Published in final edited form as:

Bone Marrow Transplant. 2013 October ; 48(10): 1350–1357. doi:10.1038/bmt.2013.61.

A systematic review and meta-analysis of changes in cognitive functioning in adults undergoing hematopoietic cell transplantation

Kristin M. Phillips, PhD[1], **Heather L. McGinty, MA**[2], **Julie Cessna, MPH**[2], **Yasmin Asvat, MA**[2], **Brian Gonzalez, MA**[2], **Mallory G. Cases, MPH**[1], **Brent J. Small, PhD**[2], **Paul B. Jacobsen, PhD**[1], **Joseph Pidala, MD**[1], and **Heather S. L. Jim, PhD**[1]

[1]Moffitt Cancer Center, Tampa, Florida, USA

[2]Department of Psychology, University of South Florida, Tampa, Florida, USA

Abstract

Evidence is mixed regarding the effects of hematopoietic cell transplantation (HCT) on changes in cognitive functioning among adults. Meta-analysis, which is designed to help reconcile conflicting findings, has not yet been conducted on studies of adults receiving HCT. To fill this gap, the current study provides a systematic review and meta-analysis of cognitive functioning in adults receiving HCT. A search of PubMed, PsycInfo, CINAHL, and Cochrane Library yielded 732 abstracts, which were independently evaluated by pairs of raters. Seventeen studies were systematically reviewed; eleven were retained for meta-analysis. There was agreement that cognitive impairments are evident for a subset of patients prior to HCT. Meta-analytic findings of 404 patients revealed no significant changes in cognitive functioning pre- to post-HCT (*P* values > .05). Age, time since transplant, and total body irradiation were not associated with changes in cognitive functioning. Patients who received autologous transplants were more likely to demonstrate improvements in attention (*P* = .004). The systematic review identified several limitations of existing literature, including small, clinically heterogeneous samples. Large, cooperative group studies are needed to address these design limitations. Nevertheless, results from the current meta-analysis suggest that cognitive functioning does not significantly change following HCT.

Keywords

cognition; hematopoietic cell transplant; neoplasms

Corresponding Author: Heather S. L. Jim Ph.D., Department of Health Outcomes and Behavior, Moffitt Cancer Center, MRC-PSY, 12902 Magnolia Drive, Tampa, FL 33612; heather.jim@moffitt.org.

Supplementary information is available at BMT's website.

Conflict of Interest: The authors have no conflicts of interest to disclose.

Introduction

Advances in hematopoietic cell transplant (HCT) have resulted in its increasing use in recent years, giving rise to a growing number of HCT survivors (1). Nevertheless, HCT remains a physically demanding treatment that may result in neurotoxicities such as delirium, seizures, and risk of significant cognitive impairment (2–4). Impairment in cognitive function can have important consequences for quality of life, such as the ability to return to work or school, function socially, and attain career and educational goals (5, 6).

Subjective reports of cognitive impairments are common before and after HCT. HCT patients often report difficulty in concentration, memory, and word-finding (7–9). Nevertheless, studies of objective neuropsychological functioning in HCT patients show mixed findings. A number of studies have reported that some patients experience impaired functioning on neuropsychological tests prior to HCT, but there are inconsistencies in the literature regarding whether cognitive functioning improves, declines, or remains stable following transplant. An ideal technique to help reconcile conflicting data is meta-analysis, in which a weighted average of effect sizes is calculated across studies. By pooling samples across studies, there is increased power to find effects where they exist.

The objective of the current systematic review and meta-analysis was to evaluate studies of cognitive functioning in adults undergoing HCT for hematological malignancies. We sought to identify all studies that assessed adults with hematologic cancers pre- and post-transplant using neuropsychological tests. We hypothesized there would be significant declines in cognitive impairment at follow-up compared to baseline. We also aimed to explore the effects of demographic and clinical factors on changes in cognitive functioning.

Method

Search Strategy

This systematic review and meta-analysis was conducted in accordance to PRISMA guidelines (10). Identification of appropriate studies began with searches of PubMed, PsycInfo, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and the Cochrane Library. Search terms are presented in Table 1. Reference lists from publications retrieved were also examined to identify studies. The search was inclusive of studies published up to September 2011 with no limit on start date.

Selection Strategy

Selection of abstracts for full review was conducted by three pairs of raters. Abstracts were independently rated and each rater generated a list of studies to retrieve for full-text review. Lists were then compared and discrepancies resolved by consensus. Study inclusion criteria are shown in Table 2.

Review Strategy

Studies selected for full-text review were examined and data were extracted independently by pairs of raters. Discrepancies in data extraction were resolved by consensus. Abstraction of results focused on the baseline assessment closest to the time of transplant and the last

post-transplant follow-up. Data extracted included neuropsychological test data (i.e., means, standard deviations, sample size), study design characteristics (i.e., timing of assessments), patient characteristics (i.e., age and education), and treatment characteristics (i.e., transplant type, time since HCT, and treatment with total body irradiation, intrathecal chemotherapy, and cranial irradiation). When published articles did not present sufficient data to calculate effect sizes, authors were contacted for the required information.

