Pre-transplant cognitive dysfunction in advanced-age hematologic cancers: predictors and associated outcomes

James C. Root, PhD¹, Claudine Campbell, OTD, OTR/L, CLT², Xiomara Rocha-Cadman, MD⁶, Nicole Kasven-Gonzalez, MOTR/L, CLT², Molly Maloy, MS⁵, Jessica Flynn, BS³, Sean M. Devlin, PhD³, Ann A. Jakubowski, PhD MD⁴

¹Department of Psychiatry and Behavioral Sciences, Weill Cornell Medical College, Cornell University, NY
²Department of Neurology, Weill Cornell Medical College, Cornell University, NY
³Department of Epidemiology and Biostatistics, Weill Cornell Medical College, Cornell University, NY
⁴Department of Medicine. Memorial Sloan-Kettering Cancer Center; Weill Cornell Medical College, Cornell University, NY
⁵Health Informatics, Weill Cornell Medical College, Cornell University, NY
⁶Department of Psychiatry, City of Hope

Abstract

Introduction—Patients presenting for treatment of hematologic cancers may be at increased risk for cognitive dysfunction before allogeneic hematopoietic stem cell transplantation (HSCT) due to advanced age, previous chemotherapy treatment, deconditioning, and fatigue. Cognitive dysfunction may affect treatment decision-making, ability to recall or follow post-HSCT treatment recommendations and overall survival (OS).

Methods—448 patients admitted for HSCT from 2011–2014, were administered the Montreal Cognitive Assessment (MoCA) by occupational therapists during admission prior to transplant, and 260 were reassessed following transplant and prior to discharge. We examined select predictor variables, including age, Karnofsky Performance Status (KPS), gender, disease type, psychotropic

Corresponding Author: James C. Root, PhD, Neurocognitive Research Laboratory, Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, 641 Lexington Avenue, 7th Floor, New York, NY 10022, Tel: (646) 888-0035 | Fax: (212) 888-2584 | rootj@mskcc.org

Financial disclosure: there is no financial disclosure to report
Conflict of interest: there is no conflict of interest to report.
Authorship disclosure: the authors had full access to all data in the study and had final responsibility and integrity of the data, the accuracy of the data analysis, and the responsibility for the decision to submit for publication.
Declarations of interest: none
Financial conflicts of interest: none

Publisher’s Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
medications, and select outcome variables, including overall survival (OS), and non-relapse mortality (NRM).

Results—Prior to transplant, 36.4% of patients met criteria for cognitive dysfunction. Age was found to be a significant predictor together with disease type (myelodysplastic syndrome [MDS]; myeloproliferative disorder [MPD]). No significant association was found between cognitive dysfunction and OS or NRM. Longitudinal analysis from pre- to post-transplant indicated significant decline following transplant. Notably one third of the study cohort showed cognitive dysfunction at hospital discharge.

Conclusion—A significant proportion of transplant candidates present with cognitive dysfunction, with older patients, and those diagnosed with MDS and MPD, at greatest risk in this cohort. Attention to cognitive dysfunction prior to transplant may alert the treatment team to high-risk cases that require increased oversight, inclusion by caregivers, and referral to occupational therapy at discharge. Longitudinal follow-up studies are needed to clarify the specific effect of HSCT on cognitive dysfunction and the impact of cognitive dysfunction on transplant outcomes.

Keywords
hematopoietic stem cell transplant; cognitive function; post-transplant; bone marrow transplant; cognition; advanced age

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) has become the ultimate curative treatment for many hematological disorders that cannot be cured by conventional therapy. The outcome of HSCT depends on many factors, including disease type and diagnosis, other medical comorbidities, age, history of prior treatment, and donor factors, among others. With increasing survival, and as the age range of HSCT candidates increases, there has been an increasing focus on pre-existing factors prior to treatment that may have an effect on outcomes and quality of life (QOL) post-transplant (1).

Growing evidence suggests that cognitive dysfunction, including memory, concentration, and psychomotor speed deficits are common and important QOL concerns for HSCT survivors (2). Most of what is known regarding objective cognitive dysfunction in the setting of HSCT is derived from limited samples of younger patients and longer post-transplant intervals. In a systematic review and meta-analysis of adults undergoing HSCT, median age was 43 years and median interval post-treatment was 360 days, with median pre- and post-transplant sample sizes of 58 and 43, respectively (3). Accuracy of reported rates of impairment from prior studies is qualified, given broad heterogeneity in cognitive measures used and in thresholds for classifying impairment, as well as potential practice effects from repeated testing. Despite these limitations, altered cognition is commonly observed post-transplant, including both declines and improvements, before discharge (4), days to months following discharge (5–8), and years to several years post-transplant (9–11). A recent review of neurocognitive dysfunction in HSCT (12) reported significant self-reported and objectively assessed cognitive dysfunction following transplant, with rates of cognitive dysfunction following treatment generally influenced by time since transplant. Potential
mechanisms for cognitive dysfunction have been suggested previously by structural and functional imaging studies. In a prospective study from this center, Correa et al. (2013) (13) examined longitudinal changes in brain structure of patients undergoing HSCT with or without total body irradiation (TBI), and found significant reduction in prefrontal gray matter and caudate volume from pre- to post-transplant, together with an increase in ventricular volume, compared to healthy controls.

