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A Prospective Evaluation of Changes in Brain Structure and Cognitive Functions in Adult Stem Cell Transplant Recipients

DD Correa¹, JC Root², R Baser³, D Moore⁴, KK Peck⁵, E Lis⁶, TB Shore⁷, HT Thaler⁸, A Jakubowski⁹, and N Relkin¹⁰

¹Department of Neurology, Memorial Sloan-Kettering Cancer Center, New York. Department of Neurology & Neuroscience, Weill Cornell Medical College, New York

²Department of Psychiatry & Behavioral Sciences, Memorial Sloan-Kettering Cancer Center, New York. Department of Psychiatry, Weill Cornell Medical College, New York

³Department of Epidemiology & Biostatistics, Memorial Sloan-Kettering Cancer Center, New York

⁴Department of Neurology & Neuroscience, Weill Cornell Medical College, New York

⁵Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York. Department of Radiology, Weill Cornell Medical College, New York

⁶Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York. Department of Radiology, Weill Cornell Medical College, New York

⁷Department of Medicine, Weill Cornell Medical College, New York

⁸Department of Epidemiology & Biostatistics, Memorial Sloan-Kettering Cancer Center, New York

⁹Department of Medicine, Weill Cornell Medical College, New York. Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York

¹⁰Department of Neurology & Neuroscience, Weill Cornell Medical College, New York

Abstract

Hematopoietic stem cell transplantation (HSCT) is an efficacious treatment for many hematologic malignancies. However, the conditioning regimen of high-dose (HD) chemotherapy with or without total body irradiation (TBI) can be associated with neurotoxicity. In this prospective study, we used quantitative neuroimaging techniques to examine regional gray matter and ventricular volumes, and standardized neuropsychological tests to assess cognitive function before and one year after HSCT in twenty-eight patients with hematologic malignancies and in ten healthy controls evaluated at similar intervals. Nineteen patients received conditioning treatment with HD chemotherapy alone and nine had both TBI and HD chemotherapy. There was a significant reduction in gray matter volume in the middle frontal gyrus bilaterally and in the left caudate nucleus in the patient group (all patients combined) but not among healthy controls over the one-year follow-up period. There was a significant increase in left lateral ventricle volume and in total

Corresponding author: Denise D Correa, PhD, ABPP-CN, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Phone: 646-888-3177, Fax: 646-888-3175, corread@mskcc.org.

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ventricle volume in the patient group, relative to healthy controls. Similar brain structural changes were seen for patients treated with HD chemotherapy alone. The neuropsychological results showed that 21% of patients could be classified as impaired at baseline. The Reliable Change Index suggested no significantly different rates of cognitive decline between patients and healthy controls. The findings suggest that HSCT patients may be at an increased risk for developing regional brain volume loss, and that subgroups may experience cognitive dysfunction prior to and one year following the transplant.

Keywords

Hematopoietic stem cell transplantation; cognitive; structural neuroimaging; voxel-based morphometry

Introduction

Hematopoietic stem cell transplantation (HSCT) is used in the treatment of many hematologic disorders. Although it can be curative, the pre-transplant myeloablative conditioning regimen including high-dose chemotherapy with or without total body irradiation (TBI) can be associated with neurotoxicity (Snider et al., 1994; Soutar & King, 1995; Sostak et al., 2003). In addition, most patients undergo chemotherapy before receiving the conditioning treatment for HSCT, as part of prior attempts to treat their illnesses (Hagemeister, 2002). In patients who undergo allogeneic HSCT, treatment-related complications such as acute or chronic graft versus host disease (GvHD), infections related to immunosuppression, and the side effects of immunosuppressive therapy, may also have neurotoxic effects (Bartynski et al., 2001; Nucci et al., 2003). These multiple factors and interventions place patients at an increased risk for central nervous system (CNS) damage and may be associated with acute or chronic cognitive dysfunction.

There is compelling evidence that chemotherapy is associated with neurotoxicity (Rzeski et al., 2004; Meyers, 2008), particularly high-dose methotrexate and cytarabine (DeAngelis and Posner 2009; Dietrich et al., 2008). Candidate mechanisms for neurotoxicity include demyelination, chemotherapy-induced oxidative stress and DNA damage, and immune dysregulation and stimulation of neurotoxic cytokines (Ahles et al., 2007). Recent animal studies suggest that higher levels of chemotherapy may reach the brain than previously assumed and that even low doses of chemotherapy can increase cell death and decrease cell division in the hippocampus (Dietrich et al., 2006). The most significant complications of radiotherapy are delayed and often produce irreversible and progressive damage to the CNS through vascular injury causing chronic ischemia, cerebral atrophy, progressive demyelination of the white matter, and necrosis (Omuro et al. 2005; DeAngelis and Posner 2009). The risk for developing radiation-related damage increases with irradiated volume, total dose and fraction size, and age. Combined treatment with radiation and chemotherapy may have a synergistic toxic effect (Keime-Guibert, 1998).

Studies addressing neuropsychological functioning in patients undergoing HSCT reported that 20–40% had cognitive dysfunction involving graphomotor speed, executive and memory abilities prior to transplant (Andrykowski et al., 1992; Chang et al., 2009; Friedman et al.,

2009; Harder et al., 2005, 2006; Jacobs et al., 2007; Meyers et al., 1994; Schulz-Kindermann et al., 2007). Several prospective studies documented cognitive decline in the *initial* months after HSCT (Ahles et al., 1996; Booth-Jones et al., 2005; Friedman et al., 2009; Syrjala et al., 2004; Schulz-Kindermann et al., 2007), but the absence of a decline was also described (Harder et al., 2007). At approximately one year post-transplant, cognitive functions were reported to return to or surpass pre-transplant levels in several studies (Chang et al., 2009; Harder et al., 2006; Jacobs et al., 2007; Syrjala et al., 2004; Wenz et al., 2000), but subgroups of patients had persistent impairment or decline on some cognitive domains (Jacobs et al., 2007; Meyers et al., 1994; Syrjala et al., 2004). Syrjala and colleagues (2011) reported further improvement in information processing speed and executive functions, but not in memory or motor dexterity in a large cohort of patients evaluated five years following allogeneic HSCT. However, more than 40% of survivors had a global deficit score indicative of mild cognitive impairment. In the few cross-sectional studies that included structural neuroimaging, white matter abnormalities and atrophy were documented in some HSCT patients treated with TBI and chemotherapy (Garrick, 2000; Padovan et al., 1998; Peper et al., 2000; Stemmer et al., 1994). In a longitudinal study (Sostak et al., 2003), a subgroup of patients treated with TBI and intrathecal chemotherapy prior to allogeneic bone marrow transplantation developed neurologic complications, white matter changes, cerebral atrophy, and cognitive deterioration one year after the transplant; chronic GvHD and immunosuppression were significant risk factors.

To date, there have been no prospective studies combining advanced neuroimaging procedures and cognitive assessment in patients undergoing HSCT conditioning regimens including chemotherapy with or without radiotherapy. In this study, we assessed changes in gray matter and ventricular volume, as well as neuropsychological functions in patients prior to HSCT and one year after the transplant. The results were compared to those obtained from a group of healthy controls evaluated at equivalent intervals.

