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Prospective assessment of white matter integrity in adult stem cell transplant recipients

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Abstract

Hematopoietic stem cell transplantation (HSCT) is often used in the treatment of hematologic disorders. Although it can be curative, the pre-transplant conditioning regimen can be associated with neurotoxicity. In this prospective study, we examined white matter (WM) integrity with diffusion tensor imaging (DTI) and neuropsychological functioning before and one year after HSCT in twenty-two patients with hematologic disorders and ten healthy controls evaluated at similar intervals. Eighteen patients received conditioning treatment with high-dose (HD) chemotherapy, and four had full dose total body irradiation (fTBI) and HD chemotherapy prior to undergoing an allogeneic or autologous HSCT. The results showed a significant decrease in mean diffusivity (MD) and axial diffusivity (AD) in diffuse WM regions one year after HSCT (p-corrected <0.05) in the patient group compared to healthy controls. At baseline, patients treated with allogeneic HSCT had higher MD and AD in the left hemisphere WM than autologous HSCT patients (p-corrected <0.05). One year post-transplant, patients treated with allogeneic HSCT had lower fractional anisotropy (FA) and higher radial diffusivity (RD) in the right hemisphere and left

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frontal WM compared to patients treated with autologous HSCT (p-corrected <0.05). There were modest but significant correlations between MD values and cognitive test scores, and these were greatest for timed tests and in projection tracts. Patients showed a trend toward a decline in working memory, and had lower cognitive test scores than healthy controls at the one-year assessment. The findings suggest a relatively diffuse pattern of alterations in WM integrity in adult survivors of HSCT.

Keywords

Hematopoietic stem cell transplantation; Cognitive; Magnetic resonance imaging; Diffusion tensor imaging

Introduction

Advances in hematopoietic stem cell transplantation (HSCT) for the treatment of chemotherapy resistant or recurrent hematological malignancies have resulted in increased survival rates. Although the treatment can be curative, the pre-transplant myeloablative conditioning regimen including high-dose (HD) chemotherapy with or without total body irradiation (TBI) can be associated with neurotoxicity (Snider et al. 1994; Soutar and King 1995; Sostak et al. 2003). In allogeneic HSCT, treatment-related complications such as 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; Hartrampf et al. 2013).

There is increasing evidence that chemotherapy is associated with neurotoxicity (Rzeski et al. 2004; Meyers 2008; Dietrich et al. 2008). Candidate mechanisms for neurotoxicity include demyelination, oxidative stress and DNA damage, and immune dysregulation and stimulation of neurotoxic cytokines (Ahles and Saykin, 2007; Seigers and Fardell 2011). Radiotherapy often produces damage to the CNS through vascular injury causing chronic ischemia, progressive demyelination of the white matter (WM), and necrosis (Omuro et al. 2005; DeAngelis and Posner 2009). There is increasing evidence that radiotherapy and chemotherapy have direct toxic effects on progenitor cells, oligodendrocytes, white matter, gliogenesis and neurogenesis (Dietrich et al. 2006; Dietrich 2010; Monje and Dietrich 2012; Monje et al. 2007).

Neuropsychological studies reported that prior to transplant, 20–40 % of patients had cognitive dysfunction involving graphomotor speed, executive and memory abilities (Andrykowski et al., 1992; Chang et al., 2009; Friedman et al. 2009; Harder et al. 2005, 2006; Jacobs et al. 2007; Meyers 1994; Schulz-Kindermann et al. 2007). At approximately one year post-transplant, cognitive improvement was noted 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 1994; Syrjala et al. 2004). Syrjala et al. (2011) reported improvement in executive functions, but not in memory or motor speed five years post-HSCT, with more than 40 % of survivors having a global deficit score indicative of cognitive impairment. Cross-sectional structural neuroimaging studies described white matter

abnormalities and atrophy 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 HSCT developed neurologic complications, white matter changes, cerebral atrophy, and cognitive deterioration one year after the transplant; chronic graft-versus-host disease (GvHD) and immunosuppression were significant risk factors. In a recent prospective study, we reported that in patients with hematologic malignancies, the conditioning regimen for HSCT consisting of HD chemotherapy alone or in combination with TBI was associated with a reduction in gray matter volume in the prefrontal cortex and an increase in ventricular volume one year post-transplant relative to healthy controls evaluated at similar intervals (Correa et al. 2013).

In this study, we used Diffusion Tensor Imaging (DTI) to assess changes in WM integrity in the same cohort of patients and healthy controls, and to further assess the possible effects of transplant type. DTI is a quantitative magnetic resonance imaging (MRI) technique that provides information about the three-dimensional diffusion of water molecules within the tissue (Basser and Pierpaoli 2011; Song et al. 2002). Recent cross-sectional and longitudinal studies using DTI in breast cancer patients treated with chemotherapy documented changes in white matter integrity (Deprez et al. 2013). Overall, these results suggest that chemotherapy may disrupt WM integrity and that DTI is a sensitive tool to quantify cancer treatment-related changes in brain structure. However, to date there are no DTI studies in adult HSCT recipients.

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 study if they had a diagnosis of a hematological malignancy and were scheduled to undergo conditioning treatment with HD chemotherapy with or without full-dose total body irradiation (fTBI), 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.