There is some indication that cognitive dysfunction exhibited post-induction may already be present before transplant. In the same meta-analysis (3) described above, impairment was exhibited in 12% to 89% of patients prior to transplant; authors note that the wide range of impairment rates is in part owing to widely varying criteria for classification of impairment. While this qualifies interpretation of extent of pre-transplant dysfunction, the authors note that the majority of studies found impairment in at least one domain, including in verbal memory, executive functioning, attention, motor speed, verbal ability, visual memory, and visuospatial skills. Significantly, in the small sample (n = 28) tested from this center by Correa et al. (2013), baseline impairment was found in 21% of patients together with altered white matter integrity both at baseline and further changes in diffusivity at follow-up in the same patients (14).

As HSCT has evolved, older patients have increasingly been identified as candidates for transplant, due to the introduction of reduced-intensity and nonmyeloablative conditioning regimens, and improved human leucocyte antigen (HLA) typing and supportive care (15). Evidence from other cancer types indicates that treatment-related cognitive effects may be more severe with advancing age (16, 17), and recent work indicates that age may be a significant risk factor for cognitive dysfunction in transplant candidates as well (15). In a sample of 140 transplant patients who underwent cognitive assessment pre- and post-transplant, patients, regardless of age, exhibited lower cognitive performance pre-transplant than controls, and patients 65 and older exhibited lower verbal memory and verbal fluency post-transplant than either younger patients or controls. While these findings are suggestive, replication and clarification of the potential effect of age in cognitive effects pre- and post-transplant is an important step given the expanded age range of transplant recipients with newer methods.

The work described is strongly suggestive for both pre- and post-transplant changes in cognition. In the present study, we sought to address some of the limitations of this literature, including: 1) relatively small sample sizes that may limit statistical power; 2) heterogeneous cognitive assessments that may have varying levels of sensitivity to transplant related cognitive dysfunction; 3) heterogeneous criteria for determination of impairment; and 4) focus on relatively younger transplant patients that may not reflect the trend of inclusion of older cohorts. In the present study, patients between the ages 18–75 awaiting transplant (n=448) underwent the Montreal Cognitive Assessment (MoCA), a validated and standardized measure of objective cognitive function with empirically derived cut-off scores for identification of cognitive dysfunction. Following transplant and prior to discharge, a subset of patients (n=260) underwent repeated assessment with the MoCA to track longitudinal change in performance. Risk factors and outcomes associated with cognitive status were also examined.
PATIENTS, MATERIALS AND METHODS

Participants
Patients undergoing autologous and allogenic transplant between November 2011 and December 2014 on the Adult Bone Marrow Transplant Service (ABMTS) at Memorial Sloan Kettering Cancer Center (MSKCC) and who underwent MoCA testing as part of their pretransplant evaluation were included in the study cohort. Patients’ psychotropic medications were recorded and categorized into the following groups: opioids, neuroleptics and hypnotics. Standard transplant demographics were extracted from the ABMTS database, medication information was obtained from the institutional database and MoCA scores were obtained by searching the institutional database and, when necessary, a manual review of the electronic medical record (EMR).

Measures
The Montreal Cognitive Assessment (www.mocatest.org) is a brief performance-based paper and pencil assessment of cognitive function originally developed to detect mild cognitive impairment. It has been used worldwide in multiple languages as a measure of general cognitive function. Domains tested include: Visuospatial/Executive (Trail Making; Figure Copying; Clock Drawing); Language (Confrontation Naming); Memory (Verbal List Learning and Recall); Attention (Digit Span; Auditory Monitoring; Serial 7s); Abstraction (Similarities); and Orientation. It is administered over approximately 10–15 minutes, with a maximum score of 30 points. The suggested normal range for the MoCA is 26–30 points (18).

Design
The MoCA test (version 7.1) was administered initially during the period from day of admission up to day of transplant (d0) (approximately 5–8 days) in the patient’s hospital room by a member of a small group of trained occupational therapists (OTs). For a subset of patients that OT staff were able to capture prior to discharge the same test was performed a second time post-transplant within one week prior to discharge whenever possible. All patients received a minimum of one OT visit/per week. Patients who presented with cognitive dysfunction prior to transplant, as indicated by a score of <26 on the initial MoCA screen, received therapy focused on improving cognitive function in addition to functional impairments. This included functional cognitive activities such as reading and following multi-step directions, remediation strategies such as memory/attention worksheets or compensatory strategy training such as taking notes or using smartphone applications. Patients without cognitive dysfunction were instructed on improving self-care performance or overall strength/endurance to address any functional impairments. The impact of cognitive dysfunction on patients’ self-care performance and functional mobility was communicated by the OTs to the medical team through EMR documentation and verbal communication during daily rounds. For this cohort of study patients, the test was only administered in English to patients who declared English as their preferred language. Patients with less than 12 years of education received an extra point added to their total score as per standardized scoring instructions. To fully administer the MoCA screen, patients
needed to be able to follow simple verbal directions and grasp a pen to perform the written components of the measure (copy an image and draw a clock).