Methods

Subjects

The majority of patients were identified and recruited by the treating physicians and nurses in the Department of Medicine at Memorial Sloan-Kettering Cancer Center (MSKCC); four patients were recruited by the staff in the Department of Medicine at Weill Cornell Medical College (WCMC). Patients were eligible to participate in the MSKCC research protocol study if they had a diagnosis of a hematological malignancy and were scheduled to undergo conditioning treatment with high-dose (HD) chemotherapy with or without full-dose total body irradiation (TBI), prior to receiving an allogeneic or autologous HSCT; were between the ages of 18 and 70 years, and fluent in English. Patients were excluded if they had evidence of disease progression at enrollment or during the study period, central nervous system disease, or history of neurological or psychiatric disorders. Healthy controls who met the same inclusion (except for cancer diagnosis) and exclusion criteria were recruited through community advertisements. Healthy controls were frequency-matched to patients on age, education, and gender. The research protocol was approved by the Institutional Review Boards at MSKCC and WCMC, and informed consent was obtained from all participants.

Thirty-nine of the originally planned forty study patients completed a baseline cognitive evaluation *prior to* undergoing conditioning treatment with high-dose (HD) chemotherapy with or without full-dose total body irradiation (fTBI) for HSCT, and twenty-eight were available for the one-year post transplant follow-up evaluation. Among the 11 patients who did not return for follow-up, 5 had disease progression at the time of the post-HSCT evaluation and were no longer eligible to continue in the study, 4 were deceased, and 2 declined to return. Sixteen of the originally planned twenty healthy controls completed a cognitive evaluation at study entry, and 10 were available for the one-year follow-up evaluation. The 6 healthy controls who did not complete the follow-up procedures either declined to return or could not be reached. Brain magnetic resonance imaging (MRI) including Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequences was available at both baseline (prior to the conditioning treatment for HSCT) and one year post transplant for 21 patients and 10 healthy controls.

Structural Neuroimaging

MRI Scan Acquisition—All participants were imaged on the same 3T scanner (GE Medical Systems, Waukesha, WI) with an 8-channel phased-array head coil. T1-weighted three dimensional magnetization prepared rapid gradient echo (MPRAGE) images were acquired with the following parameters: TR=7 ms, TE=1.5 ms, FOV=23 cm, FA=7 degrees, number of slices= 156, 1.2 mm thickness, 192×192 matrix, in plane resolution of 1.2 mm^2 . T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences were also acquired to rule out pathology.

Image Processing—Voxel-based morphometry (VBM) analysis was performed using the longitudinal processing stream in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) under the SPM8 software package (Version 8, Wellcome Department of Imaging Neuroscience, London, UK) within MATLAB (Version 7, Mathworks, Inc., Natick, MA). Following reconstruction, follow-up MPRAGE structural images were registered to baseline MPRAGE images for each subject, bias corrected, segmented into gray matter, white matter and cerebrospinal fluid compartments using the Montreal Neurologic Institute (MNI) T1 weighted template and tissue probability maps, linear and non-linear registered to MNI space, and the resulting gray-matter tissue class smoothed using an isotropic Gaussian spatial filter (FWHM=8 mm).

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer (FS) image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>). This processing includes removal of non-brain tissue, intensity normalization, and segmentation of subcortical structures (Fischl et al., 2002). For validation purposes, we also measured ventricular volume using a semi-automated algorithm, implemented in the program Brain Ventricular Quantification (BVQ; Accomazzi et al., 2005). BVQ uses a seed point/region-growing method and is optimized specifically for segmentation of the lateral ventricles.

Neuropsychological Assessment

Neuropsychological tests with documented sensitivity to the adverse effects of cancer therapy (Correa et al., 2007; Ahles et al., 2010) were selected to evaluate auditory attention

and executive functions (Digit Span of the WMS-III - DF/DB; Brief Test of Attention – BTA; Trail Making Test Parts A & B – TMTA, TMTB), verbal memory (California Verbal Learning Test-Second Edition – CVLT-II; Learning – CVLT-L, Long Delayed Recall – CVLT-LD, Discrimination Index – CVLT-DI), and visual-spatial memory (Brown Location Test – BLT; Learning – BLT-L, Long Delayed Recall – BLT-LD, Discrimination Index – BLT-DI). Mood, fatigue, and subjective memory complaints were assessed using the Center for Epidemiological Study-Depression (CES-D) scale and the Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-FS, Version 4), and the Squire Subjective Memory Questionnaire (SSMQ), respectively. The test battery was administered either by a neuropsychologist (DDC) or by a trained research assistant. Raw cognitive test scores were compared with published normative values according to age, and when available, to age and education, and converted into z-scores.

Imaging and Statistical Analyses

Descriptive statistics for demographic variables were generated with frequencies and percentages for categorical variables and with means and standard deviations, or median and ranges as appropriate, for continuous variables. Given the relatively small sample size, we combined patients treated with HD chemotherapy alone and patients who received fTBI + HD chemotherapy into one group (Combined Patient group). We also performed analyses including the Chemotherapy Alone group and the healthy controls, in order to assess if changes in the variables of interest would occur in patients who did not have fTBI as part of the conditioning regimen. Considering that MPRAGE scans were available for only 5 patients in the fTBI + Chemotherapy group, it was not feasible to conduct a separate analysis for this group.

Voxel-Based Morphometry (VBM)—In the analysis including the Healthy Control versus Combined Patient group, gray matter maps were entered into a 2 (Group: Healthy Control; Combined Patients) X 2 (Time: baseline; 1-year follow-up) flexible factorial design within SPM8. For the Healthy Control versus Chemotherapy Alone group contrast, gray matter maps were entered into a 2 (Group: Healthy Control; Chemotherapy Alone) X 2 (Time: baseline; 1-year follow-up) flexible factorial design. Following omnibus testing, pair-wise t-tests were performed at the group level to analyze within group changes over time (baseline versus 1-year follow-up) for Healthy Control, Chemotherapy Alone, and Combined Patient groups. For cross-sectional analysis between groups at baseline independent samples t-tests were used. For all contrasts, initial uncorrected voxel-wise threshold was $p \leq 0.001$; voxels were considered significant if they survived family-wise error correction across the whole volume at $p \leq 0.05$ or survived family-wise error correction for a priori small volume correction at $p \leq 0.05$ (bilateral middle frontal gyrus).

FreeSurfer (FS), Brain Ventricular Quantification (BVQ)—Repeated measures analysis of variance (ANOVA) with time as a within-subject factor (baseline and one-year follow-up) and group (all patients and healthy controls) as a between-subject factor was used to assess changes in lateral ventricle volume (FS, BVQ) and to evaluate differences in changes between patients and healthy controls. Welch t-tests were used to assess if patients and healthy controls differed on these variables at baseline. The small sample size and

reduced power limited the ability to evaluate volumetric changes in specific cortical and subcortical regions using FS image analysis.

In order to prevent large outlying observations to overly influence the results, outliers were identified according to their distances outside of the quartiles of each variable's distribution. Specifically, any observation more than 1.5 times the variable's inter-quartile range (i.e., the 25th percentile score subtracted from the 75th percentile score) below the first quartile or above the third quartile was "trimmed" to the next closest, non-outlying value (Tukey, 1997). Ventricular volume measurements were trimmed separately for patient and healthy control groups, and for each of the two assessment times. Adjustments were made for only one patient on total ventricle volume at follow-up.