Neuropsychological Domains

Neuropsychological tests were categorized according to the predominant cognitive domain they assessed (11). The eight domains were: attention, executive functioning, information processing, motor speed, verbal ability, verbal memory, visual memory, and visuospatial ability (11). Neuropsychological tests and their corresponding cognitive domains are provided in the Supplement (see Table S1).

Statistical Analysis

Meta-analytic procedures were based on those outlined by Hedges and Olkin (12). When studies presented separate means and standard deviations for patients who did and did not have delirium (6, 13), the data for these two groups were pooled. Individual effect size estimates were computed for each reported neuropsychological test. The information used to generate effect size estimates (*g*) was based upon within-subjects change from pre-HCT baseline to the last post-HCT measurement point. Random effects models were used to calculate effect sizes (14).

In addition to describing the differences between pre- and post-HCT cognitive functioning, we identified *a priori* several moderating characteristics that could potentially impact effect sizes. Age, education, time post-HCT, and percent of patients receiving autologous stem cell transplant, TBI, intrathecal chemotherapy, and cranial irradiation were identified for examination as continuous moderators using meta-regression with method of moments estimation. Meta-regression was only performed for cognitive domains that contained at least five studies. Analyses were conducted using Comprehensive Meta Analysis software (15).

Results

Search Results

Of a total of 732 abstracts were identified through searches of electronic databases, 17 studies met criteria for systematic review (6, 13, 16–30) (see Figure 1). Regarding the meta-analysis, although 13 studies assessed patients at both pre-HCT and post-HCT using standardized neuropsychological assessments, sufficient data to calculate effect sizes were not available for two studies (22, 23). Study characteristics of the 11 studies retained for meta-analysis (6, 13, 20, 21, 24–30) and the additional six studies included in the review (16–19, 22, 23) are displayed in Table 3.

Description of Study Participants

Demographic and clinical characteristics of participants in the 17 studies are presented in Table 3. Sample sizes for pre-HCT assessments ranged from 14 to 286. Sample sizes for the last post-HCT assessments ranged from 9 to 83. All studies consisted of samples that included both men and women. All studies reported age; average age ranged from 35.50 to 53.05 years (median = 42.59 years). Of the studies that reported years of education as a continuous variable (k=6) (6, 13, 18, 22, 24, 26), average education ranged from 9.90 to 15.25 years (median = 14.53 years); the study with an average of 9.90 years of education (18) included patients as young as 16 years old, who were likely still in school.

As shown in Table 3, studies included patients with variety of hematologic malignancies including lymphoma, leukemia, and/or multiple myeloma. Some studies also included a subset of patients with non-hematologic malignancies (e.g., breast carcinoma, severe aplastic anemia). Four studies contained only participants who received an allogeneic transplant (21, 23, 25, 29), three studies contained only participants who received an autologous transplant (18, 20, 30), and nine studies contained both, with the percent of patients receiving autologous transplants ranging from 12.5% to 58% (6, 13, 17, 19, 22, 24, 26–28). One study did not report type of transplant (16).

Studies varied in their reporting of induction regimens. The percent of patients who received TBI ranged from 1.8% to 100% (k=14) (6, 16–21, 23, 25–30) and was not reported in three studies (13, 22, 24). Of the studies that included patients who had received cranial irradiation (k=5), percents ranged from 2.5% to 14.5% (16–19, 23). Patients receiving cranial irradiation were excluded in five studies (25, 27–30) and were not reported in five studies (13, 21, 22, 24, 26). The remaining two studies reported one number for the percent of patients who received cranial irradiation or intrathecal chemotherapy (6, 20). Regarding intrathecal chemotherapy, studies were evenly split between excluding these patients (18, 21, 25, 29, 30), including small numbers of them (8% to 27.3%) (16, 17, 19, 27, 28), and not reporting whether they were included (13, 22–24, 26).

Characteristics of Study Designs

Information on the timing of assessments for the 17 studies is presented in Table 3. Of the 17 studies, two were cross-sectional: one study included only a pre-HCT assessment (16) and one included only a post-HCT assessment (17). Of the 15 longitudinal studies, information on baseline and last assessments are shown in Table 3. Two longitudinal studies did not assess patients pre- and post-HCT and so were not included in the meta-analysis (18, 19). Two additional studies (22, 23) did not provide sufficient data to include in the meta-analysis, resulting in a final sample of 11 studies for the meta-analysis (6, 13, 20, 21, 24–30).

Median time to last follow-up assessment in the 15 longitudinal studies ranged from during hospitalization to 8.80 years post-treatment (median = 360 days; see Table 1). However, median time to follow-up should be interpreted with caution because the measurement of time from HCT to follow-up varied across studies. That is, follow-up assessments were reported as time post-HCT (k=9) (6, 13, 20–24, 26, 29), post-baseline (k=2) (25, 28), post-

last treatment (19), or post-TBI (k=2) (18, 30). For one study it was unclear whether follow-up time was post-HCT or post-baseline (27).

The majority of studies (71%, k=12) did not contain a comparison group (6, 16, 17, 19, 20, 22–24, 26, 27, 29, 30). The comparison groups that were used (k=5) were heterogeneous: cancer patients who had undergone other treatments (k=2) (25, 28), people with no history of cancer (k=2) (13, 21), and people with renal insufficiency (k=1) (18). Due to heterogeneity, comparison groups were not included in the meta-analysis.