This retrospective study was conducted under a waiver of authorization approved by the MSKCC Institutional Review Board.

**Statistical analysis**—Select predictor variables of cognitive impairment were examined including age, Karnofsky Performance Status (KPS), gender, disease type, and use of psychotropic medications at the time of assessment. Psychotropic medications were divided into 3 categories as shown in Table 1: opioids, neuroleptics, and hypnotics. Transplant variables were also evaluated including type of transplant (ablative vs. reduced intensity vs. nonmyeloablative) and type of conditioning TBI-based vs. chemotherapy only). Univariate logistic regression was utilized to find variables associated with cognitive deficiency both pre- and post-transplant. Variables significant at p<0.05 were added to multivariate models. The relationship between early cognitive dysfunction and both overall survival (OS) and non-relapse mortality (NRM) were also assessed. OS was evaluated using Kaplan Meier methodology and was defined as time until death or last follow-up. NRM was evaluated via cumulative incidence and was defined as time until death with a competing risk of relapse.

**RESULTS**

**Demographic and Treatment Characteristics**

Four hundred forty-eight patients between the ages of 18–75 years were admitted for HSCT during the study period and underwent pre-transplant MoCA testing (pre-transplant group) (Table 2), (median age: 55.1 years; male: 62%). Approx. 70% of the entire cohort had a diagnosis of acute leukemia or myelodysplastic/myeloproliferative disorder. Conditioning was myeloablative for 61.8% of the entire group and 13.6% received high dose TBI. Nearly 70% of the patients received grafts from unrelated donors and the most common type of graft was T cell depleted (TCD)/CD34 selected in 52.2% of the patients. The group who received a TCD/CD34 selected HSCT did not receive any calcineurin inhibitor GVHD prophylaxis. Two hundred sixty of these patients who were able to be captured by OT staff for reassessment were tested again post-transplant at around the time of discharge (post-transplant group). Demographics for the group who had matched pre- and post-transplant MoCA testing were similar to the entire pre-transplant study group.

**Pre-transplant Impairment**

After admission and prior to transplant, the median total MoCA score was 26, range 10–30. Thirty-six percent of patients met criteria for cognitive dysfunction prior to transplant, as indicated by a MoCA total score <26, with a median total MoCA score for this group of 24, range 10–25. Distribution of scores for the 8 categories tested are shown in Table 3.

**Risk Factors for Pre-transplant Impairment**

Impairment rates based on a number of standard demographic variables as well as use of 3 categories of medications within 5 days of testing are shown in Table 4a. In univariate analysis (Table 5a) of these and a number of other patient/transplant demographics, age and
a diagnosis of MDS or MPD were statistically significant risk factors associated with an abnormal score, p=0.002 and 0.025, respectively.

Pre- versus Post-transplant Longitudinal Analysis

Demographics and results of testing for the patients who were tested pre- and post-transplant – the ‘matched group’ – are shown in Table 3. Median time between test and retest was 24 days. The median post-transplant total MoCA score was 27. Overall, 33% of the patients demonstrated a deficit at or around the time of discharge, similar to pre-transplant. Impairment rates based on a number of standard demographic variables as well as use of the 3 categories of medications within 5 days of testing are shown in Table 4b. In univariate analysis (Table 5b) of these and a number of other patient/transplant, demographics, only HCT CI was a significant predictor (p=0.03) at discharge.

The crosstabs table of longitudinal changes in impairment status are shown in Table 6. Of 97 patients who were impaired pre-transplant, 52% remained impaired post-transplant. Of 163 patients who were unimpaired pre-transplant, 77% remained unimpaired post-transplant. No association of longitudinal change in performance with interval between testing was observed (rank correlation = −0.08).

Given the relatively stable total MoCA scores at pre- and post-transplant (pre-median = 26; post-median = 27), the observation that 48% of patients converted from impaired to unimpaired post-transplant, and the fact that the same form of the MoCA was administered at test and retest (median interval: 24 days), additional analysis was undertaken to determine whether a practice effect might exist. Since learning and memory are subject to significant practice effects when the same items are presented at test (pre-transplant) and retest (post-transplant) over a relatively brief interval, Delayed Recall was examined for potential exclusion from longitudinal analysis. As expected, the greatest improvement in scores from pre- to post-transplant was in Delayed Recall. When Delayed Recall was not included in the total score, results indicated a significant decline from pre- to post-transplant (pre-median = 24; post-median = 23; p=0.029)

Association of Impairment with Treatment Outcomes

Regarding standard transplant outcomes, no significant association was found between an abnormal score pre- or post-transplant with 100-day landmark OS, NRM or aGVHD (Figure 1(a–c)).

Discussion

Results of this study indicate that a significant proportion of patients being admitted for allogeneic HSCT have cognitive dysfunction prior to transplant. The pre-transplant results described here are similar to those previously reported at this center using more extensive neurocognitive testing and MR imaging in a small sample of transplant cases (13), and is broadly consistent with studies described in a review of the literature of younger transplant candidates prior to transplant (12). Results also indicate a significant decline in cognitive function from pre- to post-transplant in a proportion of the patients. This pattern suggests that one or more aspects of past treatment, prior to transplant, may have significant effects
on cognitive function, and that aspects of the transplant itself further impact cognitive abilities. Strengths of the current study include a large sample size with a wide age range, and uniformity of cognitive testing and threshold for determining impairment.