Neuropsychological Tests and Self-Report Scales—Repeated measures analysis of variance (ANOVA) with time as a within-subject factor (baseline and one-year follow-up) and group (all patients and healthy controls) as a between-subject factor was used to assess changes in the cognitive test z-scores and self-report scale scores, and to evaluate differences in changes between patients and healthy controls. Welch t-tests were used to assess if patients and healthy controls differed on these variables at baseline. The relationship between specific demographic or clinical variables and cognitive test scores was assessed using Pearson's correlation and t-tests.

Cognitive test z-scores were trimmed separately for patient and healthy control groups, and for each of the two assessment times with the same procedure described above. In the Combined Patient group, adjustments were made for one patient on the TMTA and CVLT-DI, and for two patients on the CVLT-L z-scores at baseline and follow-up. Among the healthy controls, adjustments were performed for one subject's z-score on the BTA at both assessments times; adjustments were made for two subjects on the CVLT-DI and for three subjects on the BLT-DI at baseline.

Cognitive impairment was defined as two or more z-scores ≥ 1.5 standard deviations below the normative mean, consistent with other studies (Wefel et al., 2004). Changes in neurocognitive test performance between baseline and follow-up at the individual level were assessed using the reliable change index (RCI; Jacobson and Truax, 1991), using published normative data. The RCI is derived from the standard error of measurement for each test, and represents the 90% confidence interval for the difference in raw scores from baseline to follow-up on the same test that could be expected, as a function of measurement error alone. All RCI thresholds were rounded to the nearest whole number. Changes that did not meet the RCI criteria for decline or improvement were classified as stable.

Results

The patients and healthy controls were predominantly men (70%) and right-handed (90%) (Table 1). There were no significant differences between groups in education, estimated IQ, or length of follow-up, but patients who received conditioning treatment with fTBI + HD chemotherapy were significantly younger than patients who received HD chemotherapy alone ($t(19) = 2.34$, $p=0.03$). The Combined Patient group did not differ significantly in age

from the Healthy Control group. An assessment of employment status showed that 6 patients (21%) were working at the time of enrollment, and 20 (71%) were employed one-year following HSCT. All healthy controls were working at study entry and one individual was unemployed at the one-year follow-up.

Table 1 describes the diagnoses, conditioning treatments and transplant type for all patients. Patients were diagnosed with lymphoma (39%), leukemia (29%), multiple myeloma (18%), or myelodysplastic syndrome (14%). All patients had received chemotherapy to treat their illness prior to becoming a candidate for HSCT. Nineteen patients received conditioning treatment with HD chemotherapy, and nine patients had fTBI (1200–1375 cGy) and HD chemotherapy. Sixteen patients (57%) received an allogeneic HSCT (7 related, 9 unrelated), and twelve (43%) had an autologous HSCT. Most patients (N=15) received T cell depleted grafts. The duration of the pre-transplant conditioning HD-chemotherapy regimens ranged from 6 to 9 days and fTBI was given over a period of four days. The transplants were infused within 24–36 hours after the conditioning regimens, consistent with standard clinical practice (Devine et al., 2011; Hamadani et al., 2011; Jakubowski et al., 2007; Mounier et al., 2012). Following HSCT, three patients had additional treatment with rituximab and one patient had cytarabine. Only three patients developed acute graft-versus-host disease (GvHD), and five patients had chronic GvHD and were treated with prednisone, tacrolimus or methotrexate.

Structural Neuroimaging

Voxel Based Morphometry (VBM), FreeSurfer (FS), and Brain Ventricular Quantification (BVQ)—

Cross-sectional assessment revealed no significant differences between the combined patient group and the healthy controls in regional brain volume or in lateral ventricle volume at baseline.

Longitudinal Assessment – Group by Time Interaction

1) VBM: In the Healthy Control versus Combined Patient group analysis, no voxels survived whole brain family-wise error (FWE) correction. Small volume correction with a bilateral middle frontal gyrus mask (Automated Anatomical Labeling; AAL), yielded a trend toward a significant difference ($t(29)=4.47$, $p=0.070$) in the left middle frontal gyrus (−32, 21, 55) with smaller volume in the Combined Patient group versus the Healthy Controls.

In the Healthy Control versus Chemotherapy Alone group analysis, no voxels survived whole brain FWE correction. Small volume correction with a bilateral middle frontal gyrus mask (AAL), yielded a *significant decrease* ($t(24)=5.05$, $p=0.032$) in the left middle frontal gyrus (−32, 21, 57) for the Chemotherapy Alone group.

2) FS & BVQ: Repeated measures ANOVA comparing the Combined Patient group and Healthy Controls revealed a significant time effect for mean total lateral ventricle volume (BVQ; $F(1,29)=6.25$, $p=0.018$), left lateral ventricle volume (FS; $F(1,29)=9.24$, $p=0.005$), and right lateral ventricle volume (FS; $F(1,29)=12.29$, $p=0.002$). *There was a significant group by time interaction for mean left lateral ventricle volume* (FS; $F(1,29)=4.49$, $p=0.044$) and a marginally significant interaction for mean total lateral ventricle volume (BVQ;

$F(1,29)=3.25$, $p=0.07$), suggesting a greater increase in ventricular volume in the Combined Patient Group in comparison to Healthy Controls (Figure 1). A comparison of absolute change in total lateral ventricular volume between groups showed significantly greater ventricular enlargement in the Combined Patient group versus the Healthy Controls ($t(18)=1.95$, $p=0.033$).

Repeated measures ANOVA comparing the Chemotherapy Alone group and Healthy Controls revealed a significant time effect for mean *left* lateral ventricle volume (FS; $F(1,24)=11.24$, $p=0.002$) and *right* lateral ventricle volume (FS; $F(1,24)=16.85$, $p<0.001$), and a marginally significant time effect for mean total lateral ventricle volume (BVQ; $F(1,24)=4.09$, $p=0.055$). *There was a significant group by time interaction for mean left lateral ventricle volume* (FS; $F(1,24)=5.76$, $p=0.025$), suggesting a greater increase in the Chemotherapy Alone Group in comparison to Healthy Controls (Figure 1). A comparison of absolute change in total lateral ventricular volume between groups showed that there was greater ventricular enlargement in Chemotherapy Alone group versus the Healthy Controls, but it did not reach statistical significance ($t(18)=1.42$, $p=0.086$).

Longitudinal Assessment – Within Group

1) VBM: Pair-wise t-tests for longitudinal changes within for the Combined Patient group showed a *significant decrease* in the mean volume of the right and left middle frontal gyri (left MFG: -30 , 12 , 58 FWE-corr $p=0.008$; right MFG: 34 , 14 , 51 FWE-corr $p=0.048$) and left caudate (-3 , 12 , -2 FWE-corr $p=0.030$) one year after HSCT (Figures 2a, 2b, 2e; Table 2). Among patients treated with chemotherapy alone, there were *significant decreases* in mean volume in the left middle frontal gyrus (-34 , 12 , 48 FWE-corr $p=0.032$) from baseline to the one year follow-up (Figures 2c, 2d; Table 2). Pair-wise t-tests for longitudinal changes within the Healthy Control group found no significant volumetric change from baseline to the one-year follow-up either for whole brain or small volume correction.