Prevalence of cognitive impairment pre-HCT

As nearly all patients receive cancer treatments prior to their candidacy for HCT, it is likely that cognitive functioning may be impaired prior to transplant. The majority of studies (k=10) evaluated the percent of patients who were cognitively impaired on neuropsychological tests prior to transplant (16, 18, 22–24, 26, 27, 29, 31, 32). However, criteria for impairment varied widely. Despite differences in how it was defined, the majority of studies reported impairments in at least one domain of cognitive functioning pre-HCT. The study that found the highest rates of impairment (89% for measures of motor speed) used the most lenient criteria of z-scores ≤ 1 SD below normative means (22). The study that found the lowest rates of impairment (12% of patients having impaired scores on more than 20% of the neuropsychological tests) used the most stringent criteria of z-scores ≤ 1.5 SD below normative means on at least four subtests (32). Deficits in pre-HCT functioning were reported in the domains of verbal memory (k=5) (16, 24, 26, 29, 31), executive functioning (k=4) (23, 24, 26, 27), attention (k=3) (24, 26, 29), motor speed (k=3) (22, 27, 32), verbal ability (k=3) (18, 23, 31), visual memory (k=2) (18, 32), and visuospatial skills (k=1) (32). Thus, there was consensus that cognitive impairment is evident prior to HCT, although rates of cognitive impairment varied widely.

Changes in cognitive functioning

The longitudinal studies report a mix of significant changes and no changes across neuropsychological domains. Findings were mixed regarding whether patients demonstrated improvements (k=4) (22, 24, 27, 30), declines (k=3) (20, 26, 29), both improvements and declines (k=3) (21, 23, 25), or no change (k=1) (28) on neuropsychological tests. Of the studies that found improvements in one or more domains, (21–25, 27, 30) improvements were observed in tests of attention (24, 30), executive functioning (21, 24, 30), verbal ability (21), and visual or verbal memory (24, 25, 27, 30). One study (22) found improvements in all domains they assessed except attention. Of the studies that found declines (20, 23, 25, 26, 29) or persistent deficits (21, 28) in one or more domain, domains affected were attention (29), executive functioning (20, 23, 28), motor speed (21, 25, 28), verbal ability (20), and verbal memory (26). Such inconsistencies in the existing literature support the need for meta-analysis.

Meta-Analytic Findings

The meta-analysis is based on a final sample of 404 patients who had pre- and post-treatment neuropsychological assessments. Weighted average effect sizes for each cognitive domain are shown in Table 4. There were no significant changes in any domain, including

executive functioning (k=11), attention (k=10), verbal ability (k=10), verbal memory (k=8), motor speed (k=4), visual memory (k=3), visuospatial ability (k=3), or information processing (k=2), *P* values > .05.

Meta-regression was used to determine whether effect sizes varied systematically across level of continuous variables. Domains with five or more studies (i.e., executive functioning, attention, verbal ability, and verbal memory) were evaluated. Results indicated that studies with a higher percentage of patients who received autologous stem cell transplants had greater improvement over time in attention scores (b=1.58, *P* = .004). There were no significant effects of age, number of days post-HCT, or percentage of patients who received TBI (*P* values > .05) on any of the domains. The paucity of studies that reported average years of education (k=5) or included participants who received intrathecal chemotherapy (k=2), cranial irradiation (k=1) or did not specify which of these treatments patients received (k=2) prohibited meaningful analysis of these potential moderators.

Discussion

We identified 17 studies that evaluated adults receiving HCT with neuropsychological tests. Our systematic review revealed that studies varied widely with regard to demographic and clinical variables reported and how cognitive impairment was defined. There was general consensus that cognitive impairments are evident in a subset of patients prior to HCT. However, there were conflicting reports about whether cognitive functioning improved, declined, or remained stable at follow-up. We therefore conducted a meta-analysis based on 11 studies that had means and standard deviations available for pre- and post-transplant assessments. Results of the meta-analysis indicated no significant within-patient changes in cognitive functioning pre- to post-transplant.

Regarding rates of pre-HCT cognitive impairment, the review identified 10 studies that reported the percentage of patients who demonstrated cognitive impairment. These percentages ranged from 12% to 89%, depending on how impairment was defined. These discrepant results underscore the importance of determining a standard criterion for cognitive impairment in cancer patients, such as that proposed by the International Cancer and Cognition Task Force (i.e., two or more tests at or below −1.5 SD from the normative mean or one or more tests at or below −2.0 SD from the mean) (33). Despite differing criteria for impairment, there was consensus among reviewed studies that a subset of patients have impaired functioning in one or more domain prior to transplant.