While the specific mechanism is not known, pre-transplant cognitive dysfunction has been found by other groups (7, 19, 20) and may be related to previous and potentially multiple chemotherapy treatments (21), polypharmacy at the time of the assessment (22), and potentially a shared predisposition to cancer and cognitive decline even without treatment (23). While conditioning therapy in the early phase of an admission for transplant has been identified as a potential contributor to cognitive decline (24, 25), these effects are typically not demonstrated acutely, and rather are cumulative and appear later in the course of the hospital stay and/or post-discharge. Our results suggest that advancing age and disease type (MDS; MPD) may interact with one or more of these variables to increase the risk of cognitive dysfunction prior to transplant. Notably, the effect of disease type may be also related to age, since MDS and MPD patients on average were 10 years older than the other disease types. While we did not find an association with polypharmacy, several medications can have pronounced anticholinergic effects influencing cognition, including antihistamines, dopamine antagonists, H2 blockers, antipsychotics, antibiotics, benzodiazepines, and opioids (26).

Cognitive dysfunction related to cancer and cancer treatment has been firmly established following diagnosis and treatment for heterogeneous cancers (for review, 27). Self-report of survivors suggests difficulties returning to daily activities in both home-life and work, increased stress, the need for more time and effort in their work, increased frustration, work conflicts, financial impact, and decreased quality of life (QOL) (28, 29). Similar associations between cognition and quality of life have been reported in pediatric and adult transplant survivors (9, 30). In the transplant cohort studied here, a high rate of cognitive dysfunction prior to transplant and further decline post-transplant raises the concern for risk of poor adherence and compliance with post-discharge maintenance treatment, follow-up medical appointments for disease monitoring, and resumption of prior responsibilities and activities in daily life. These may include financial decision making, instrumental and general activities of daily living, and functional independence. We did not find this association in our analysis, which was restricted to disease specific outcomes, including OS, NRM and aGVHD. Not captured in our analysis are other factors that may detract from an association, specifically caregiver support, family support, and marital status, all of which may obscure the potential association of cognitive dysfunction and disease outcomes. This is particularly significant in our patients, since a standard requirement to be considered a transplant candidate is availability of 24/7 caregiver support for the first 100 days following transplant; absent mandatory caregiver support, cognitive dysfunction following transplant may have been demonstrated to play a significant role in treatment outcomes.

While the results reported here are suggestive, there are limitations to the data available for analysis that limit further interpretation. As a tertiary care facility, many patients presenting for transplant have a history of one or more frontline treatments from an outside facility. As such, complete records of pre-transplant treatment are often not available or complete and therefore such data could not be included for analysis of its impact on pre-transplant
cognition in this study. This is an important limitation given that previous treatment is a primary potential explanation for pre-transplant dysfunction. Interpretation of longitudinal change in cognitive function from pre- to post-treatment is also limited given that identical forms of the MoCA were administered at both time-points, leading to a likely practice effect on learning and memory items, specifically. Exclusion of the Delayed Recall domain resulted in significantly lower MoCA performance post-treatment as predicted. Presently, we have now instituted use of alternate forms of the MoCA that will limit practice effects so that longitudinal change in rates of impairment can be clarified.

Attention to cognitive dysfunction prior to transplant, and identification of patients most at risk, may alert the treatment team to those with greater need for oversight and involvement of caregivers, and referral for occupational therapy. This may be especially pertinent for the older adult patients, who are the fastest growing population undergoing transplant, but who often have limited options for caregivers. Longitudinal follow-up studies are needed to clarify variables that increase risk for cognitive dysfunction and to define the impact of cognitive changes on outcomes past d100 when caregivers become less involved.

ACKNOWLEDGEMENTS

The authors thank the Neurology and Adult Bone Marrow Transplant Services and the Department of Psychiatry and Behavioral Sciences for the review and constructive feedback of this manuscript.

Sources of funding: This work was supported by NIH/NCI Cancer Center Support Grant P30 CA008748.