2) BVQ: In the combined patient group, there was a *significant increase* in the mean total lateral ventricular volume (BVQ; 8.1% (± 9.5), $p=0.003$) one year after HSCT. Among patients treated with chemotherapy alone, there was a *significant increase* in mean total lateral ventricle volume (BVQ; 6% (± 9.1), $p=0.02$). There were no significant changes in ventricular volume in the healthy control group over the follow-up period (percent increase = $2.9\% \pm 8.4$).

Neuropsychological Evaluation—*Cross-sectional assessment* revealed that at baseline, the Healthy Control group had significantly higher z-scores than the Combined Patient group in the CVLT-Learning, $t(14)=-4.2$, $p=0.001$ and BLT-Discrimination Index, $t(34)=2.1$, $p=0.041$.

Longitudinal Assessment – Group by Time Interaction

1. Combined Patient Group and Healthy Controls: Repeated measures ANOVA revealed a significant group by time interaction for TMTA ($F(1,36)=5.18$, $p=0.029$), as Healthy Controls but not the Combined Patient group improved significantly at the one year follow-up (Table 3). On the BLT-Learning, there was a significant time main effect ($F(1,36)=20.85$,

$p < 0.001$) and a marginally significant group by time interaction ($F(1,36)=4.02$, $p=0.053$), as Healthy Controls showed marginally greater improvement than patients one year post-HSCT. On the BLT-Discrimination Index, there was a significant group by time interaction ($F(1,36)=5.96$, $p=0.02$), as scores improved significantly for Healthy Controls but not for the Combined Patient group at follow-up (Table 3). On the CVLT-Learning and CVLT-Delay, there was a significant time main effect ($F(1,36)=25.86$, $p < 0.001$; $F(1,36)=6.25$, $p=0.017$). There were no significant changes over time in any other cognitive tests or in the self-report measures of mood, fatigue and subjective memory.

2. Chemotherapy Alone Group and Healthy Controls: Repeated measures ANOVA revealed a significant group by time interaction for TMTA ($F(1,27)=5.52$, $p=0.026$), as Healthy Controls but not the Chemotherapy Alone group improved significantly at the one year follow-up (Table 3). On the BLT-Learning and BLT-Delay, there was a significant time main effect ($F(1,27)=19.16$, $p < 0.001$; $F(1,27)=7.13$, $p=0.013$). On the BLT-Discrimination Index, there was a marginally significant group by time interaction ($F(1,27)=3.55$, $p=0.07$), as scores improved significantly for Healthy Controls but not for the Chemotherapy Alone group at follow-up (Table 3). On the CVLT-Learning and CVLT-Delay, there was a significant time main effect ($F(1,27)=19.66$, $p < 0.001$; $F(1,27)=8.94$, $p=0.006$). There were no significant changes over time in any other cognitive tests or in the self-report measures of mood, fatigue and subjective memory.

Within-subject evaluation of change in cognitive test performance: Mean z-scores were within the average range across most cognitive tests in all groups at baseline and at the one-year follow-up (Table 3). Evaluation of individual scores revealed that at baseline, 6 patients (21%) and one healthy control met criteria for cognitive impairment. In comparing the baseline and one-year follow-up performance using the RCI, the rates of cognitive decline or improvement did not differ significantly between patients and healthy controls. Seven of 28 patients (25%) had a reliable decline on *at least* one test, and 3 of 10 (30%) healthy controls, had a reliable decline on one test. On the other hand, a reliable improvement on *at least* one test was seen in 11 of 28 patients (39%) and in 5 of 10 (50%) healthy controls across all tests.

Correlations between structural imaging and cognitive scores and self-report measures: There were no significant correlations between regional gray matter volumes and the cognitive tests, or between the cognitive tests and the self-reported fatigue (FACIT-FS) or depression (CESD-D) scales. Scores on the SSMQ were significantly correlated with DB ($r=0.33$, $p < 0.05$), and TMTA and TMTB ($r=0.38$, $p < 0.05$). However, after adjusting for multiple comparisons (using the false discovery rate (FDR) method) none of the correlations remained significant.

Discussion

This prospective study documented significant brain structural changes across imaging modalities in HSCT recipients one year following conditioning treatment with HD chemotherapy with and without fTBI, suggesting that this treatment may be associated with the development of neurotoxicity. Group by time interactions indicated a significant

reduction in gray matter volume in the left middle frontal gyrus in the Chemotherapy Alone group and a marginally significant reduction in this region in the Combined Patient group, relative to Healthy Controls. Within group analyses showed significant reductions in gray matter volume in the middle frontal gyrus bilaterally and in the left caudate in the Combined Patient group, and in the left middle frontal gyrus in the Chemotherapy Alone group one year after HSCT. There were no significant reductions in gray matter volume among the Healthy Controls. Group by time interactions indicated a significant increase in left lateral ventricle volume in the Combined Patient group and in the Chemotherapy Alone group relative to Healthy Controls at the one-year follow-up; marginally significant interactions were also seen for total lateral ventricular volume (BVQ). Within group analyses indicated a significant increase in total lateral ventricle volume in the Combined Patient group and in the Chemotherapy Alone group, but not among the Healthy Controls. The relatively small number of patients and healthy controls most likely reduced the power to detect some of the interactions, and variability in the extent of brain structural changes among patients may have also contributed to some of the marginally significant results. The within subjects analyses was conducted to further explore the pattern of changes. Cross-sectional analysis showed no significant differences in ventricular or gray matter volume between the Combined Patient group and Healthy Controls at baseline, and this may have been also in part related to the reduced sensitivity of the between-subject versus within-subject analysis to detect differences in this relatively small cohort.

The earlier studies describing white matter abnormalities and atrophy in subgroups of HSCT patients treated with TBI and chemotherapy were mostly retrospective and did not include a healthy control group (Garrick, 2000; Padovan et al., 1998; Peper et al., 2000; Stemmer et al., 1994). In addition, some studies reported that neurological and neuroradiological abnormalities in this population were associated with GvHD and immunosuppressive therapy (Padovan et al., 1998; Sostak et al., 2003). This is the first prospective study to document reductions in regional gray matter volume and ventricular enlargement in HSCT patients treated with HD chemotherapy with or without fTBI. In this study, almost half of the sample had an autologous transplant and most of the patients who underwent an allogeneic transplant received T cell depleted grafts which do not require the use of calcineurin inhibitors; only five patients developed chronic GvHD. This suggests that the documented brain structural abnormalities including atrophy and regional gray matter reductions may be related primarily to the conditioning treatment with HD chemotherapy with or without fTBI. Considering that all patients had received chemotherapy prior to becoming a candidate for HSCT, the cumulative neurotoxic effects of multiple regimens, including fTBI in some patients, most likely contributed to the development of brain structural abnormalities. However, the contribution of disease-related factors or the possible interaction of disease and treatment cannot be excluded given the absence of a pre-treatment baseline. The small number of patients who received fTBI and HD chemotherapy also limited the evaluation of the more specific contribution of radiotherapy. In a recent study (Jim et al., 2012), clinical risk factors such as pre-transplant treatment, transplant type and the development of complications, were found to have a cumulative adverse effect on cognitive function in HSCT patients.