Twenty-eight patients completed brain MRI including DTI sequences and cognitive evaluations *prior to* conditioning treatment with HD chemotherapy with or without fTBI for HSCT, and *one-year* post transplant. Ten healthy controls completed the MRI and cognitive evaluations at study entry and at the one-year follow-up. DTI sequences were available at baseline and at the one-year follow-up for 22 patients and 10 healthy controls. DTI

sequences from 6 patients were excluded due to poor image quality or movement artifact. A complete description of the participants was included in our prior study (Correa et al. 2013).

Structural neuroimaging

MRI scan acquisition—All participants were imaged on the same 3 T GE Signa scanner (GE Medical Systems, Waukesha, WI) with an 8-channel phased-array head coil. DTI acquisition was conducted using a whole brain two-dimensional spin-echo sequence with an echo-planar readout (SE-EPI-DTI) and a pair of diffusion weighting gradients positioned symmetrically around the 180° pulse (Basser and Pierpaoli 2011). DTI parameters: TE = *70–80 ms*, TR = 15.*2 s*, 72 axial slices with *1.8 mm* thickness with no gap between slices, field of view = 230 mm × 230 mm, voxel size was $1.8 \times 1.8 \times 1.8\ mm^3$. Diffusion gradients were applied along 42 non-collinear directions with a *b* value of $1000\ s/mm^2$; one non-diffusion-weighted set of images was acquired. T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences were also acquired to rule out pathology.

Image processing—DTI image processing, including artifact correction due to eddy-current and motion correction, was performed with the MRI software library (FSL). Subsequently, DTIFIT was used to compute the fractional anisotropy (FA), mean diffusivity (MD), (axial diffusivity) DA and radial diffusivity (DR) maps. Tract-based spatial statistics (TBSS) were used for statistical analysis. All individual FA maps were nonlinearly registered to the template and then affine-transformed into standard Montreal Neurological Institute (MNI) space. A mean WM skeleton was generated based on the mean FA image of all subjects. Each subject's aligned FA image was projected onto the mean FA skeleton, and voxel-wise group comparisons of FA values were conducted along the skeleton. Voxel-wise analysis of MD, DA and DR maps was conducted in the same manner using the same FA skeleton.

Neuropsychological assessment

The neuropsychological evaluation included tests of auditory attention and executive functions (Digit Span of the WMS-III - DSF/DSB, Wechsler 1997; Brief Test of Attention – BTA, Schretlen et al. 1996; Trail Making Test Parts A & B – TMTA, TMTB, Heaton et al. 2004), verbal memory (California Verbal Learning Test-Second Edition – CVLT-II; Learning – CVLT-L, Long Delayed Recall – CVLT-LD, Discrimination Index – CVLT-DI, Delis et al. 2000), and visual-spatial memory (Brown Location Test – BLT; Learning – BLT-L, Long Delayed Recall – BLT-LD, Discrimination Index – BLT-DI, Brown et al. 2007). 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

All skeletonized DTI maps were included in voxel-wise group statistical analyses using a generalized linear model approach with age and gender as covariates. To test for voxel-wise group differences, the threshold-free cluster enhancement (TFCE) method (Smith and Nichols 2009) was used. TFCE was carried out using the "randomize" program within FSL, which performs permutation testing (5000 permutations) that does not rely on a Gaussian distribution (Nichols and Holmes 2002). The 95th percentile of this distribution was then

used as a TFCE-threshold and the significance level calculated from this distribution. Thus, the maps were fully corrected for family-wise error (FWE) of multiple comparisons at $p < 0.05$. A two factor analysis of co-variance (ANCOVA) with time as a within-subject factor (baseline and one-year follow-up) and group (all patients, allogeneic, autologous, and healthy controls) as a between-subject factor, and age and gender as covariates was used to assess changes in the DTI parameters (i.e., FA, MD, DA, DR). For all contrasts, voxels were considered significant if they survived FWE correction across the whole volume at $p <=0.05$.

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. Repeated measures analysis of variance (ANOVA) with time as a within-subject factor (baseline and one-year follow-up) and group (patients and healthy controls) as a between-subject factor was used to assess changes in the cognitive test z-scores. A repeated measures ANOVA with time as a within-subject factor (baseline and one-year follow-up) and transplant (allogeneic and autologous) as a between-subject factor was used to evaluate changes in cognitive test z-scores according to transplant type. Welch t-tests were used to assess if patients and healthy controls differed on these variables at baseline and at follow-up.

Results

Subject characteristics

As shown in Table 1, the 22 patients and 10 healthy controls were predominantly men (75 %) and right-handed (90 %). There were no significant differences between the groups in age, education, estimated IQ, or length of follow-up. Table 1 also describes the diagnoses, conditioning treatments for all patients, and according to transplant type. Patients were diagnosed with lymphoma (45 %), leukemia (23 %), multiple myeloma (23 %), or myelodysplastic syndrome (9 %). Eighteen patients received conditioning treatment with HD chemotherapy and four patients had fTBI (1200–1375 cGy) and HD chemotherapy. Ten patients (45 %) received an allogeneic HSCT (3 related, 7 unrelated), and twelve (55 %) had an autologous HSCT. 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 h after the conditioning regimens, consistent with standard clinical practice (Devine et al. 2011; Hamadani et al. 2011; Jakubowski et al. 2007). Following HSCT, three patients had additional treatment with rituximab. Five patients developed graft-versus-host disease (GvHD) and were treated with prednisone, tacrolimus or methotrexate.