REFERENCES

1. Saleh US, Brockopp DY. Quality of life one year following bone marrow transplantation: psychometric evaluation of the quality of life in bone marrow transplant survivors tool. Oncology nursing forum. 2001;28(9):1457–64. [PubMed: 11683315]
2. Meyers CA, Weitzner M, Byrne K, Valentine A, Champlin RE, Przepiorka D. Evaluation of the neurobehavioral functioning of patients before, during, and after bone marrow transplantation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1994;12(4):820–6. [PubMed: 8151324]
3. Phillips KM, McGinty HL, Cessna J, Asvat Y, Gonzalez B, Cases MG, et al. A systematic review and meta-analysis of changes in cognitive functioning in adults undergoing hematopoietic cell transplantation. Bone Marrow Transplant. 2013;48(10):1350–7. [PubMed: 23645166]
4. Ahles TA, Tope DM, Furstenberg C, Hann D, Mills L. Psychologic and neuropsychologic impact of autologous bone marrow transplantation. J Clin Oncol. 1996;14(5):1457–62. [PubMed: 8622059]
5. Beglinger LJ, Duff K, Van Der Heiden S, Moser DJ, Bayless JD, Paulsen JS, et al. Neuropsychological and psychiatric functioning pre- and posthematopoietic stem cell transplantation in adult cancer patients: a preliminary study. J Int Neuropsychol Soc. 2007;13(1):172–7. [PubMed: 17166316]
6. Chang G, Meadows ME, Orav EJ, Antin JH. Mental status changes after hematopoietic stem cell transplantation. Cancer. 2009;115(19):4625–35. [PubMed: 19551887]
7. Friedman MA, Fernandez M, Wefel JS, Myszkka KA, Champlin RE, Meyers CA. Course of cognitive decline in hematopoietic stem cell transplantation: a within-subjects design. Arch Clin Neuropsychol. 2009;24(7):689–98. [PubMed: 19767298]
8. Jacobs SR, Small BJ, Booth-Jones M, Jacobsen PB, Fields KK. Changes in cognitive functioning in the year after hematopoietic stem cell transplantation. Cancer. 2007;110(7):1560–7. [PubMed: 17685391]
9. Harder H, Cornelissen JJ, Van Gool AR, Duivenvoorden HJ, Eijkenboom WM, van den Bent MJ. Cognitive functioning and quality of life in long-term adult survivors of bone marrow transplantation. Cancer. 2002;95(1):183–92. [PubMed: 12115332]

10. Peper M, Steinworth S, Schraube P, Fruehaufl S, Haas R, Kimmig BN, et al. Neurobehavioral toxicity of total body irradiation: a follow-up in long-term survivors. Int J Radiat Oncol Biol Phys. 2000;46(2):303–11. [PubMed: 10661336]

11. Syrjala KL, Artherholt SB, Kurland BF, Langer SL, Roth-Roemer S, Elrod JB, et al. Prospective neurocognitive function over 5 years after allogeneic hematopoietic cell transplantation for cancer survivors compared with matched controls at 5 years. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(17):2397–404. [PubMed: 21537032]

12. Buchbinder D, Kelly DL, Duarte RF, Auletta JJ, Bhatt N, Byrne M, et al. Neurocognitive dysfunction in hematopoietic cell transplant recipients: expert review from the late effects and Quality of Life Working Committee of the CIBMTR and complications and Quality of Life Working Party of the EBMT. 2018;53(5):535–55.

13. Correa DD, Root JC, Baser R, Moore D, Peck KK, Lis E, et al. A prospective evaluation of changes in brain structure and cognitive functions in adult stem cell transplant recipients. Brain Imaging Behav. 2013;7(4):478–90. [PubMed: 23329358]

14. Correa DD, Wang Y, West JD, Peck KK, Root JC, Baser RE, et al. Prospective assessment of white matter integrity in adult stem cell transplant recipients. Brain Imaging Behav. 2016;10(2):486–96. [PubMed: 26153467]

15. Hoogland AI, Nelson AM, Small BJ, Hyland KA, Gonzalez BD, Booth-Jones M, et al. The Role of Age in Neurocognitive Functioning among Adult Allogeneic Hematopoietic Cell Transplant Recipients. Biol Blood Marrow Transplant. 2017;23(11):1974–9. [PubMed: 28797784]

16. Ahles TA, Saykin AJ, McDonald BC, Li Y, Furstenberg CT, Hanscom BS, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol. 2010;28(29):4434–40. [PubMed: 20837957]

17. Vega JN, Dumas J, Newhouse PA. Cognitive Effects of Chemotherapy and Cancer-Related Treatments in Older Adults. Am J Geriatr Psychiatry. 2017;25(5):1415–26. [PubMed: 28495470]

18. Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. Neurology. 2011;77(13):1272–5. [PubMed: 21917776]

19. Harder H, Van Gool AR, Cornelissen JJ, Duivenvoorden HJ, Eijkenboom WM, Barge RM, et al. Assessment of pre-treatment cognitive performance in adult bone marrow or haematopoietic stem cell transplantation patients: a comparative study. Eur J Cancer. 2005;41(7):1007–16. [PubMed: 15862749]

20. Schulz-Kindermann F, Mehnert A, Scherwath A, Schirmer L, Schleimer B, Zander AR, et al. Cognitive function in the acute course of allogeneic hematopoietic stem cell transplantation for hematological malignancies. Bone Marrow Transplant. 2007;39(12):789–99. [PubMed: 17417661]

21. Dietrich J, Monje M, Wefel J, Meyers C. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. Oncologist. 2008;13(12):1285–95. [PubMed: 19019972]

22. Rawle MJ, Cooper R, Kuh D, Richards M. Associations Between Polypharmacy and Cognitive and Physical Capability: A British Birth Cohort Study. J Am Geriatr Soc. 2018;66(5):916–23. [PubMed: 29574684]

23. Olson B, Marks DL. Pretreatment Cancer-Related Cognitive Impairment-Mechanisms and Outllook. Cancers (Basel) 2019;11(5).