The study results provide further evidence for the neurotoxicity associated with chemotherapy documented in recent structural imaging studies of breast cancer patients (Ferguson et al., 2007; Inagaki et al., 2007; Deprez et al., 2011, 2012; Koppelmans et al., 2012). McDonald and colleagues (2010) documented a decrease in gray matter volume in bilateral frontal, temporal and cerebellar regions in breast cancer patients one month following chemotherapy, and partial recovery after one year. These results were replicated on a separate cohort, and provided additional evidence that chemotherapy was associated with reductions in frontal gray matter (McDonald et al., 2012). Our findings of decreased gray matter volume in prefrontal regions are overall consistent with these results, and provide convergent data suggesting that brain regions may be differentially affected by disease and treatment. The small number of patients treated with FTBI and HD chemotherapy precluded an evaluation of the specific effects of this combined regimen, but the synergistic toxic effect of HD chemotherapy in combination with radiotherapy has been documented in patients with brain tumors (DeAngelis and Posner, 2009; Correa et al., 2012). The etiology of chemotherapy- and radiotherapy-related brain structure abnormalities is unknown, but proposed mechanisms include oxidative stress and DNA damage, inhibition of neurogenesis, inflammation, immune dysregulation and stimulation of neurotoxic cytokines (Ahles et al., 2007; Seigers & Fardell, 2011), and vascular damage and demyelination (DeAngelis and Posner, 2009). The percent and absolute changes in ventricular enlargement in the Combined Patient group over one year was similar to the rates reported in patients with Mild Cognitive Impairment in a recent study using BVQ (Nestor et al., 2008); however, similar to our sample the authors also documented large intra-group variations among patients and controls. Accelerated atrophy and decrease in regional gray matter volume could place these patients at increased risk for future age-related decline in cognitive function.

The longitudinal assessment of neuropsychological test performance showed significant group by time interactions on a timed test of visual scanning and graphomotor speed and on a visual-spatial recognition memory task, as Healthy Controls but not the Combined Patient group improved significantly at follow-up. Similar results were seen for comparisons including the Chemotherapy Alone group and the Healthy Controls. Patients and healthy controls improved significantly on tests of verbal and visual-spatial learning, and showed no significant changes on self-report measures of mood, fatigue or subjective memory from baseline to the one-year follow-up. Cross-sectional analysis showed that at baseline, the Combined Patient group had significantly lower scores on verbal learning and visual-spatial recognition memory than Healthy Controls. Although there was a one-year interval between the two evaluations, the findings suggest that prior exposure to the neuropsychological tests may have resulted in practice effects on some of the tests, which were greater for the healthy controls than for the patients on several measures, consistent with some studies of breast cancer patients (Ahles et al., 2012).

An evaluation of individual cognitive scores showed that 21% of patients met criteria for cognitive impairment at baseline. These results are overall consistent with the literature reporting that 20–40% of HSCT candidates have cognitive dysfunction prior to transplant (Andrykowski et al., 1992; Chang et al., 2009; Friedman et al., 2009; Harder et al., 2005, 2006; Jacobs et al., 2007; Meyers et al., 1994; Schulz-Kindermann et al., 2007); however,

different criteria for the definition of impairment may have been used across studies. Disease and prior exposure to chemotherapy, and possibly circulating levels of cytokines (Meyers et al., 2005) and anemia (Jacobsen et al., 2004; Wood et al., 2011) may contribute to these findings, but factors that place some patients at a greater risk for cognitive dysfunction remain unknown. Studies of breast cancer patients reported that 20% to 30% of patients performed below expected levels based on age norms at diagnosis and prior to treatment, and this was not associated with mood or fatigue (Ahles et al., 2008; Wefel et al., 2004). In this population, possible risk factors for cognitive dysfunction include an interaction of age, cognitive reserve and exposure to chemotherapy (Ahles et al., 2010), and genetics (Ahles et al., 2003; Small et al., 2011).

At the one-year follow-up, only 14% of our patients met criteria for cognitive impairment. Within-subject evaluation of change in cognitive test performance using the RCI showed that 25% of the patients had a reliable decline on *at least* one test, and 30% of the healthy controls declined on *only one* test. On the other hand, a reliable improvement on *at least* one test was seen in 39% of patients and in 50% of the healthy controls. There were no significant differences between patients and healthy controls in rate of cognitive decline. The RCI analyses provided complementary information to the group comparisons, suggesting that it is useful in identifying subgroups of patients that may develop cognitive dysfunction (Friedman et al., 2009). The findings are in part consistent with longitudinal studies reporting that one year post-HSCT, cognitive functions returned to or surpassed pre-transplant levels (Chang et al., 2009; Harder et al., 2006, 2007; Jacobs et al., 2007; Syrjala et al., 2004; Wenz et al., 2000), but that subgroups of patients showed persistent impairment or declined on some cognitive domains (Jacobs et al., 2007; Meyers et al., 1994; Syrjala et al., 2011). Studies including patients with other non-CNS cancers also described that subgroups have cognitive dysfunction following chemotherapy (Vardy et al., 2008). There were no significant correlations between scores on any of the cognitive tests and self-reported fatigue or mood, and this is consistent with other studies (Friedman et al., 2009; Ahles et al., 2008; Wefel et al., 2004). More than 70% of patients were employed one year post-HSCT.

In this study, the group changes in brain structure were more pronounced than in cognitive test performance one year post-HSCT. Also, there were no significant associations between regional gray matter volume and cognitive test scores. These results may be in part related to reduced power to detect small changes and associations, and possibly to practice effects on the cognitive tests. A recent prospective study using functional MRI in patients with breast cancer treated with or without chemotherapy (McDonald et al., 2012) showed baseline increased activation in bifrontal regions and decreased left parietal activation compared to controls. One month after chemotherapy, there was a decrease in frontal activation in patients compared to controls, with partial return to baseline levels one year later. However, performance accuracy and reaction time on a working memory task did not differ between groups at baseline or over time for the individual task conditions, suggesting that hyperactivation of the underlying brain circuitry may have been required to support adequate working memory performance. An earlier fMRI study (Ferguson et al., 2007) also reported comparable working memory task performance and increased activation in the frontal lobes in a monozygotic twin with breast cancer treated with chemotherapy, relative to her healthy twin; these findings were thought to suggest that more cortical activation and recruitment of

additional regions were needed to compensate for dysfunction in the neural circuitry possibly disrupted by chemotherapy. Therefore, it is possible that some patients in our study were able to maintain cognitive performance at age-expected levels through the use of compensatory mechanisms in the context of reductions in regional gray matter volume.

