not improve over time (Figure 1). Patients with greater increases in sTNF-RII demonstrated worsening TNP over time compared to patients with less increase in sTNF-RII (Figure 2). Patients with greater decreases in CRP demonstrated improvements in TNP relative to patients with smaller decreases in CRP (Figure 3). There were no significant associations between change in IL-1ra and change in TNP over time (p>.05), nor between any of the biomarkers of inflammation and subjective cognition over time (ps>.05).

Based on findings of significant and trending relationships of changes in IL-6, sTNF-RII, and CRP with change in TNP, post hoc analyses were conducted to explore relationships of these biomarkers with the objective cognitive domains that comprise TNP. Results indicated that patients with greater increases in IL-6 demonstrated worse verbal memory and a trend toward worsening attention and executive functioning over time compared to patients with less increase in IL-6. Patients with greater increases in sTNF-RII demonstrated worse attention and a trend toward worsening verbal memory over time compared to patients with less increase in sTNF-RII. Patients with greater decreases in CRP demonstrated improvements in verbal memory and visual memory compared to patients with smaller decreases in CRP.

4. Discussion

This is the first study to our knowledge to examine relationships among changes in inflammation and changes in subjective and objective cognition during the acute transplant period in patients receiving allogeneic HCT. As hypothesized, increases in IL-6 and sTNF-RII from pre-HCT to 90 days after HCT were associated with declines in TNP, verbal memory, attention, and executive functioning. Similarly, decreases in CRP over time were associated with improvements in TNP, verbal memory, and visual memory. There were no associations between systemic inflammation and subjective cognition.

Existing literature indicates that patients receiving HCT often have higher levels of inflammation[22,48–50] which increase from pre- to post-HCT.[51] Elevated levels of inflammation in this population could be due to factors such as previous treatment, disease, transplant related factors (e.g., donor match), and post-HCT progression. Consistent with research examining pre-to post-treatment changes in other cancer samples not receiving HCT, there were increases in circulating levels of IL-6[28,34,52] and sTNF-RII[23] while IL-1ra remained unchanged[23,28,34] from pre-to post-transplantation. Conversely, CRP levels, which were very elevated, decreased post-HCT. We speculate that the reduction in CRP levels over time may have been due to a negative impact of HCT on liver function as levels of IL-6 and sTNF-RII (more direct measures of systemic inflammation) increased from pre- to post-HCT. With respect to neurocognitive deficits, worsening and/or stable performance on all neurocognitive domains was consistent with a 2013 meta-analysis[6] of patients receiving HCT indicating a lack of expected improvements over time on neurocognitive tests due to repeated testing (i.e., practice effects).

Few studies have examined changes in both inflammation and cognition from pre-to post-treatment, but in this study there were robust patterns of association between increasing inflammation (IL-6 and sTNF-RII) and worsening neurocognitive performance. There were significant associations between IL-6, sTNF-RII, and/or CRP within every neurocognitive domain, with the most robust relationships observed for TNP and verbal memory. Existing literature suggests that patients receiving allogeneic HCT may be particularly vulnerable to deficits in verbal memory,[2,7] and our data show a clear and consistent association between higher levels of systemic inflammation and verbal memory deficits.

Subjective reports of cognitive deficits are common after receiving HCT,[53] but patients receiving HCT may not perceive changes in cognition from pre-to post-HCT.[54] In this study, patients receiving HCT did not perceive worsening cognition during the acute transplant period. Further, in contrast to previous studies with mostly breast cancer patients,[23,30,31,34] changes in inflammation were not associated with changes in subjective cognition from pre-to post-HCT. Cognitive deficits may be less noticeable due to other factors such as morbidities throughout the acute transplant period. Moreover, a large body of research indicates that subjective cognition is not significantly correlated with objective cognition in cancer patients.[55]