24. Bartynski WS, Zeigler Z, Spearman MP, Lin L, Shadduck RK, Lister J. Etiology of cortical and white matter lesions in cyclosporin-A and FK-506 neurotoxicity. AJNR Am J Neuroradiol. 2001;22(10):1901–14. [PubMed: 11733324]

25. Bartynski WS, Zeigler ZR, Shadduck RK, Lister J. Pretransplantation conditioning influence on the occurrence of cyclosporine or FK-506 neurotoxicity in allogeneic bone marrow transplantation. AJNR Am J Neuroradiol. 2004;25(2):261–9. [PubMed: 14970028]

26. Lopez-Alvarez J, Sevilla-Llewellyn-Jones J, Aguera-Ortiz L. Anticholinergic Drugs in Geriatric Psychopharmacology. Front Neurosci. 2019;13:1309. [PubMed: 31866817]
27. Ahles TA, Root JC. Cognitive Effects of Cancer and Cancer Treatments. Annual review of clinical psychology. 2018;14:425–51.

28. Von Ah D, Habermann B, Carpenter JS, Schneider BL. Impact of perceived cognitive impairment in breast cancer survivors. European journal of oncology nursing : the official journal of European Oncology Nursing Society. 2013;17(2):236–41. [PubMed: 22901546]

29. Selamat MH, Loh SY, Mackenzie L, Vardy J. Chemobrain experienced by breast cancer survivors: a meta-ethnography study investigating research and care implications. PloS one. 2014;9(9):e108002. [PubMed: 25259847]

30. Parsons SK, Phipps S, Sung L, Baker KS, Pulsipher MA, Ness KK. NCI, NHLBI/PBMTC First International Conference on Late Effects after Pediatric Hematopoietic Cell Transplantation: health-related quality of life, functional, and neurocognitive outcomes. Biol Blood Marrow Transplant. 2012;18(2):162–71. [PubMed: 22155139]
Highlights

- Prior to hematopoietic stem cell transplant, 36% of patients meet criteria for cognitive dysfunction
- Age and disease type are risk factors for cognitive dysfunction
- Post-transplant, 33% of patients meet criteria for cognitive dysfunction
Figure 1.
(a-c): (a) Survival probability associated with cognitive status at pre- and post-transplant. (b) Non-relapse mortality associated with cognitive status at pre- and post-transplant (c) GVHD associated with cognitive status at pre- and post-transplant.
### Table 1. Medication list

| OPIOIDS      | NEUROLEPTICS | HYPNOTICS |
|--------------|--------------|-----------|
| Fentanyl     | Thorazine    | Lorazepam |
| Hydromorphone| Risperidone  | Clonazepam|
| Morphine     | olanzapine   | Alprazolam|
| Oxycodone    | Temazepam    |           |
| Hydroxcodeine| Zolpidem     |           |
|              | Zaleplon     |           |
|              | Eszopiclone  |           |
|              | Diphenhydramine |     |
Table 2.

Patient characteristics and outcomes

| Characteristics | Whole Group (n=448) | Matched Group * (n=260) |
|----------------|---------------------|------------------------|
|                | Median (Range)      | Median (Range)         |
| Age            | 55.1 (18–75)        | 54.4 (21–75)           |
| KPS            | 90 (40–100)         |                        |
| Sex            | n (%)               | n (%)                  |
| Male           | 279 (62%)           | 157 (60%)              |
| Disease        | n (%)               | n (%)                  |
| Leukemia       | 211 (47)            | 130 (50)               |
| Lymphoma       | 93 (21)             | 54 (20)                |
| MDS/MPD        | 86 (19)             | 45 (17)                |
| MM             | 55 (12)             | 30 (12)                |
| Other-nonmalignant | 3 (<1)       | 1 (<1)                 |
| HCT-CI         | Median (Range)      | Median (Range)         |
|                | 3 (0–10) *          | 2 (0–10) **            |
| Donor type     | n (%)               | n (%)                  |
| HLA-identical related | 132 (30)      | 80 (31)                |
| HLA-mismatched related | 4 (<1)         | 1 (<1)                 |
| HLA-matched unrelated | 184 (41)     | 103 (40)               |
| HLA-mismatched unrelated | 128 (29)  | 76 (29)                |
| Source of stem cells | n (%)               | n (%)                  |
| BM             | 17 (4)              | 9 (3)                  |
| PBSC           | 360 (80)            | 208 (80)               |
| BM and PBSC    | 2 (<1)              | 0 (0)                  |
| Cords          | 69 (15)             | 43 (17)                |
| BMT type       | n (%)               | n (%)                  |
| Conventional   | 145 (32)            | 83 (32)                |
| TCD            | 234 (52)            | 134 (52)               |
| Cord(s)        | 69 (15)             | 43 (17)                |
| Conditioning   | n (%)               | n (%)                  |
| Chemo Base d   | 271 (61)            | 154 (59)               |
| High TBI Based | 61 (14)             | 38 (15)                |
| Low TBI Based  | 116 (26)            | 68 (26)                |
| Intensity      | n (%)               | n (%)                  |
| Ablative       | 277 (62)            | 157 (60)               |
| Reduced        | 131 (29)            | 79 (30)                |
| Characteristics | Whole Group (n=448) | Matched Group* (n=260) |
|-----------------|--------------------|------------------------|
| Nonablative     | 40 (9)             | 24 (9)                 |

*Matched group includes patients administered the MoCA pre- and post-transplant.