The longitudinal study design provided new and relevant information regarding changes in brain structure and cognitive function in HSCT recipients. However, an assessment of several important factors including the specific contribution of disease type, conditioning regimen and transplant type, and of known risk factors such as GvHD and immunosuppressive therapy, was limited by the small sample size, the absence of pre-treatment assessments, non-randomization to treatment, and attrition bias. Attrition contributed to a reduction in our projected sample size, and it is a significant limitation in many longitudinal studies of cancer patients (Correa et al., 2008); the relatively small sample size most likely limited the power to detect small changes in brain structure and cognitive functions. As there has been an increase in the number of cancer patients who undergo HSCT, additional prospective studies are needed to further characterize the neurotoxicity associated with commonly used conditioning regimens, and improve our ability to identify individuals who may be at an increased risk for cognitive decline. Research including a systematic evaluation of possible risk factors, such as genetics, age, disease and treatment-related factors in large cohorts would be particularly relevant. Studies designed to test potential interventions to minimize or compensate for changes in cognitive function and quality of life in HSCT patients are also warranted.

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References

- Accomazzi, VLR., Barlow, CJ., Davey, B. US Patent Application. 2005. Inventors; Cedara Software Corp., assignee. Image region segmentation system and method.
- Ahles TA, Tope DM, Furstenberg C, Hahn D, Mills L. Psychologic and neuropsychologic impact of autologous bone marrow transplantation. *Journal of Clinical Oncology*. 1996; 14:1457–1462. [PubMed: 8622059]
- 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. *Psychooncology*. 2003; 12:612–619. [PubMed: 12923801]
- Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nature Reviews Cancer*. 2007; 7:192–201. [PubMed: 17318212]
- Ahles TA, Saykin AJ, McDonald BC, et al. Cognitive function in breast cancer patients prior to adjuvant treatment. *Breast Cancer Research and Treatment*. 2008; 110:143–152. [PubMed: 17674194]
- Ahles T, Saykin A, McDonald B, 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. *Journal of Clinical Oncology*. 2010; 28:4434–4440. [PubMed: 20837957]
- Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatment-associated cognitive change: an update on the state of the science. *Journal of Clinical Oncology*. 2012; 30:3675–3686. [PubMed: 23008308]

- Andrykowski MA, Schmitt FA, Gregg ME, Brady MJ, Lamb DG, Henslee-Downey PJ. Neuropsychologic impairment in adult bone marrow transplant candidates. *Cancer*. 1992; 70:2288–2297. [PubMed: 1394058]
- Bartynski WS, Zeigler Z, Spearman MP, Lin L, Shaddock RK, Lister J. Etiology of cortical and white matter lesions in cyclosporin-A and FK-506 neurotoxicity. *American Journal of Neuroradiology*. 2001; 22:1901–1914. [PubMed: 11733324]
- Booth-Jones M, Jacobsen PB, Ransom S, Soety E. Characteristics and correlates of cognitive functioning following bone marrow transplantation. *Bone Marrow Transplantation*. 2005; 36:695–702. [PubMed: 16086044]
- Chang G, Meadows ME, Orav EJ, Antin JH. Mental status changes after hematopoietic stem cell transplantation. *Cancer*. 2009; 115:4625–4635. [PubMed: 19551887]
- Correa DD, Maron L, Harder H, Klein M, Armstrong CL, Calabrese P, et al. Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines. *Annals of Oncology*. 2007; 18:1145–1151. [PubMed: 17284616]
- Correa DD, Shi W, Thaler HT, Cheung AM, DeAngelis LM, Abrey LE. Longitudinal cognitive follow-up in low grade gliomas. *Journal of Neurooncology*. 2008; 86:321–327.
- Correa DD, Shi W, Abrey LE, Deangelis LM, Omuro AM, Deutsch MB, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro-oncology*. 2012; 14:101–108. [PubMed: 22013168]
- DeAngelis, LM., Posner, JB. Side effects of radiation therapy. In: DeAngelis, LM., Posner, JB., editors. *Neurologic Complications of Cancer*. 2. Oxford University Press; New York: 2009. p. 551–544.
- Deprez S, Amant F, Yigit R, Porke K, Verhoeven J, Van den Stock J, et al. Chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired functioning in breast cancer patients. *Human Brain Mapping*. 2011; 32:480–493. [PubMed: 20725909]
- Deprez S, Amant F, Smeets A, Peeters R, Leemans A, Van Hecke W, et al. Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning. *Journal of Clinical Oncology*. 2012; 30:274–281. [PubMed: 22184379]
- Devine SM, Carter S, Soiffer RJ, Pasquini MC, Hari PN, Stein A, et al. Low risk of chronic graft-versus-host disease and relapse associated with T cell-depleted peripheral blood stem cell transplantation for acute myelogenous leukemia in first remission: results of the blood and marrow transplant clinical trials network protocol 0303. *Biology of Blood and Marrow Transplantation*. 2011; 9:1343–1351.
- Dietrich J, Han R, Yang Y, et al. CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and vivo. *Journal of Biology*. 2006; 5:1–23. [PubMed: 16515716]
- Dietrich J, Monje M, Wefel J, Meyers C. Clinical patterns and biological correlates of cognitive dysfunction associated with cancer therapy. *Oncologist*. 2008; 13:1285–1295. [PubMed: 19019972]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33:341–355. [PubMed: 11832223]
- Ferguson RJ, McDonald BC, Saykin AJ, Ahles TA. Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy. *Journal of Clinical Oncology*. 2007; 25:3866–3870. [PubMed: 17761972]
- 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. *Archives of Clinical Neuropsychology*. 2009; 24:689–698. [PubMed: 19767298]
- Garrick, R. *Neurologic Complications*. In: Atkinson, K., editor. *Clinical bone marrow and blood stem cell transplantation*. Cambridge, UK: Cambridge University Press; 2000.
- Hagemeister FB. Treatment of relapsed aggressive lymphomas: regimens with and without high-dose therapy and stem rescue. *Cancer Chemotherapy and Pharmacology*. 2002; 49:13–20.
- Hamadani M, Craig M, Phillips GS, Abraham J, Tse W, Cumpston A, et al. Higher busulfan dose intensity does not improve outcomes of patients undergoing allogeneic haematopoietic cell

transplantation following fludarabine, busulfan-based reduced toxicity conditioning. *Hematological Oncology*. 2011; 4:202–210.