This study had several strengths, including the focus on allogeneic HCT, the inclusion of both subjective and objective measures of cognitive performance, and a longitudinal study design. Limitations include a relatively homogenous sample in terms of race and ethnicity (predominantly white and non-Hispanic) and a high level of education that limits generalizability of findings to less educated patients. Thus, additional research is needed to confirm our results in more heterogeneous samples. Despite these limitations, these results extend our understanding of the role of systemic inflammation and neurocognitive impairment to HCT recipients. Future research on inflammation and cognition in this population should include a comparison group, larger samples, and interventions to preserve or improve neurocognitive performance in patients with higher inflammation during the transplant period. Existing nonpharmacological efforts including cognitive behavioral therapy delivered via videoconferencing[56] and computerized training programs[57,58] have

demonstrated preliminary success in patients with breast cancer, but these interventions have not been implemented with patients being treated with HCT. In addition, regular exercise decreases inflammation[59] and improves neurocognitive function[60] in non-cancer populations and may be a useful intervention target for patients undergoing allogeneic HCT. In summary, inflammation may be a mechanism by which cognitive deficits occur in allogeneic transplant patients. Further research is needed to improve supportive care to reduce inflammation and improve cognition during the survivorship period as patients prepare to return to the cognitive demands of their daily lives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- In acute transplant period, inflammation and neurocognitive deficits increased
- Over time, increasing inflammation and worsening neurocognition robustly associated
- No association with systemic inflammation and subjective cognition

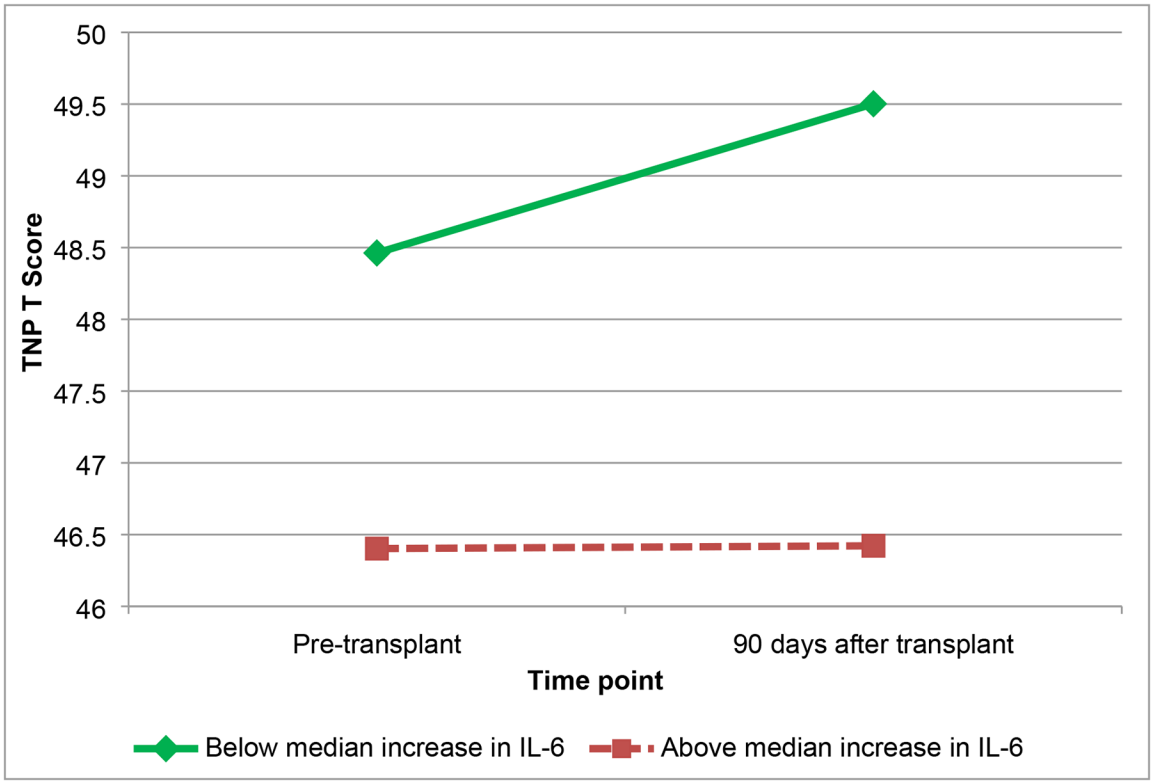

Figure 1.