All patients had chemotherapy to treat their illness prior to becoming candidates for HSCT. Previous regimens for the 12 autologous transplant candidates were as follows: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) chemotherapy in combination with several additional agents for 7 (58 %) patients; chemotherapy with multiple other agents for 5 (42 %) patients. For the 10 allogeneic transplant candidates, prior therapy was as follows: cytarabine in combination with methotrexate or additional agents for 8 (80 %) patients; various other chemotherapies for 2 (20 %) patients.

DTI results

Cross-sectional analysis—There were no statistically significant differences when comparing *all* patients to healthy controls at baseline or at the one-year follow-up. Comparisons by transplant type showed that *at baseline*, candidates for allogeneic HSCT had higher MD (p-corrected <0.05) in the left anterior corona radiata, left posterior thalamic radiation and splenium of the corpus callosum, and higher AD (p-corrected <0.05) in the left anterior corona radiata, compared to autologous HSCT candidates (Fig. 1a). *One year post-transplant*, patients treated with allogeneic HSCT had lower FA and higher RD (p-corrected <0.05) in the right internal capsule and genu of the corpus callosum, and higher RD (p-corrected <0.05) in the left anterior corona radiata in comparison to autologous HSCT patients (Fig. 1b). There were no statistically significant differences between allogeneic HSCT patients and healthy controls at either time point.

Longitudinal analysis—The results of TBSS analysis indicated that patients had a significant decrease in MD in diffuse WM regions one year after HSCT (p-corrected <0.05) compared to healthy controls (Fig. 2). A significant decrease in AD (p-corrected <0.05) in similar regions was also observed. There were no significant time by group interactions for comparisons including all patients versus healthy controls, or for comparisons including patients treated with autologous or allogeneic HSCT and healthy controls.

Region of interest (ROI) analysis—Region of interest (ROI) analyses were performed to further examine the diffuse changes in MD, based on the pertinent available DTI anatomic templates. ROIs were defined on individual FA maps at the threshold of 0.2 for each main WM track on the pertinent available DTI anatomic templates (ICBM-DTI-81 parcellation map and Johns Hopkins University DTI-based WM atlas) (Mori et al. 2008). These ROIs were applied for all subsequent between and within group comparisons. Average FA, MD, RA, and RD values were calculated for all ROIs for each subject.

The results of paired t-tests showed a significant decrease in MD ($p < 0.05$) in several WM tracts one year post-HSCT among all patients but not healthy controls (Table 2). There were significant group by time interactions showing that (1) relative to autologous transplant patients and healthy controls, patients treated with allogeneic transplants had a significant decrease in MD in the genu of the corpus callosum ($p = 0.028$) and middle cerebellar peduncle ($p = 0.012$), and an increase in the fornix ($p = 0.001$) at the one-year follow-up; (2) relative to allogeneic transplant patients and healthy controls, patients treated with autologous HSCT had a significant decrease in MD in the right external capsule ($p = 0.047$), right uncinate fasciculus ($p = 0.024$), and fornix ($p = 0.001$) at follow-up.

Neuropsychological assessment

Cross-sectional analysis—Mean cognitive test z-scores at baseline and follow-up are reported in Table 3. At baseline, there were no significant differences between patients and healthy controls on any of the cognitive tests, except for the CVLT-L with patients scoring lower than controls ($p = 0.001$). At the follow-up evaluation, patients had lower scores than healthy controls on the DSF, BTA, TMTA, CVLT-L and CVLT-LD, and BLT-LD ($p < 0.05$).

Longitudinal analysis—Repeated measures ANOVA revealed a significant or marginally significant ($p < 0.10$) *group effect* for DSF ($F(1,30) = 3.6$, $p = 0.068$), BTA ($F(1,30) = 4.2$, $p = 0.049$), TMTA ($F(1, 30) = 9.4$, $p = 0.005$), TMTB ($F(1,30) = 3.2$, $p = 0.086$, CVLT-L ($F(1,30) = 14.5$, $p < 0.001$) and CVLT-LD ($F(1, 30) = 3.2$, $p = 0.083$, as healthy controls tended to have slightly higher scores relative to patients at baseline and substantially higher scores at follow-up.

There was a significant or marginally significant *time effect* for the TMTA ($F(1,30) = 3.6$, $p = 0.068$), CVLT-L ($F(1, 30) = 22.1$, $p < 0.001$), CVLT-LD ($F(1,30) = 4.4$, $p = 0.045$), BLT-L ($F(1,30) = 21.8$, $p < 0.001$), and BLT-LD ($F(1, 30) = 5.2$, $p = 0.03$), as both groups improved at follow-up. There was a trend toward a decline in DSF and BTA in the patient group, but it did not reach significance. On the BLT-DI, there was a marginally significant group by time interaction ($F(1,30) = 4.1$, $p = 0.053$), as scores improved for healthy controls and declined for the patient group at follow-up.