**one HCT-CI unavailable. Abbreviations: MDS=Myelodysplastic syndrome; MPD = myeloproliferative disorder; GVHD=Graft versus Host Disease; MM=Multiple Myeloma; HCT-CI = Hematopoietic cell transplantation-specific comorbidity index; HLA=Human Leucocyte Antigen; BM=Bone marrow; PBSC = Peripheral blood stem cells; TCD=T Cell Depleted; TBI=Total Body Irradiation
| Variables                  | Pre-HCT (n=448) (%) | Post-HCT (n=260) (%) |
|----------------------------|---------------------|----------------------|
| Abstraction score (2):     |                     |                      |
| 0                         | 1.1                 | 0.8                  |
| 1                         | 6                   | 5.4                  |
| 2                         | 93                  | 94                   |
| Abnormal                  | 71                  | 6.2                  |
| Attention score (6):       |                     |                      |
| 0                         | 0                   | 0                    |
| 1                         | 0.4                 | 1.2                  |
| 2                         | 2                   | 3.8                  |
| 3                         | 4.5                 | 3.7                  |
| 4                         | 5.8                 | 7.7                  |
| 5                         | 16                  | 20                   |
| 6                         | 72                  | 64                   |
| Abnormal                  | 28.7                | 36.4                 |
| Delayed recall score (5):  |                     |                      |
| 0                         | 8.9                 | 5.4                  |
| 1                         | 11                  | 4.2                  |
| 2                         | 21                  | 12                   |
| 3                         | 26                  | 25                   |
| 4                         | 18                  | 26                   |
| 5                         | 15                  | 28                   |
| Abnormal                  | 84.9                | 72.6                 |
| Language fluency score (1):|                     |                      |
| 0                         | 31                  | 32                   |
| 1                         | 69                  | 68                   |
| Abnormal                  | 31                  | 32                   |
| Repeat score (2):          |                     |                      |
| 0                         | 4.9                 | 3.1                  |
| 1                         | 12                  | 15                   |
| 2                         | 83                  | 82                   |
| Abnormal                  | 16.9                | 18.1                 |
| Naming score (3):          |                     |                      |
| 0                         | 0                   | 0                    |
| 1                         | 0.9                 | 0                    |
| 2                         | 7.1                 | 8.1                  |
| 3                         | 92                  | 92                   |
| Variables                      | Pre-HCT (n=448) (%) | Post-HCT (n=260) (%) |
|-------------------------------|---------------------|----------------------|
| Abnormal                      | 8                   | 8.1                  |
| Orientation score (6):        |                     |                      |
| 0                             | 0                   | 0                    |
| 1                             | 0                   | 0                    |
| 2                             | 0.2                 | 0                    |
| 3                             | 0                   | 0.8                  |
| 4                             | 0.9                 | 3.5                  |
| 5                             | 14                  | 22                   |
| 6                             | 85                  | 74                   |
| Abnormal                      | 15.1                | 26.3                 |
| Visuospatial-executive score (5): |                   |                      |
| 0                             | 0.4                 | 0.4                  |
| 1                             | 1.3                 | 1.5                  |
| 2                             | 2.7                 | 5                    |
| 3                             | 8                   | 9.2                  |
| 4                             | 27                  | 27                   |
| 5                             | 61                  | 57                   |
| Abnormal                      | 39.4                | 43.1                 |
| MoCA Total Score (30)         |                     |                      |
| Abnormal (<26)                | 36                  | 33                   |
| Normal                        | 64                  | 67                   |
### Table 4

Impairment rates

#### A. Pre-transplant

| Variable | abnormal n (%) | normal n (%) |
|----------|----------------|--------------|
|          | 162            | 286          |
| Age      | 58 (24, 76)    | 54 (18, 75) |
| KPS      | 90 (80, 90)    | 90 (80, 90) |
| Sex-Male | 55 (34)        | 114 (40)     |
| Disease groups |       |              |
| Leukemia | 76 (48)        | 135 (47)     |
| Lymphoma | 27 (17)        | 66 (23)      |
| MDS/MPD  | 39 (24)        | 47 (16)      |
| MM       | 18 (7)         | 37 (13)      |
| Medication groups | |              |
| Opioids  | 137 (85)       | 246 (86)     |
| Neuroleptics |        | 91 (32) |
| Hypnotics| 4 (2.5)        | 7 (2.4)      |

#### B. Post-transplant

| Variable | abnormal n (%) | normal n (%) |
|----------|----------------|--------------|
|          | 87             | 173          |
| Age      | 56 (23, 74)    | 54 (22, 75) |
| Sex-Male | 36 (41)        | 67 (39)      |
| Disease groups |       |              |
| Leukemia | 50 (58)        | 80 (46)      |
| Lymphoma | 15 (17)        | 39 (23)      |
| MDS/MPD  | 16 (19)        | 29 (17)      |
| MM       | 5 (5.8)        | 25 (14)      |
| Conditioning intensity | |          |
| Ablative | 49 (56)        | 108 (62)     |
| Reduce intensity | | 46 (27) |
| Nonablative |     | 19 (11)    |
| Regimen type |       |              |
| Chemotherapy | 51 (59) | 103 (60) |
| High dose TBI | 15 (17) | 23 (13) |
| Low dose TBI | 21 (24) | 47 (27) |
| Graft type |       |              |
| TCD      | 41 (47)        | 93 (54)      |
| Conventional | 29 (33) | 54 (31) |
| Cord     | 17 (20)        | 26 (15)      |
| Medication groups | Group 1 | Group 2 |
|-------------------|---------|---------|
| Opioids           | 83 (89) | 148 (84) |
| Neuroleptics      | 30 (32) | 40 (23)  |
| Hypnotics         | 6 (6.5) | 4 (2.3)  |
Table 5:

Univariate analysis: normal v. abnormal

| Characteristic | n %     | OR    | 95% CI      | p-value |
|----------------|---------|-------|-------------|---------|
| **A. Pre-transplant** |         |       |             |         |
| Age            | 55 (45, 64) | 1.03  | 1.01, 104   | 0.002   |
| Sex (M/F)      | 279 (62)/169 (38) | 0.78  | 0.52, 1.16  | 0.2     |
| **Disease group** |         |       |             |         |
| Lymphoma       | 93 (21)  | -     | -           | -       |
| Leukemia       | 211 (47) | 1.38  | 0.82, 2.36  | 0.2     |
| MDS + MPD      | 86 (19)  | 2.03  | 1.10, 3.79  | 0.025   |
| Myeloma        | 55 (12)  | 1.19  | 0.57, 2.43  | 0.6     |
| Other          | 3 (1)    |       |             |         |
| **HCT-Ci**     |         |       |             |         |
| <4             | 326 (73) | -     | -           | -       |
| ≥4             | 122 (27) | 0.90  | 0.58, 1.39  | 0.6     |
| **Medications** |         |       |             |         |
| Opioid         | 383 (85) | 0.89  | 0.52, 1.55  | 0.7     |
| Neuroleptic    | 133 (30) | 0.75  | 0.48, 1.15  | 0.2     |
| Hypnotic       | 11 (2.5) | 1.01  | 0.26, 3.39  | >0.9    |
| **KPS**        |         |       |             |         |
| ≤80            | 197 (44) | -     | -           | -       |
| >80            | 247 (56%)| 0.80  | 0.54, 1.19  | 0.3     |
| unknown        | 4        |       |             |         |
| **B. Post-transplant** |         |       |             |         |
| Age            | 54 (45, 64) | 1.01  | 0.99, 1.03  | 0.2     |
| Sex (M/F)      | 157 (60)/103 (40) | 1.12  | 0.66, 1.89  | 0.7     |
| **Disease group** |         |       |             |         |
| Lymphoma       | 54 (21)  | -     | -           | -       |
| Leukemia       | 130 (50) | 1.62  | 0.83, 3.32  | 0.2     |
| MDS + MPD      | 45 (17)  | 1.43  | 0.61, 3.39  | 0.4     |
| Myeloma        | 30 (12)  | 0.52  | 0.15, 1.53  | 0.3     |
| unknown        | 3        |       |             |         |
| **HCT-Ci**     |         |       |             |         |
| <4             | 192 (74) | -     | -           | -       |
| ≥4             | 68 (26)  | 1.87  | 1.05, 3.31  | 0.031   |
| **Medications** |         |       |             |         |
| Opioid         | 108 (42) | 0.99  | 0.58, 1.67  | >0.9    |
| Neuroleptic    | 132 (51) | 1.06  | 0.63, 1.78  | 0.8     |
| Hypnotic       | 60 (23)  | 1.32  | 0.72, 2.39  | 0.4     |
| KPS  | <=80   | 110 (42) | -   | -   | -   |
|      | >80    | 149 (58) | 0.81| 0.48, 1.36 | 0.4 |
| unknown | 4   |           |     |     |     |
| Conditioning |        |            |     |     |     |
| Chemo | 154 (59) | -   | -   | -   |
| TBI   | 106 (41) | 1.04| 0.61, 1.75 | 0.9 |
| Graft |        |            |     |     |     |
| Conventional | 83 (32) | -   | -   | -   |
| Cord  | 43 (17)  | 1.22| 0.56, 2.60 | 0.6 |
| TCD   | 134 (52) | 0.82| 0.46, 1.48 | 0.5 |
| Intensity |        |            |     |     |     |
| Ablative | 157 (60) | -   | -   | -   |
| Nonablative | 24 (9.2) | 0.58| 0.18, 1.54 | 0.3 |
| Reduced | 79 (30)  | 1.58| 0.90, 2.77 | 0.11|
| Graft |        |            |     |     |     |
| BM    | 9 (3.5)  | -   | -   | -   |
| Cord  | 43 (17)  | 0.82| 0.19, 3.71 | 0.8 |
| PB    | 208 (80) | 0.58| 0.15, 2.41 | 0.4 |
Table 6.
Longitudinal MoCA Performance from Pre- to Post-transplant

| Post-transplant (n=260) | Abnormal 87/260 | Normal 173/260 |
|------------------------|-----------------|----------------|
| Pre-transplant          |                 |                |
| Abnormal 97/260        | 50              | 47             |
| Normal 163/260         | 37              | 126            |