Total neuropsychological (TNP) scores by change in interleukin-6 (IL-6) (below median increase, and above median increase) from pre-transplant to 90 days after transplant

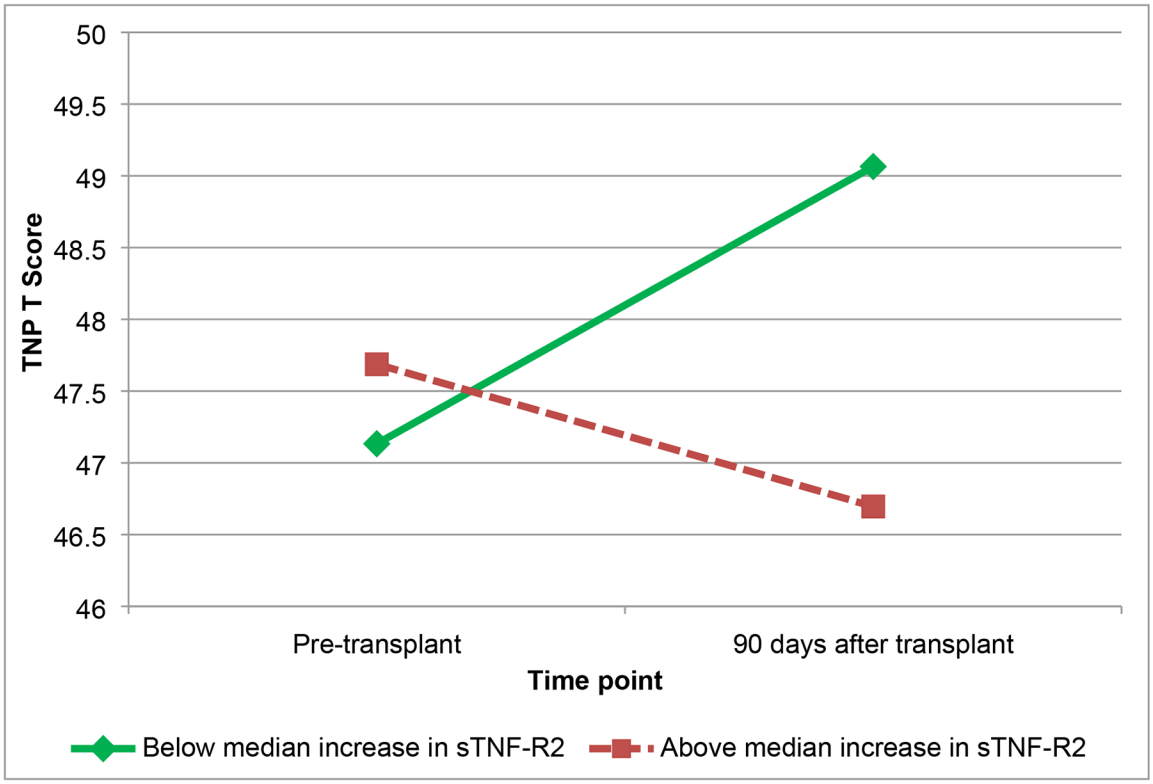

Figure 2.

Total neuropsychological (TNP) scores by change in soluble tumor necrosis factor receptor 2 (sTNF-RII) (below median increase, and above median increase) from pre-transplant to 90 days after transplant