Comparisons by transplant type—Mean cognitive test z-scores at baseline and follow-up according to transplant type are reported in Table 4. Repeated measures ANOVA revealed a significant *transplant type effect* for TMTA ($F(1,20) = 6.41$, $p = 0.02$), TMTB ($F(1,20) = 3.14$, $p = 0.09$), CVLT-LD ($F(1,20) = 9.22$, $p = 0.007$), as patients treated with an allogeneic HSCT obtained slightly lower scores than autologous HSCT patients at baseline and substantially lower scores at follow-up. On the BLT-L and BLT-LD, there were significant transplant type by time interactions ($F(1,20) = 5.92$, $p = 0.024$; $F(1,20) = 6.04$, $p = 0.023$), as scores improved for patients treated with autologous HSCT and declined for allogeneic HSCT patients.

Correlations – MD and cognitive test Z-scores

Change scores (Time 2 - Time 1) were calculated for regions that showed significant longitudinal changes in MD in the patient group. Cognitive change z-scores (Time 2 – Time 1) were also calculated. The results of partial correlations controlling for age and gender showed modest but significant negative correlations between MD values in WM association and projection tracts and the TMTA, CVLT-L, CVLT-LD and CVLT-DI, BLT-DI, and DSB (Table 5). Specifically, a decrease in MD in several WM tracts from Time 1 to Time 2 was associated with an increase in cognitive test scores. There were also significant positive correlations between MD values in commissural tracts and the TMTB and BLT-L.

Discussion

The present findings indicated significant changes in WM integrity one year following conditioning treatment with HD chemotherapy with or without fTBI in HSCT recipients. Specifically, there was a significant decrease in MD and AD in diffuse WM regions in the patient group relative to the healthy controls, including the corpus callosum, cingulum, fornix, inferior fronto-occipital fasciculi, corona radiata, and internal and external capsule, suggesting regional changes in WM microstructure and integrity. The changes in MD in some of the association and projection tracts correlated with changes in attention, graphomotor speed and memory, suggesting that as MD decreased, the cognitive test scores improved. Further comparisons by transplant type indicated that patients treated with

allogeneic HSCT had higher MD and AD in the left hemisphere WM at baseline, and lower FA and higher RD in the in the right hemisphere and left frontal WM one year post-transplant, compared to patients treated with autologous HSCT. ROI analysis by transplant type suggested a more variable pattern of results with a decrease in MD post-HSCT in different WM tracts for allogeneic and autologous HSCT patients. FA characterizes the degree of directionality of water diffusion and MD measures the overall average amount of diffusion and is determined by AD, which reflects the diffusion of water parallel to WM tracts and by RD, which reflects the diffusion of water perpendicular to WM tracts (Basser and Pierpaoli 2011; Pierpaoli et al. 1996; Pierpaoli et al. 2001). The biological substrate of tensor changes is not completely understood and the diffusion signal may reflect alterations in several tissue properties, including axonal density, myelination, inflammation, and permeability of cell membranes (Deprez et al. 2013); therefore, the interpretation of changes in DTI parameters should be made with caution (Wang et al. 2012).

To date, only a few studies have used DTI to examine chemotherapy-related changes in WM integrity in patients with non-CNS cancers, and most of these studies involved patients with breast cancer (Deprez et al. 2013). Deprez et al. (2011) reported decreased FA in frontal and temporal WM tracts, and increased MD in patients with breast cancer four months after treatment with chemotherapy, relative to healthy controls. In a cross-sectional study, de Ruiter et al. (2012) reported decreased FA and increased MD in the inferior and superior longitudinal fasciculus and corpus callosum in breast cancer survivors ten years after treatment with HD chemotherapy combined with stem-cell transplantation. In a recent prospective study, Deprez et al. (2012) studied breast cancer patients prior to and 3–4 months post-chemotherapy, and patients not exposed to chemotherapy and healthy controls seen at similar intervals. The authors reported a significant decrease in FA in frontal, parietal, and occipital WM tracts after chemotherapy, but no change in the other two groups. DTI studies of adult survivors of childhood acute lymphoblastic leukemia treated with prophylactic whole-brain radiation and/or intrathecal chemotherapy also documented widespread decreases in FA after treatment (Dellani et al. 2008; Schuitema et al. 2013; Edelmann et al. 2014). Animal studies have reported damage to myelinated WM tracts after administration of chemotherapy (Dietrich et al. 2006; Han et al. 2008).