With regard to pre- to post-HCT changes in functioning, the review found inconsistencies regarding whether patients declined, improved or remained stable over time and which domains of cognitive functioning were affected. The meta-analysis found trends toward improvement in verbal memory and visual memory (*P* values < .10), but no statistically significant change over time in any of the eight cognitive domains. The lack of significant change over time is contrary to our hypothesis that HCT would be associated with declines in cognitive functioning. Nevertheless, lack of pre- to post-treatment change is notable because practice effects, or improvement due to familiarity with neuropsychological tests, are typically expected upon repeated cognitive testing. The failure of HCT patients to

demonstrate improvements over repeated tests may itself be a sign of a deficit. It should be noted that patients have typically been treated with one or more rounds of standard-dose chemotherapy prior to transplant, which may contribute to pre-HCT impairment as well as a lack of practice effects observed in this sample. The issue of practice effects underscores the importance of including matched non-cancer control groups in longitudinal studies of cognitive functioning to contrast normal expected improvement to patient change.

The general lack of significant improvement from pre- to post-HCT demonstrated by the current meta-analysis is an important finding given that many patients experienced deficits prior to HCT. It may be the case that cognitive functioning is impaired prior to HCT, with minimal recovery or decline thereafter. It may also be the case that cognitive functioning declines for a subset of patients during the acute recovery period, but later returns to baseline levels. The results of the current study suggest that for patients who are experiencing cognitive difficulties prior to HCT, it is likely that they will not significantly improve post-transplant. Nevertheless, it should be noted that the median time to last follow up was 360 days; it may be that cognitive functioning improves significantly over a longer period of time (21).

Using moderator analyses, the current meta-analysis examined the question of whether patient sociodemographic or clinical characteristics were predictive of change in cognitive functioning. Meta-regression analyses were conducted on age, time since HCT, transplant type, and TBI. Of these, only transplant type was predictive of change; studies with a higher percentage of participants receiving autologous HCT reported larger improvements in attention. This difference may occur because autologous patients do not routinely receive corticosteroids, which have been associated with worse cognitive functioning (23, 31) and show evidence of neurotoxicity in animal studies (34). It is somewhat surprising that age was not significantly associated with change in cognition, as older cancer patients are more likely to demonstrate cognitive impairments (35). Nevertheless, patients included in the meta-analysis tended to be young (median age of 42) and thus may not have been as vulnerable to the negative effects of age on cognitive recovery.

The quality of a meta-analysis depends upon the quality of the studies analyzed. Studies included in the current meta-analysis are characterized by several strengths, such as use of well-known and well-validated tests of cognitive function and longitudinal comparisons to a pre-HCT baseline. Nevertheless, limitations are evident in the existing literature. One limitation is the lack of well-matched control groups. There were only two studies eligible for inclusion in the meta-analysis that provided a healthy comparison group (13, 21) and three studies with control patients who did not receive HCT (i.e., control patients receiving imatinib mesylate, hyroxyurea, or interferon (25), non-myeloablative cancer treatments (28), or diagnosed with renal insufficiency (18)). It can be difficult to identify an appropriate control sample of cancer patients due to adverse or poorly-understood effects of other cancer treatments on cognition. Control samples of individuals without cancer, or multiple control samples, may be more appropriate (33). Ideally, control groups should be matched to patients on age, education, and gender. Another limitation is that studies were characterized by small, heterogeneous samples of HCT patients. The largest sample in the current review had 286 patients (22) and studies commonly reported on samples with a mix of cancer

diagnoses, conditioning regimens, and transplant types. Study heterogeneity has resulted in limited power to examine potentially important predictors of cognitive change, such as severity of graft-versus-host disease and history of intensive chemotherapy prior to HCT, although more recent, higher-quality studies are starting to examine these questions (36). Similarly, recent studies are starting to examine impaired cognition as one aspect of a constellation of negative psychosocial effects of HCT (37, 38). Cooperative group studies have been suggested to address design limitations and increase statistical power (33). Cooperative transplant research groups such as the Blood and Marrow Clinical Trials Network and the Center for International Blood and Marrow Transplant Research are ideal for conducting these types of large studies. Thus, while there are significant limitations in existing literature, there is also an excellent HCT research infrastructure in place to support large, high-quality future studies.

Clinically, our findings suggest that patients considering HCT should be educated that, on average, they can expect post-HCT cognitive functioning to be similar to that prior to HCT. However, there may be subgroups of patients, such as those who receive autologous HCT, who are more likely to experience cognitive improvement. Patients reporting cognitive difficulties that interfere with daily functioning should be referred to a neuropsychologist for evaluation and management of cognitive deficits. Although research on a group-based neuropsychological training program found it does not produce significant improvements in cognitive functioning post-HCT (19), individual therapy to learn compensatory strategies has been recommended (19). Pharmacological treatments, such as modafinil, may also be tried (39). Additional research is needed to identify patients at risk for clinically significant cognitive impairment and to develop effective management strategies to help them achieve the best possible cognitive outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

HJ is supported in part by K07-CA138499.