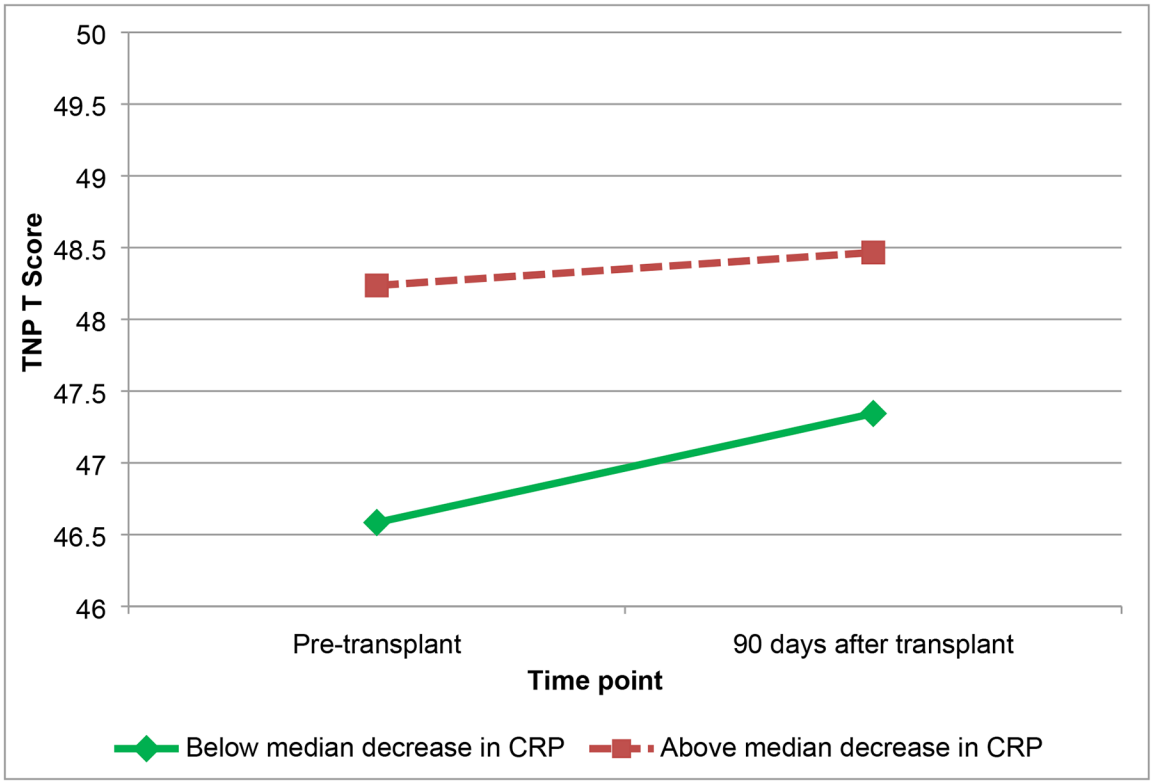

Figure 3.

Total neuropsychological (TNP) scores by change in c-reactive protein (CRP) (below median decrease, and above median decrease) from pre-transplant to 90 days after transplant

Table 1.

Participant characteristics, *N*=85

Variable	Means (SD) / N (%)
Age	52.0 (12.9)
PreMorbid IQ	104.8 (10.5)
Comorbidities	3.0 (1.8)
Sex (female)	36 (42%)
Ethnicity (non-Hispanic)	72 (86%)
Race (Caucasian)	80 (94%)
Marital Status (married)	64 (75%)
Education	
High school or less	20 (24%)
Post-high school or college graduate	55 (65%)
Post-college education	10 (12%)
Annual household income (% ge $40k)	44 (69%)
Disease type	
AML	26 (31%)
MDS	15 (18%)
NHL, B-Cell	13 (15 %)
ALL	10 (12%)
Other	21 (25%)
Conditioning regimen	
Full intensity	65 (73%)
Reduced intensity	24 (27%)
Pre-HCT disease status	
Complete remission	44 (53%)
Partial remission	15 (18%)
Stable disease or no response	17 (20%)
Progressive disease	7 (8%)
Length of stay in hospital	23.7 (5.8)
Donor	
Related	27 (32%)
Matched unrelated	42 (49%)
Mismatched unrelated	16 (19%)
Body mass index (BMI)	28.4 (5.5)
Total Body Irradiation (TBI)	10 (13%)
Prophylactic Cranial Irradiation (PCI)	1 (1%)

Note: AML=acute myeloid leukemia, MDS=myelodysplastic syndrome, NHL=non-Hodgkin lymphoma, ALL=acute lymphocytic leukemia.