There were several differences in our results compared to DTI studies involving breast cancer patients treated with chemotherapy. In our patients, there was a decrease in overall diffusion magnitude one year post-treatment and no significant longitudinal change in FA. The decrease in MD was an unexpected finding, and its significance is unclear. Possible interpretations may include restricted diffusivity related to tissue scarring or axonal swelling due to cytotoxicity (Trivedi et al., 2012), and WM matter atrophy, considering our prior report of ventricular enlargement in these patients (Correa et al., 2013), and in the context of lower cognitive scores or absence of practice effects compared to healthy controls. However, cellular repair at long intervals post-treatment may also be considered in the context of the negative correlations with the cognitive test scores. Further research and validation in a larger cohort of patients would be required to clarify these findings. Although beyond the scope of this report, additional analysis such as WM tractography or connectivity analysis might also provide complementary information. The findings of higher MD and AD baseline values in candidates of allogeneic relative to autologous HSCT may be related to their prior

chemotherapy regimens, which included cytarabine and methotrexate for several of the allogeneic transplant candidates. These agents are known to be associated with neurotoxicity (Magge & DeAngelis, 2015; Dietrich, 2010); however, the contribution of disease-related factors or the possible interaction of disease and treatment cannot be excluded. The findings that *one year post-transplant*, allogeneic HSCT patients had lower FA and higher RD in the right hemisphere and left frontal WM in comparison to patients treated with autologous HSCT may suggest greater neurotoxicity, possibly associated with the conditioning treatment for allogeneic transplants as four patients had fTBI and some developed GvHD. The findings that allogeneic HSCT patients had lower scores in processing speed and executive functions and declined on a test of visual memory relative to autologous HSCT patients, would further support this interpretation. There is recent evidence that GvHD, a frequent complication after allogeneic HSCT, can be a risk factor for neurotoxicity. Hartrampf et al. (2013) documented that the central nervous system can be a direct target of alloreactive T cells following allogenic transplant in mice, and that recipients with GvHD had deficits in spatial memory. In this study, longitudinal comparisons according to transplant type were not significant but additional studies would be needed to clarify if some pre-transplant regional WM abnormalities may improve over time while additional WM changes may develop following allogeneic or autologous HSCT.

There were significant negative correlations between a subset of the WM association and projection tracts showing a longitudinal decrease in MD, including the cingulum, inferior fronto-occipital fasciculus, internal and external capsule, and corona radiata, and tests of attention, graphomotor speed and memory. Several of these regions have been shown to participate in various aspects of cognitive functions (Schmahmann et al. 2008). Changes in WM integrity in the corpus callosum, corona radiata, and association tracts, such as the inferior and superior longitudinal fasciculus, have been shown to correlate with attention and processing speed in other studies (Deprez et al. 2013; Kerchner et al. 2012). The improvement in the memory tests may have been in part related to practice effects, which were greater for healthy controls than for the patients, suggesting that patients benefitted less from repeated exposure to the tests. This is consistent with other cognitive studies involving breast cancer patients (Ahles et al. 2012). Interestingly, there was a trend toward a decline on tests of working memory among patients, and they obtained significantly lower scores than healthy controls on tests of attention and working memory, graphomotor speed and verbal memory at the one-year assessment.

This prospective study is the first to document a diffuse pattern of changes in WM microstructure and integrity in HSCT recipients one year following conditioning treatment with HD chemotherapy with and without fTBI as measured by DTI. In our previous study including the same cohort of patients (Correa et al. 2013), there was a significant reduction in gray matter volume in the middle frontal gyrus bilaterally and in the left caudate nucleus, and a significant increase in ventricular volume among patients relative to healthy controls over the one-year follow-up period. Overall, these results suggest that HSCT may be associated with structural abnormalities involving both gray and white matter. However, our findings require further study and replication in a larger cohort of patients and healthy controls. An assessment of important factors including the specific contribution of disease type, conditioning regimen type, and risk factors such as GvHD was limited by the small

sample size, non-randomization to treatment, and attrition bias. The small number of patients and unequal number of healthy controls may have limited the power to detect small to moderate effect sizes, and identify subgroups of patients at increased risk for neurotoxicity. As more middle-aged an older cancer patients are undergoing HSCT, additional studies examining the mechanisms and risk factors associated with the neurotoxicity of commonly used conditioning regimens are needed. These lines of research would improve the ability to identify individuals who may be at risk for cognitive dysfunction, and assist in the development of interventions to prevent or reduce cancer treatment-related neurotoxicity.