References

1. Pasquini M, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides. 2011
2. Ahles TA, Saykin AJ, Noll WW, Furstenberg CT, Guerin S, Cole B, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. Psycho-Oncology. 2003; 12(6):612–619. [PubMed: 12923801]
3. Ahles TA, Saykin A. Cognitive effects of standard-dose chemotherapy in patients with cancer. Cancer Invest. 2001; 19(8):812–820. [PubMed: 11768035]
4. Fliessbach K, Helmstaedter C, Urbach H, Althaus A, Pels H, Linnebank M, et al. Neuropsychological outcome after chemotherapy for primary CNS lymphoma: a prospective study. Neurology. 2005; 64(7):1184–1188. [PubMed: 15824344]
5. de Brabander C, Cornelissen J, Smitt PA, Vecht CJ, van den Bent MJ. Increased incidence of neurological complications in patients receiving an allogenic bone marrow transplantation from alternative donors. J Neurol Neurosurg Psychiatry. 2000; 68(1):36–40. [PubMed: 10601399]

6. Fann JR, Alfano CM, Roth-Roemer S, Katon WJ, Syrjala KL. Impact of delirium on cognition, distress, and health-related quality of life after hematopoietic stem-cell transplantation. J Clin Oncol. 2007; 25(10):1223–1231. [PubMed: 17401011]
7. Andrykowski MA, Cordova MJ, Hann DM, Jacobsen PB, Fields KK, Phillips G. Patients' psychosocial concerns following stem cell transplantation. Bone Marrow Transplant. 1999; 24(10): 1121–1129. [PubMed: 10578162]
8. Booth-Jones M, Jacobsen PB, Ransom S, Soety E. Characteristics and correlates of cognitive functioning following bone marrow transplantation. Bone Marrow Transplant. 2005; 36(8):695–702. [PubMed: 16086044]
9. Heinonen H, Volin L, Zevon MA, Uutela A, Barrick C, Ruutu T. Stress among allogeneic bone marrow transplantation patients. Patient Educ Couns. 2005; 56(1):62–71. [PubMed: 15590224]
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009; 6(7):e1000100. [PubMed: 19621070]
11. Lezak, MD.; Howieson, DB.; Loring, DW. Neuropsychological Assessment. 4 ed.. New York: Oxford University Press; 2004.
12. Hedges, L.; Olkin, I. Statistical methods for meta-analysis. San Diego, CA: Academic Press; 1985.
13. Beglinger LJ, Mills JA, Vik SM, Duff K, Denburg NL, Weckmann MT, et al. The neuropsychological course of acute delirium in adult hematopoietic stem cell transplantation patients. Arch Clin Neuropsychol. 2011; 26(2):98–109. [PubMed: 21183605]
14. Borenstein, M.; Hedges, L.; Higgins, J., et al. Introduction to meta-analysis. Chichester, West Sussex, UK: John Wiley & Sons, Ltd.; 2009.
15. Comprehensive Meta Analysis, 2.2.057. 2010
16. Andrykowski MA, Schmitt FA, Gregg ME, Brady MJ, Lamb DG, Henslee-Downey PJ. Neuropsychologic impairment in adult bone marrow transplant candidates. Cancer. 1992; 70(9): 2288–2297. [PubMed: 1394058]
17. 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):183–192. [PubMed: 12115332]
18. Peper M, Steinvorth S, Schraube P, Fruehauf 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):303–311. [PubMed: 10661336]
19. Poppelreuter M, Weis J, Mumm A, Orth HB, Bartsch HH. Rehabilitation of therapy-related cognitive deficits in patients after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2008; 41(1):79–90. [PubMed: 17934527]
20. 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):1457–1462. [PubMed: 8622059]
21. 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. J Clin Oncol. 2011; 29(17):2397–2404. [PubMed: 21537032]
22. 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):1560–1567. [PubMed: 17685391]
23. Sostak P, Padovan CS, Yousry TA, Ledderose G, Kolb HJ, Straube A. Prospective evaluation of neurological complications after allogeneic bone marrow transplantation. Neurology. 2003; 60(5): 842–848. [PubMed: 12629244]
24. 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): 172–177. [PubMed: 17166316]