Table 2.

Biomarkers of inflammation and measures of cognitive performance, Means (SD) (*N*=85)

Variables	Pre-HCT	90 Days After HCT	p-value
Serum Biomarker Concentrations[a]			
IL-6 (pg/mL)			
Absolute	5.9 (12.7)	6.4 (6.1)	
Log-transformed	13 (.8)	15 (.9)	0.03
sTNF-RII (pg/mL)			
Absolute	4510 (3401)	5253 (2389)	
Log-transformed	8.3 (.5)	8.5 (.4)	<.0001
CRP (mg/L)			
Absolute	7.9 (10.8)	7.0 (12.6)	
Log-transformed	1.3 (1.3)	9 (1.5)	<.01
IL-1ra (pg/mL)			
Absolute	632 (744)	439 (204)	
Log-transformed	6.1 (.7)	6.0 (.5)	0.35
Cognitive Performance			
Global cognition	9.3 (3.1)	9.5 (4.0)	0.52
TNP[b]	47.4 (7.1)	47.9 (7.7)	0.79
Verbal memory	41.0 (11.3)	42.2 (10.8)	0.26
Verbal fluency	45.6 (11.4)	43.8 (11.7)	0.05
Visual memory	47.6 (11.0)	49.3 (11.5)	0.07
Attention	52.1 (7.4)	51.7 (8.1)	0.60
Executive functioning	51.0 (8.3)	50.2 (9.4)	0.40

Note: IL-1ra=Interleukin-1 receptor antagonist, IL-6=interleukin-6, sTNF-RII=soluble tumor necrosis factor receptor 2, CRP=C-reactive protein, TNP=total neuropsychological performance.

a: Serum concentrations of circulating biomarkers were natural log-transformed. Mean concentrations are shown in absolute values for ease of interpretation.

b: Objective cognitive performance domain scores are t-scores, which were averaged to generate the TNP.

Table 3.

Linear mixed model unstandardized parameter estimates for cognitive performance

Biomarker of inflammation	Effect	Global cognition	TNP	Verbal memory	Verbal fluency	Visual memory	Attention	Executive functioning
	Intercept	8.76**	48.52***	36.14***	41.50***	63.06***	56.74***	43.64***
IL-6	Time	0.01	8.67*	6.86	8.58	14.93*	7.40^	2.80
	Time*IL-6	−0.15	−1.73^	−4.40**	−2.30	−0.95	−2.06^	−1.92^
	Intercept	8.82**	47.51***	35.71***	41 14***	62.01***	56.39***	42 73***
sTNF-RII	Time	0.37	8.05*	8.12	10.51	14.30*	6.84	2.47
	Time*sTNF-RII	0.88	−3.85*	−5.12^	−0.42	−4.13	−5.23**	−2.91
	Intercept	9.02	47.40***	34.37***	41.30***	61.12***	56.08***	42.92***
CRP	Time	0.34	7.29^	5.61	8.84	12.31^	7.23	2.00
	Time*CRP	0.08	−1.10*	−2.00*	−1.34	−1.91*	−0.63	−0.68
	Intercept	8.43**	48.91***	-	-	-	-	-
IL-1ra	Time	0.08	8.36*	-	-	-	-	-
	Time*IL-1ra	−0.01	−0.53	-	-	-	-	-

Note: IL-6=interleukin-6, sTNF-RII=soluble tumor necrosis factor receptor 2, CRP=C-reactive protein, IL-1ra=Interleukin-1 receptor antagonist, TNP=total neuropsychological performance. Models adjusted for gender, mean–centered IQ, BMI, age, and each covariate*time interaction. Biomarkers of inflammation were log-transformed and mean–centered. The intercept represents the value of the outcome at 90 days after HCT. Longitudinal changes are modeled as time effects, and the association between each biomarker and time is examined using the time x biomarker interaction.

*** =p<.001

** =p<.01

* =p<.05

^ =p<.10