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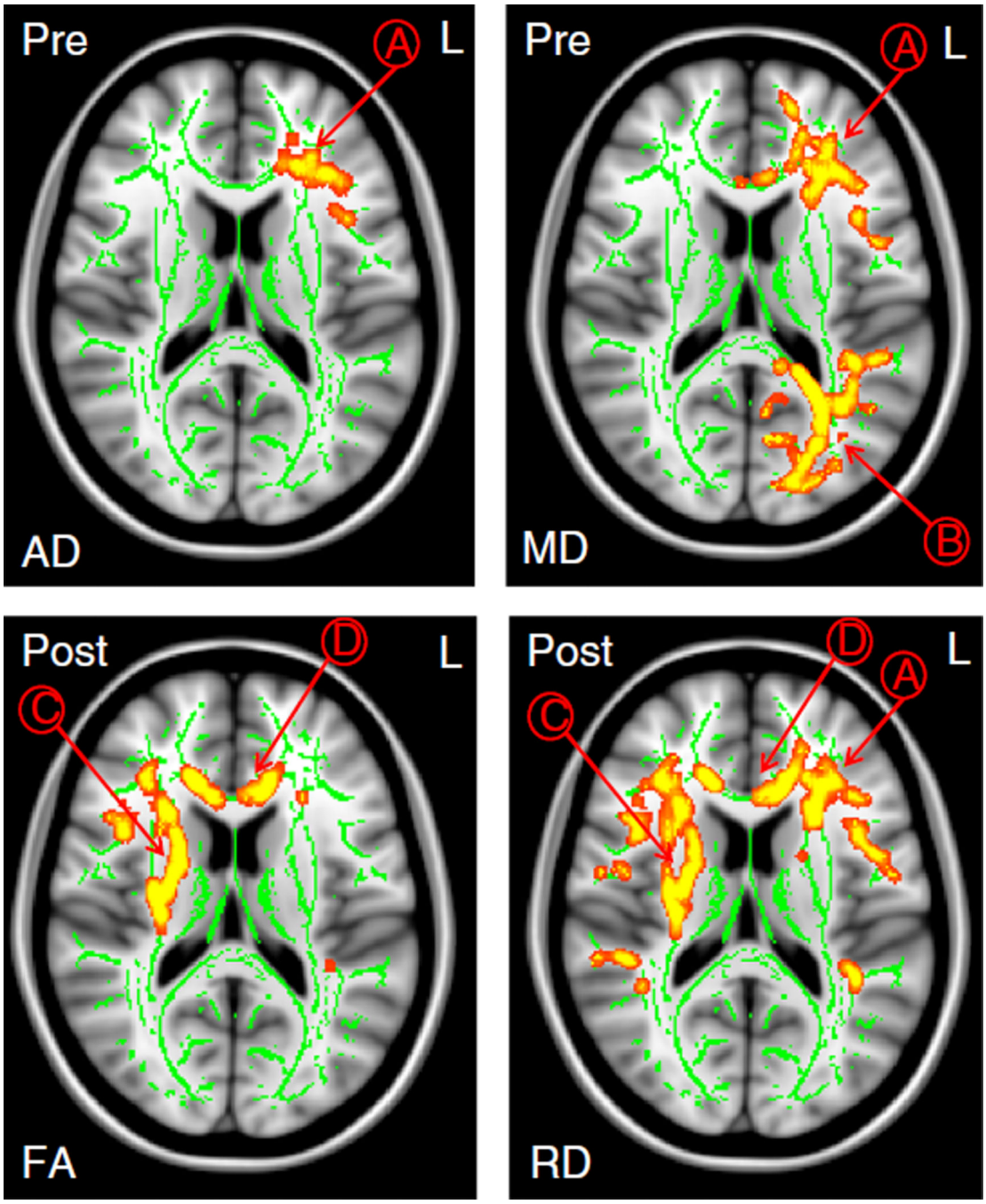

Fig. 1.

1a Areas of significantly increased MD and AD *pre-HSCT*, and **1b** areas of decreased FA and increased RD one-year *post-HSCT* in patients treated with allogeneic compared to autologous HSCT and healthy controls (TBSS analysis, p-corrected <0.05). **a** left anterior corona radiata; **b** left posterior thalamic radiation and splenium of the corpus callosum; **c** right internal capsule; **d** genu of the corpus callosum. Red/Yellow = All areas of change are expanded for ease of visualization; Green = Mean skeletonized FA of all subjects