- Harder H, van Gool AR, Cornelissen JJ, Duivenvoorden HJ, Eijkenboom WM, van den Bent MJ. Assessment of pre-treatment cognitive performance in adult bone marrow or hematopoietic stem cell transplantation patients: a comparative study. *European Journal of Cancer*. 2005; 41:1007–1016. [PubMed: 15862749]
- Harder H, Duivenvoorden HJ, van Gool AR, Cornelissen JJ, van den Bent MJ. Neurocognitive functions and quality of life in haematological patients receiving hematopoietic stem cell grafts: a one-year follow-up pilot study. *Journal of Clinical and Experimental Neuropsychology*. 2006; 28:283–293. [PubMed: 16618620]
- Harder H, van Gool AR, Duivenvoorden HJ, Cornelissen JJ, Eijkenboom WM, Barge RM, et al. Case-referent comparison of cognitive functions in patients receiving hematopoietic stem cell transplantation for haematological malignancies: two-year follow-up results. *European Journal of Cancer*. 2007; 43:2052–2059. [PubMed: 17719220]
- Inagaki M, Yoshikawa E, Matsuoka Y, Sugawara Y, Nakano T, Akechi T, et al. Smaller regional volumes of brain gray and white matter demonstrated in breast cancer survivors exposed to adjuvant chemotherapy. *Cancer*. 2007; 109:146–156. [PubMed: 17131349]
- Jakubowski AA, Small TN, Young JW, Kernan NA, Castro-Malaspina H, Hsu KC, et al. T cell depleted stem-cell transplantation for adults with hematologic malignancies: sustained engraftment of HLA-matched related donor grafts without the use of antithymocyte globulin. *Blood*. 2007; 110:4552–4559. [PubMed: 17717135]
- Jim HSL, Small B, Hartman S, Franzen J, Millay S, Phillips K, et al. Clinical predictors of cognitive function in adults treated with hematopoietic cell transplantation. *Cancer*. 2012; 118:3407–3416. [PubMed: 22139882]
- Keime-Guibert F, Napolitano M, Delattre JY. Neurological complications of radiotherapy and chemotherapy. *Journal of Neurology*. 1998; 245:695–708. [PubMed: 9808237]
- Koppelmans V, de Ruiter MB, van der Lijn F, Boogerd W, Seynaeve C, van der Lugt A, et al. Global and focal brain volume in long-term breast cancer survivors exposed to adjuvant chemotherapy. *Breast Cancer Research Treatment*. 2012; 132:1099–1106. [PubMed: 22205140]
- 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; 110:1560–1567. [PubMed: 17685391]
- Jacobsen PB, Garland LL, Booth-Jones M, Donovan KA, Thors CL, Winters E, et al. Relationship of hemoglobin levels to fatigue and cognitive functioning among cancer patients receiving chemotherapy. *Journal of Pain and Symptom Management*. 2004; 28:7–18. [PubMed: 15223080]
- Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*. 1991; 59:12–19. [PubMed: 2002127]
- McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. *Breast Cancer Research and Treatment*. 2010; 123:819–828. [PubMed: 20690040]
- McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Alterations in brain activation during working memory processing associated with breast cancer and treatment: a prospective functional magnetic resonance imaging study. *Journal of Clinical Oncology*. 2012; 30:2500–2508. [PubMed: 22665542]
- McDonald, BC., Conroy, SK., Smith, DJ., West, JD., Saykin, AJ. Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study. *Brain Behavior and Immunity*. 2012. <http://dx.doi.org/10.1016/i.bbi.2012.05.007>
- Meyers CA. Neuropsychological aspects of cancer and cancer treatment. *Physical Medicine and Rehabilitation: State of the Art Reviews*. 1994; 8:229–241.
- Meyers CA, Albitar M, Estey E. Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome. *Cancer*. 2004; 104:788–793.
- Meyers CA. How chemotherapy damages the central nervous system. *Journal of Biology*. 2008; 7:11. [PubMed: 18439322]

- Mounier N, Canals C, Gisselbrecht C, Cornelissen J, Foa R, Conde E, et al. High-dose therapy and autologous stem cell transplantation in first relapse for diffuse large B cell lymphoma in the rituximab era: an analysis based on data from the European Blood and Marrow Transplantation Registry. *Biology of Blood and Marrow Transplantation*. 2012; 18:788–793. [PubMed: 22005647]
- Nestor SM, Rupsingh R, Borrie M, Smith M, Accomazzi V, Wells JL, et al. Ventricular enlargement as a possible measure of Alzheimer's disease progression validated using the Alzheimer's disease neuroimaging initiative database. *Brain*. 2008; 31:2443–2454.
- Nucci M, Andrade F, Vigorito A, Trabasso P, Aranha JF, Maiolino A, et al. Infectious complications in patients randomized to receive bone marrow or peripheral blood transplantation. *Transplant Infectious Disease*. 2003; 5:167–173. [PubMed: 14987200]
- Omuro AM, Ben-Porat LS, Panageas KS, Kim AK, Correa DD, Yahalom J, et al. Delayed neurotoxicity in primary central nervous system lymphoma. *Archives of Neurology*. 2005; 62:1595–1600. [PubMed: 16216945]
- Padovan CS, Yousry TA, Schleuning M, Holler E, Kolb HJ, Straube A. Neurological and neuroradiological findings in long-term survivors of allogeneic bone marrow transplantation. *Annals of Neurology*. 1998; 43:627–633. [PubMed: 9585357]
- 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. *International Journal of Radiation Oncology, Biology, Physics*. 2000; 46:303–311.
- Rzeski W, Pruski S, Macke A, Felderhoff-Mueser U, Reiher AK, Hoerster F, et al. Anticancer agents are potent neurotoxins in vitro and in vivo. *Annals of Neurology*. 2004; 56:351–360. [PubMed: 15349862]
- Small BJ, Rawson KS, Walsk E, Jim HS, Hughes TF, Iser L, et al. Catechol-o-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. *Cancer*. 2011; 117:1369–1376. [PubMed: 21425136]
- Schulz-Kindermann F, Mehert 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 Transplantation*. 2007; 39:789–799. [PubMed: 17417661]
- Snider S, Bashir R, Bierman P. Neurologic complications after high-dose chemotherapy and autologous bone marrow transplantation for Hodgkin's disease. *Neurology*. 1994; 44:681–684. [PubMed: 8164825]
- Soutar RL, King DJ. Bone marrow transplantation. *British Medical Journal*. 1995; 310:31–36. [PubMed: 7827553]
- Sostak P, Padovan CS, Yousry TA, Ledderose G, Kolg H-J, Straube A. Prospective evaluation of neurological complications after allogeneic bone marrow transplantation. *Neurology*. 2003; 60:842–848. [PubMed: 12629244]
- Stemmer SM, Stears JC, Burton BS, Jones RB, Simon JH. White matter changes in patients with breast cancer treated with high-dose chemotherapy and autologous bone marrow support. *American Journal of Neuroradiology*. 1994; 15:1267–1273. [PubMed: 7976937]
- Syrjala KL, Dikmen S, Langer SL, Roth-Roemer S, Abrams JR. Neuropsychologic changes from before transplantation to 1 year in patients receiving myeloblastic allogeneic hematopoietic cell transplant. *Blood*. 2004; 104:3386–3392. [PubMed: 15251983]
- Syrjala KL, Artherholt SB, Kurlan 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 to matched controls at 5 years. *Journal of Clinical Oncology*. 2011; 29:2397–2404. [PubMed: 21537032]
- Tukey, JW. *Exploratory Data Analysis*. 1977. Section 2C
- Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB. Cancer and cancer-therapy related cognitive dysfunction: An international perspective from the Venice cognitive workshop. *Annals of Oncology*. 2008; 19:623–629. [PubMed: 17974553]
- Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. *Cancer*. 2004; 100:2292–2299. [PubMed: 15160331]

- 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). *International Journal of Radiation Oncology Biology, Physics*. 2000; 48:1497–1501.
- Wood SM, Meyers CA, Faderi S, Kantarjian HM, Pierce SH, Garcia-Manero G. Association of anemia and cognitive dysfunction in patients with acute myelogenous leukemia and myelodysplastic syndrome. *American Journal of Hematology*. 2011; 86:950–952. [PubMed: 21919036]

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Figure 1.