25. Chang G, Meadows ME, Orav EJ, Antin JH. Mental status changes after hematopoietic stem cell transplantation. Cancer. 2009; 115(19):4625–4635. [PubMed: 19551887]
26. Friedman MA, Fernandez M, Wefel JS, Myszka KA, Champlin RE, Meyers CA. Course of cognitive decline in hematopoietic stem cell transplantation: A within-subjects design. Arch Clin Neuropsychol. 2009; 24(7):689–698. [PubMed: 19767298]
27. Harder H, Duivenvoorden HJ, van Gool AR, Cornelissen JJ, van den Bent MJ. Neurocognitive functions and quality of life in haematological patients receiving haematopoietic stem cell grafts: a one-year follow-up pilot study. J Clin Exp Neuropsychol. 2006; 28(3):283–293. [PubMed: 16618620]
28. Harder H, Van Gool AR, Duivenvoorden HJ, Cornelissen JJ, Eijkenboom WM, Barge RM, et al. Case-referent comparison of cognitive functions in patients receiving haematopoietic stem-cell transplantation for haematological malignancies: two-year follow-up results. Eur J Cancer. 2007; 43(14):2052–2059. [PubMed: 17719220]
29. 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):789–799. [PubMed: 17417661]
30. Wenz F, Steinvorth S, Lohr F, Fruehauf S, Wildermuth S, van Kampen M, et al. Prospective evaluation of delayed central nervous system (CNS) toxicity of hyperfractionated total body irradiation (TBI). Int J Radiat Oncol Biol Phys. 2000; 48(5):1497–1501. [PubMed: 11121654]
31. Syrjala KL, Dikmen S, Langer SL, Roth-Roemer S, Abrams JR. Neuropsychologic changes from before transplantation to 1 year in patients receiving myeloablative allogeneic hematopoietic cell transplant. Blood. 2004; 104(10):3386–3392. [PubMed: 15251983]
32. 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):1007–1016. [PubMed: 15862749]
33. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. Lancet Oncol. 2011; 12(7):703–708. [PubMed: 21354373]
34. Saykin AJ, Ahles TA, McDonald BC. Mechanisms of chemotherapy-induced cognitive disorders: neuropsychological, pathophysiological, and neuroimaging perspectives. Semin Clin Neuropsychiatry. 2003; 8(4):201–216. [PubMed: 14613048]
35. 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):4434–4440. [PubMed: 20837957]
36. Scherwath A, Schirmer L, Kruse M, Ernst G, Eder M, Dinkel A, et al. Cognitive functioning in allogeneic hematopoietic stem cell transplantation recipients and its medical correlates: a prospective multicenter study. Psychooncology. 2012
37. Skucek E, Butler S, Gaspar HB, Titman P. Social outcome in children treated by haematopoietic cell transplant for congenital immunodeficiency. Bone Marrow Transplant. 2011; 46(10):1314–1320. [PubMed: 21339750]
38. Packman W, Weber S, Wallace J, Bugescu N. Psychological effects of hematopoietic SCT on pediatric patients, siblings and parents: a review. Bone Marrow Transplant. 2010; 45(7):1134–1146. [PubMed: 20383219]
39. Kohli S, Fisher SG, Tra Y, Adams MJ, Mapstone ME, Wesnes KA, et al. The effect of modafinil on cognitive function in breast cancer survivors. Cancer. 2009; 115(12):2605–2616. [PubMed: 19309747]
40. Fann JR, Roth-Roemer S, Burington BE, Katon WJ, Syrjala KL. Delirium in patients undergoing hematopoietic stem cell transplantation. Cancer. 2002; 95(9):1971–1981. [PubMed: 12404292]

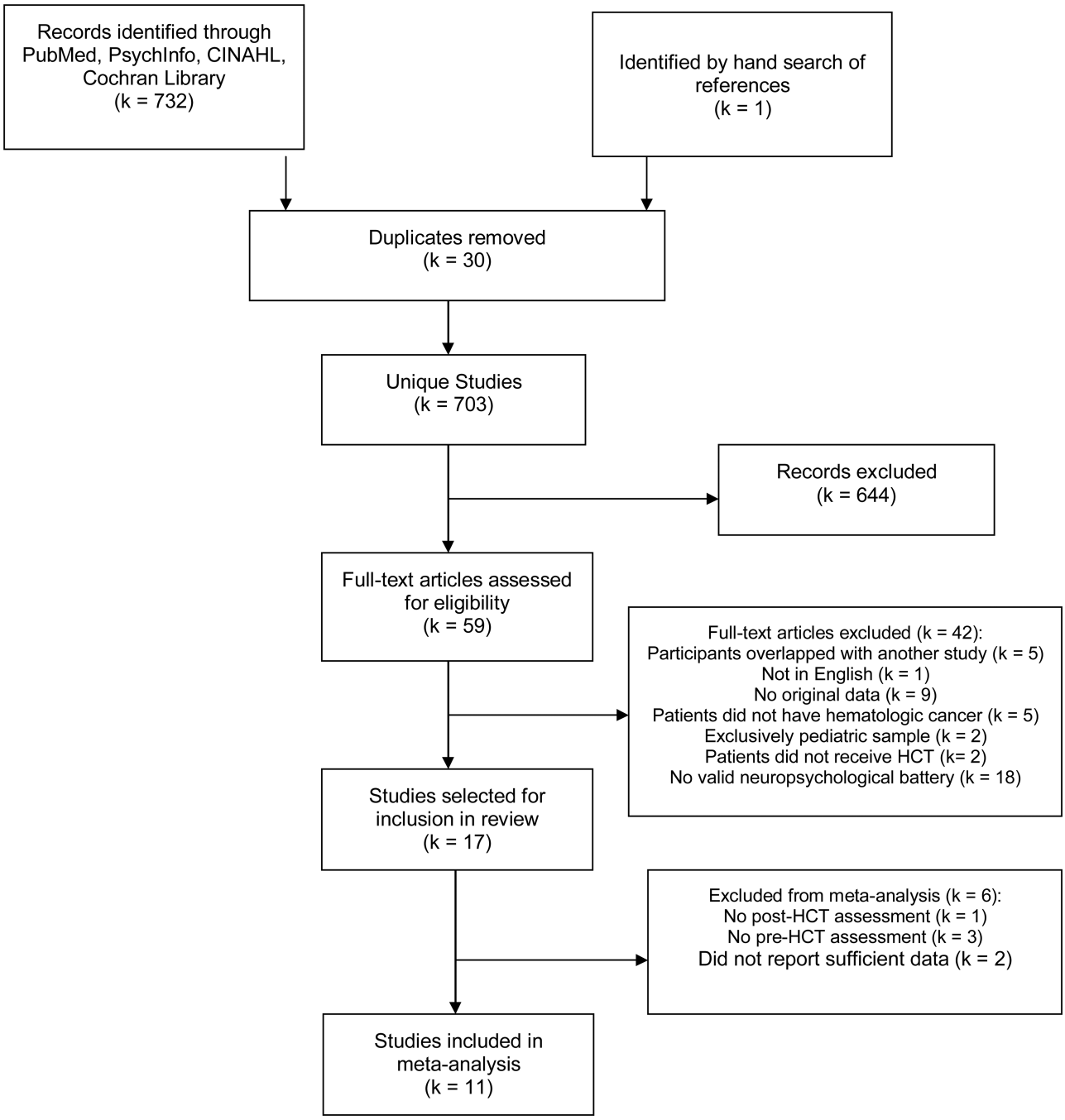

Figure 1.
PRISMA Flow Diagram.