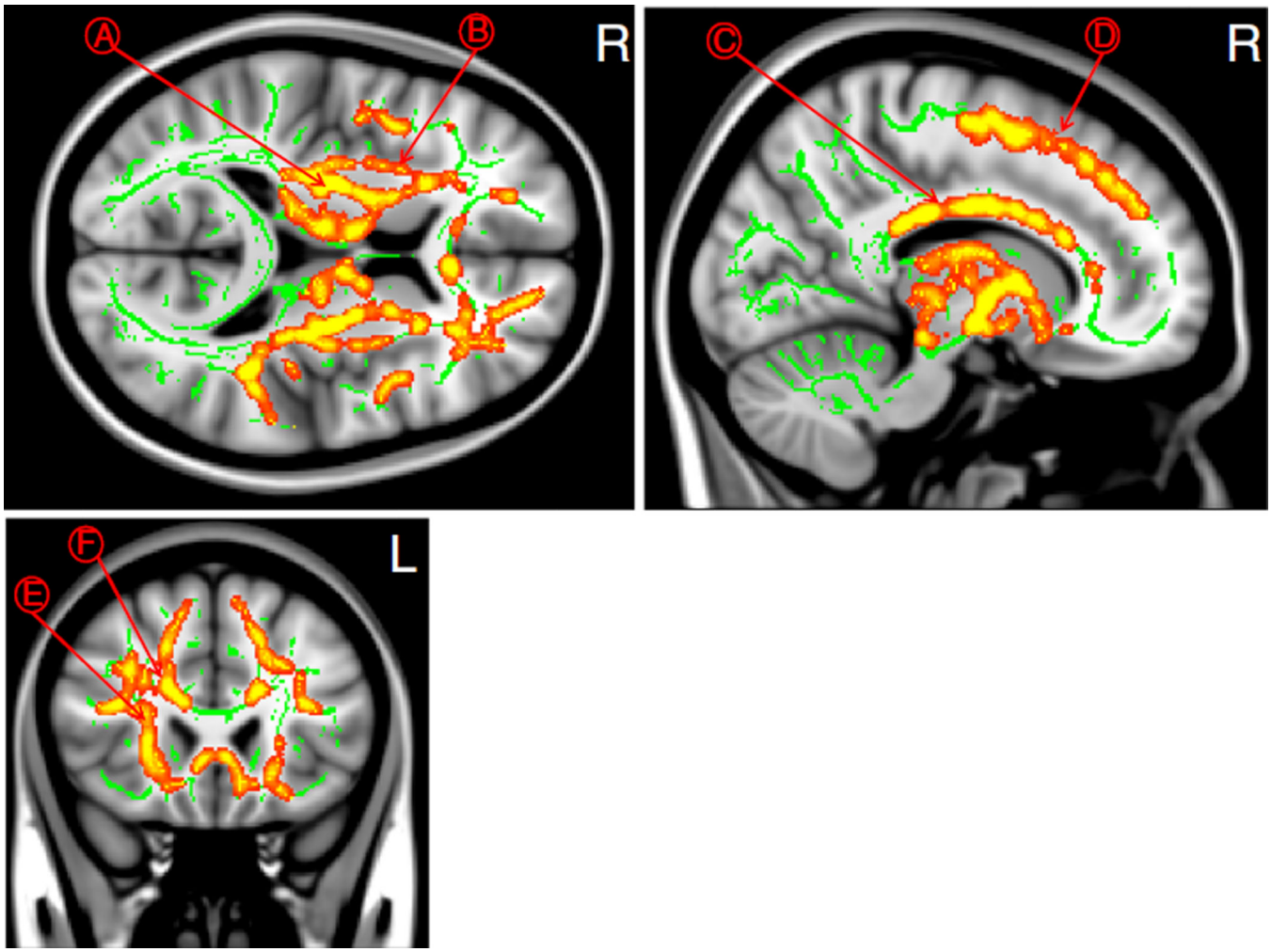

Fig. 2.

Areas of significantly decreased MD from pre- to post-HSCT in all patients compared to healthy controls (TBSS analysis, p-corrected <0.05). **a** Internal Capsule; **b** External Capsule; **c** Body of Corpus Callosum; **d** Superior Corona Radiata; **e** Anterior Corona Radiata; **f** Genu of Corpus Callosum. Red/Yellow = All areas of change are expanded for ease of visualization; Green = Mean skeletonized FA of all subjects.

Table 1

Demographic Characteristics and Treatment History

Demographics/Treatment	Patients			Healthy Controls
	All Patients *N*=22	Allogeneic *N*=10	Autologous *N*=12	*N*=10
Sex (M/F)	17/5	7/3	10/2	7/3
Handedness (R/L)	21/1	10/0	11/1	9/1
Age at Baseline (yrs)				
Mean (SD)	48.6 (13.2)	44.6 (12.7)	53.17 (12.8)	46.4 (13.2)
Median (range)	53.5 (25– 65)	42.5 (26– 65)	58 (27– 66)	47.5 (30– 65)
Mean Education (yrs)	16.3 (2.9)	15.2 (2.4)	16.8 (3.2)	17.3 (2.5)
Mean Est.VIQ	114 (5.9)	112 (6.4)	115 (5.8)	117 (2.8)
Follow-up Interval (days)				
Mean (SD)	394.1 (34.7)	383.6 (32.6)	395.0 (37.7)	372.5 (10.6)
Diagnosis				
AML	5	5	0	NA
Lymphoma	10	2	8	NA
Multiple Myeloma	5	1	4	NA
Myelodysplastic Syndrome	2	2	0	NA
Conditioning Treatment				
Bu/Mel/Flu	7	6	1	NA
BEAM	6	0	6	NA
Cytoxan/Mel/Cy	5	0	5	NA
fTBI+Thio/Flu/Cy/MTX	4	4	0	NA

Est.VIQ Estimated Verbal IQ (NAART or Barona Index). *Follow-up Interval* time betweenMRIs/cognitive assessments, *AML* Acute myeloid leukemia, *Bu/Mel/Flu* Busulfan/Melphalan/Fludarabine, *BEAM* carmustine/etoposide/cytarabine/melphalan, *fTBI* full-dose total body irradiation, *Thio/Flu/Cy/MTX* Thiotepa/Fludarabine/ Cyclophosphamide/Methotrexate

Table 2

White Matter ROIs showing a significant decrease in MD post-HSCT

White Matter Region	*P*
Commissural tracts	
Genu & body of corpus callosum	*p*=.030
Cingulum (cingulate gyrus) - Left & Right	*p*=.011
Cingulum (hippocampus) - Left	*p*=.018
Association tracts	
Fornix (crus) / Stria terminalis - Left & Right	*p*=.034
Uncinate fasciculus - Left & Right	*p*=.029
Inferior fronto-occipital fasciculus - Left & Right	*p*=.010
Projection tracts	
Anterior limb of internal capsule - Left & Right	*p*=.049
Posterior limb of internal capsule - Left & Right	*p*=.021
Retrolenticular part of internal capsule - Left & Right	*p*=.027
External capsule - Left & Right	*p*=.044
Anterior corona radiata - Right	*p*=.001
Superior corona radiata - Right	*p*=.004
Cortical spinal tract – Left	*p*=.032