Baseline and follow-up *left* lateral (1a) and *total* lateral (1b) ventricle mean volume for the combined patient and chemotherapy alone groups, and the healthy controls. *p=0.044; **p=0.025, group by time interaction.

Figure 2.

Regional gray matter reductions (VBM) from baseline to the one-year follow-up in the left and right middle frontal gyrus (MFG) in the Combined Patient group (Left MFG FWE-corr $p=0.008$; Right MFG FWE-corr $p=0.048$) (2a & 2b), and in the Chemotherapy Alone group (Left MFG FWE-corr $p=0.032$) (2c & 2b). Gray matter reductions in the left caudate nucleus from baseline to the one-year follow-up in the Combined Patient group (FWE-corr $p=0.030$) (2e).

Table 1

Demographic Characteristics and Treatment History

Demographics/Treatment	fTBI + Chemotherapy (N=9)	Chemotherapy Alone (N=19)	Healthy Controls (N=10)
Sex (M/F)	7/2	13/6	7/3
Handedness (R/L)	9/0	18/1	9/1
Age at Baseline (yrs)			
Mean (SD)	41.6 (10.4)	52.1 (12.6) *	46.4 (13.2)
Median (range)	39.0 (31–62)	56.0 (25–65)	47.5 (30–65)
Mean Education (yrs)	16.0 (2.1)	16.5 (3.2)	17.3 (2.5)
Mean Est. VIQ	112 (5.6)	114 (5.7)	117 (2.8)
Follow-up Interval (days)			
Mean (SD)	396.4 (74.3)	403.4 (41.2)	372.5 (10.6)
Diagnosis			
AML	3/9	2/19	NA
ALL	3/9	0/19	NA
Lymphoma	3/9	8/19	NA
Multiple Myeloma	0/9	5/19	NA
Myelodysplastic Syndrome	0/9	4/19	NA
Transplant Type			
Allogeneic	9/9	7/19	NA
Autologous	0/9	12/19	NA
Conditioning Chemotherapy			
Thio/Flu/Cy	5/9	0/19	NA
Cy/MTX/Ara-C	4/9	0/19	NA
Bu/Mel/Flu	0/9	7/19	NA
BEAM	0/9	6/19	NA
Cytoxan/Mel	0/9	6/19	NA

Est. VIQ= Estimated Verbal IQ (NAART or Barona Index). AML=Acute myeloid leukemia; ALL= Acute lymphocytic leukemia; Thio/Flu/Cy=Thiotepa/Fludarabine/Cyclophosphamide; MTX/Ara-C= Methotrexate/Cytarabine; Bu/Mel/Flu=Busulfan/Melphalan/Fludarabine; BEAM=carmustine/etoposide/cytarabine/melphalan.

* p= 0.03, fTBI + Chemotherapy vs. Chemotherapy Alone.

Table 2

Significant Regional Mean Volume Changes – Voxel-Based Morphometry (VBM)

MNI Coordinates (x y z)	<i>p</i> FWE-corr	<i>T</i>	Region Description
Group x Time Interaction			
<i>Healthy Controls vs. Combined Patient Group</i>			
-32 21 55	0.070 *	4.47	L Middle Frontal Gyrus
<i>Healthy Controls vs. Chemotherapy Group</i>			
-32 21 57	0.032 *	5.05	L Middle Frontal Gyrus
Within Group – Time Effect			
<i>Combined Patient Group (N=21)</i>			
-30 12 58	0.008	7.62	L Middle Frontal Gyrus
34 14 51	0.048	6.56	R Middle Frontal Gyrus
-3 12 -2	0.030	6.85	L Caudate
<i>Chemotherapy Alone Group (N=16)</i>			
-34 12 48	0.032	8.09	L Middle Frontal Gyrus

* Middle Frontal Gyrus (bMFG) Small Volume Corrected

MNI=Montreal Neurological Institute; FWE-corr=family-wise error corrected.

Table 3

Cognitive Test Z-Scores (Means and Standard Deviations)

Measures	All Patients (N=28)		FTBI+Chemo (N=9)		Chemo Alone (N=19)		Controls (N=10)	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
<i>Attention/Executive</i>								
DF	0.3 (0.9)	0.4 (1.0)	0.4 (0.9)	0.4 (1.0)	0.3 (0.9)	0.3 (1.0)	0.8 (0.8)	1.1 (0.6)
DB	0.4 (0.9)	0.3 (1.0)	0.3 (0.8)	0.0 (1.0)	0.5 (0.9)	0.5 (0.9)	0.7 (1.0)	1.0 (1.2)
BTA	-0.1 (0.9)	-0.4 (1.1)	0.0 (0.8)	-0.3 (1.3)	-0.1 (0.9)	-0.4 (1.0)	0.1 (1.0)	0.4 (0.6)
TMTA	-0.1 (0.6)	-0.1 (0.9)	-0.2 (0.7)	0.0 (0.9)	-0.1 (0.6)	-0.2 (0.9)	0.3 (1.2)	1.1 (1.3)*
TMTB	-0.05 (0.9)	0.02 (0.8)	-0.2 (0.8)	-0.2 (0.6)	0.0 (1.0)	0.2 (0.8)	0.4 (1.4)	1.0 (1.6)
<i>Verbal Memory</i>								
CVLT-L	0.5 (0.6)	1.2 (0.7)*	0.4 (0.6)	1.2 (1.1)*	0.5 (0.5)	1.2 (0.8)*	1.4 (0.6)	2.0 (0.9)*
CVLT-LD	0.5 (0.7)	0.8 (1.0)	0.4 (0.7)	0.6 (1.1)	0.6 (0.7)	0.9 (1.0)*	0.8 (0.5)	1.3 (0.5)*
CVLT-DI	0.6 (0.8)	0.7 (0.9)	0.7 (0.4)	0.4 (0.8)	0.5 (0.9)	0.8 (0.9)*	0.8 (0.5)	0.7 (0.8)
<i>Visual Memory</i>								
BLT-L	-0.2 (1.2)	0.2 (1.1)*	0.2 (1.5)	0.3 (1.3)	-0.4 (1.1)	0.2 (1.0)*	-0.3 (1.4)	0.8 (1.6)*
BLT-LD	-0.3 (1.3)	-0.1 (1.3)	0.5 (1.1)	0.2 (1.6)	-0.6 (1.2)	-0.3 (1.1)	-0.1 (1.2)	0.5 (1.0)*
BLT-DI	0.2 (1.3)	-0.1 (1.4)	0.4 (1.2)	-0.1 (1.4)*	0.1 (1.3)	-0.1 (1.5)	-0.4 (0.3)	0.4 (1.1)*

DF= Digit Span Forward; DB= Digit Span Backward; BTA= Brief Test of Attention; TMTA= Trail Making Test A; TMTB= Trail Making Test B; CVLT-L= California Verbal Learning Test- Learning; CVLT-LD= California Verbal Learning Test- Long Delay; CVLT-DI= California Verbal Learning Test- Discrimination Index; BLT-L= Brown Location Test- Learning; BLT-LD= Brown Location Test- Long Delay; BLT-DI= Brown Location Test- Discrimination Index.

* Indicates significant within-group difference ($p < 0.05$) between the pre- and post-HSCT scores on the given cognitive test.