Table 1

Search Terms and Limits.

Cognitive Terms		**HCT Terms**
cognitive disorders OR	AND	bone marrow transplantation OR
cognition OR		stem cell transplantation OR
cognitive effects OR		cord blood stem cell transplantation OR
cognitive disorders OR		hematopoietic stem cell transplantation OR
neurocognitive function OR		mesenchymal stem cell transplantation OR
neuropsychological tests		peripheral blood stem cell transplantation

Limits: English AND cancer

Table 2

Eligibility Criteria for the Systematic Review.

• **Participants had received HCT for hematologic cancer** Studies with mixed samples of patients receiving HCT for hematologic cancers or other diagnoses were retained.
• **Participants were a minimum of 16 years of age at time of the pre-transplant assessment**
• **Objective neuropsychological data were reported** Studies reporting data from screening measures only (e.g., Mini Mental Status Exam, High Sensitivity Cognitive Screen, Blessed Information-Memory-Concentration test) were excluded
• **Original data were reported** Reviews, commentaries, and case reports were excluded.
• **Patients had completed pre- and post-transplant assessments** Data to calculate effect sizes (i.e., means and standard deviations or standard errors) must have been available or provided upon request.

Table 3

Study Characteristics (k=17).

Author (year)	Diagnoses	N	% Autologous	% TBI	% Cranial irradiation	% Intrathecal chemo-therapy	% Female	Average age	Average education	Domains assessed
Ahles et al(20) †	Hematologic (n=14) BR (n=20)	Pre-HCT: 54 Post-HCT (1–2 days before discharge, M hospitalization = 36.2 days): 34	100%	14.7%	20.37% of patients with baseline data received cranial radiation or intrathecal chemotherapy		85%	39.28 years	Not stated	Executive functioning, Visual memory, Verbal ability
Andrykowski et al(16) ‡	AL (n=20) CL (n=22) Lymphoma (n=9) MDS (n=2) MM (n=1) Myelofibrosis (n=1)	Pre-HCT: 55	Not stated	1.8%	14.5%	27.3%	40%	35.9 years	47% some college or greater	Attention, Executive functioning, Information processing, Motor speed, Verbal memory, Visual memory
Beglinger et al(24)	Lymphoma (n=13) Leukemia (n=7) Myeloma (n=6) Other (n=4)	Pre-HCT: 30 Post-HCT (100 days): 22	50%	Not stated	Not stated	Not stated	33.3%	47.6 years	15.0 years	Attention, Executive functioning, Verbal memory, Verbal ability, Visuospatial ability
Beglinger et al(13)	Lymphoma (n=21) Leukemia (n=10) Myeloma (n=13) Other (n=8)	Pre-HCT: 52 Post-HCT (discharge or up to 4 weeks): 41	58%	Not stated	Not stated	Not stated	34.6%	53.05 years	14.46 years	Attention, Executive functioning, Verbal memory, Verbal ability
Chang et al(25) †	CML (n = 42) MDS (n=3)	Pre-HCT: 106 Post-baseline (18 months, (M=585 days): 45	0%	94%	0%	0%	53.3%	40.60 years	40% college graduates	Attention, Executive functioning, Motor speed, Verbal ability
Fann et al(6, 40) †	CML (n=38) ALL or AML (n=25) BR or OV (n=11) MDS or MM (n=10) NHL (n=6)	Pre-HCT: 90 Post-HCT (80 days): 59	19%	59%	15% received cranial radiation or intrathecal chemotherapy		40%	41.44 years	15.25 years	Attention, Executive functioning, Verbal memory, Verbal ability
Friedman et al(26)	ALL (n=7) AML (n=11) CLL (n=4) CML (n=18) HD (n=16) NHL (n=35) Myeloma (n=22) MDS (n=4)	Pre-HCT: 117 Post-HCT (28 weeks, M=196.7 days): 33	51.3%	30.3%	Not stated	Not stated	41%	45.40 years	14.59 years	Attention, Executive functioning, Verbal memory, Verbal ability
Harder et al(17) ‡	ALL (n=8) AML (n=10) CML (n=6) NHL (n=6) MDS (n=4) MM (n=4) SAA (n=2)	Post-HCT (22–82 months; M = 45.1 months): 40	12.5%	100%	2.5%	12.5%	40%	40.80 years	32.50% college graduates	Attention, Executive functioning, Information processing, Motor speed, Verbal memory, Visual memory, Verbal ability, Visuospatial ability
Harder et al(28, 32)	Lymphoma (n=30) HD (n=4) AL (n=27) CL (n=17) MM (n=17) MDS (n=3)	Pre-HCT: 101 Post-baseline (20 months): 55	34%	74%	0%	11%	39%	42 years	29% college graduates	Attention, Executive functioning, Information processing, Motor speed, Verbal memory, Visual memory,