Table 3

Cognitive Test Z-Scores at Baseline and One Year Follow-up (Patients and Controls)

Measures	Baseline		Follow-up	
	Controls *N*=10 Mean (SD)	Patients *N*=22 Mean (SD)	Controls *N*=10 Mean (SD)	Patients *N*=22 Mean (SD)
Attention/Executive				
DF	0.79 (0.78)	0.42 (0.85)	1.08 (0.56)	0.38 (0.96) *
DB	0.73 (0.97)	0.55 (0.72)	0.97 (1.21)	0.37 (0.91)
BTA	0.11 (0.93)	−0.18 (0.93)	0.37 (0.60)	−0.61 (1.11) **
TMTA	0.34 (1.17)	−0.15 (0.61)	1.07 (1.26)	−0.24 (0.81) *
TMTB	0.37 (1.35)	−0.02 (0.94)	0.97 (1.63)	0.05 (0.80)
Verbal Memory				
CVLT-L	1.43 (0.64)	0.40 (0.60) **	1.99 (0.91)	1.01 (0.87) *
CVLT-LD	0.80 (0.54)	0.45 (0.77)	1.30 (0.54)	0.66 (1.10) *
CVLT-DI	0.75 (0.54)	0.48 (0.81)	0.70 (0.75)	0.64 (0.93)
Visual Memory				
BLT-L	−0.29 (1.35)	−0.48 (1.12)	0.80 (1.57)	0.08 (1.11)
BLT-LD	−0.10 (1.15)	−0.48 (1.18)	0.53 (1.00)	−0.31 (1.24)
BLT-DI	−0.38 (0.30)	0.06 (1.31)	0.39 (1.08)	−0.16 (1.48)

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

* $p<0.05$,

** $p<0.01$

Table 4

Cognitive Test Z-Scores Pre- and One Year Post-HSCT (Patients per Transplant Type)

Measures	PRE-HSCT		POST-HSCT	
	Allogeneic *N*=10 Mean (SD)	Autologous *N*=12 Mean (SD)	Allogeneic *N*=10 Mean (SD)	Autologous *N*=12 Mean (SD)
Attention/Executive				
DF	0.56 (0.61)	0.31 (1.02)	0.34 (1.05)	0.42 (0.91)
DB	0.46 (0.72)	0.62 (0.75)	0.21 (0.87)	0.50 (0.96)
BTA	0.14 (0.84)	−0.45 (0.95)	−0.62 (1.24)	−0.60 (1.05)
TMTA	−0.27 (0.53)	−0.06 (0.67)	−0.69 (0.74)	0.14 (0.68)*
TMTB	−0.14 (1.05)	0.09 (0.88)	−0.37 (0.30)	0.41 (0.92)*
Verbal Memory				
CVLT-L	0.17 (0.69)	0.60 (0.46)	0.68 (0.71)	1.29 (0.93)*
CVLT-LD	0.10 (0.74)	0.75 (0.69)*	0.05 (1.07)	1.17 (0.86)*
CVLT-DI	0.35 (0.82)	0.58 (0.82)	0.30 (0.89)	0.92 (0.90)
Visual Memory				
BLT-L	−0.29 (1.40)	−0.64 (0.86)	−0.24 (1.07)	0.35 (1.13)
BLT-LD	−0.36 (1.42)	−0.58 (1.01)	−0.73 (1.25)	0.04 (1.17)
BLT-DI	−0.23 (1.48)	0.30 (1.16)	−0.65 (1.30)	0.25 (1.55)

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

*$p<0.05$

Table 5

Significant Correlations between Differences in Cognitive. Test Z-scores and MD ROIs values (post-pre) in HSCT Patients

White Matter Region	Cognitive Test	*rho*	*P*
Commissural tracts			
GCC	BLT-L	0.488	0.029
TAP-Left	Trails - B	0.495	0.026
Association tracts			
SLF-Right	Trails - A	−0.460	0.041
SFO-Right	Trails - A	−0.519	0.019
IFO-Left	CVLT-DI	−0.447	0.048
IFO-Right	DS Backward	0.465	0.039
UNC	BLT-DI	−0.446	0.049
Projection tracts			
ALIC-Right	Trails - A	−0.523	0.018
EC-Right	Trails - A	−0.523	0.018
ML-Right	CVLT-L	−0.541	0.014
	CVLT-DR	−0.584	0.007
CST-Left	DS Forward	−0.481	0.032

GCC Genu of corpus callosum, *TAP Tapetum, SLF* superior longitudinal fasciculus, *SFO* superior fronto-occipital fasciculus, *IFO* Inferior fronto-occipital fasciculus, *UNC* uncinate fasciculus, *ALIC* Anterior limb of the internal capsule, *EC* External capsule, *ML* Medial lemniscus, *CST* Cortical spinal tract, *BLT-T* Brown Location Test-Learning, *BLT-DI* Brown Location Test- Discrimination Index, *CVLT-L* California Verbal Learning Test-Learning, *CVLT-DR* California Verbal Learning Test-Delayed Recall, *CVLT-DI* California Verbal Learning Test- Discrimination Index, *DS* Digit Span