Author (year)	Diagnoses	N	% Autologous	% TBI	% Cranial irradiation	% Intrathecal chemo-therapy	% Female	Average age	Average education	Domains assessed
	Other (n=3)									Verbal ability, Visuospatial ability
Harder et al(27)	ALL (n=1) AML (n=2) CML (n=2) MM (n=7) MDS (n=2) HD (n=3) NHL (n=4) SAA (n=4)	Pre-HCT: 25 Post (12 months): 9	23.8%	85.7%	0%	8%	36%	47 years	Mdn: vocational or trade school	Attention, Executive functioning, Information processing, Motor speed, Verbal memory, Visual memory, Verbal ability, Visuospatial ability
Jacobs et al(22) † ‡	AML (n=27) BR (n=23) HD (n=12) MM (n=244) NHL (n=39) Other (n=43)	Pre-HCT: 286 Post-HCT (12 months): 83	78.9%	Not stated	Not stated	Not stated	45.8%	50.07 years	13.89 years	Attention, Executive functioning, Motor speed, Verbal memory, Visual memory
Peper et al(18) ‡	AML (n=5) ALL (n=1) NHL (n=7) Burkitt's lymphoma(n=1)	Pre-TBI: 14 Post-TBI (7–10.8 (M=8.8 years): 12	100% of post sample	100% of post-sample (0% of pre-TBI group)	7.14%	0% pre sample	30%	35.50 years	9.9 years	Attention, Executive functioning, Verbal memory, Visual memory, Verbal ability, Visuospatial ability
Poppelreuter et al(19) ‡	AL (n=34) Lymphoma (n=23) Myeloproliferative syndromes (n=15) MDS (n=3)	Post-last treatment (0–71 months, M=7.28 months) & pre-randomization: 17	17.3%	46.7%	9.3%	9.3%	49.33%	42.59 years	38.7% polytechnic or college	Attention, Executive functioning, Verbal memory, Visual memory
Schulz-Kindermann et al(29) †	AML (n=4) CML (n=3) MM (n=2) Lymphoma (n=2) MDS (n=2) Osteomyelofibrosis(n=3) ALL (n=1) CMML (n=1) SAA (n=1)	Pre-HCT: 39 Post-HCT (100 days): 19	0%	10.6%	0%	0%	36.8%	46.50 years	36.9% college	Attention, Executive functioning, Verbal memory, Verbal ability,
Syrjala et al(21, 31) †	AL (n=14) CML (n=35) Lymphoma (n=6) MDS (n=7) Other (n=4)	Pre-HCT: 76 Post-HCT (5 years): 66	0%	59.5%	Not stated	0%	53%	46.20 years	30% college graduates	Attention, Executive functioning, Motor speed, Verbal memory, Verbal ability
Sostak et al(23) ‡	ALL (n=8) AML (n=22) CML (n=32) HD (n=2) NHL (n=1) MDS (n=2) PC (n=3) SAA (n=1)	Pre-HCT: 71 Post-HCT (14 months): 55	0%	64.8%	4%	Not stated	39%	37 years	Not stated	Attention, Executive functioning, Verbal ability
Wenz et al(30) †	NHL (n=10) MM (n=3) AML (n=6) CLL (n=1) CML (n=1)	Pre-TBI: 58 post- TBI (6–36 months, Mdn=27 months): 21	100%	100%	0%	0%	42.9%	45 years	Not stated	Attention, Executive functioning, Verbal memory, Visual memory

k, number of studies; AL, Acute leukemia; ALL, Acute lymphatic leukemia; AML, Acute myeloid leukemia; BR, breast carcinoma; CL, Chronic leukemia; CLL, Chronic lymphocytic leukemia; CML, Chronic myeloid leukemia; CMML, Chronic-myelomonocytic leukemia; HD, Hodgkin's disease; MDS, Myelodysplastic syndrome; MM, Multiple myeloma; NHL, Non-Hodgkin's lymphoma; OV, ovarian carcinoma; PC, plasmocytoma; SAA, Severe aplastic anemia.

†Demographics based on post-HCT sample.

‡Study not included in meta-analysis.

Bone Marrow Transplant. Author manuscript; available in PMC 2014 April 01.

Table 4

Weighted Average Effect Sizes By Cognitive Domain.

Domain	k	Effect size (g)	95% CI	*P* values
Attention	10	−.10	−.30 to .10	.331
Executive Functioning	11	.07	−.15 to .30	.531
Information Processing	2	−.21	−.63 to .21	.329
Motor Speed	4	−.17	−.54 to .21	.392
Verbal Ability	10	.09	−.05 to .23	.209
Verbal Memory	8	.18	−.02 to .39	.081
Visual Memory	3	.22	−.04 to .48	.092
Visuospatial Ability	3	.01	−.33 to .35	.955

k, number of studies; CI, Confidence Interval