Treatment-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients.

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Introduction

Impaired cognitive functioning has been recognized as a potential adverse effect of adjuvant systemic treatment in breast cancer patients. A subset of breast cancer patients (10 to 40%) experiences mild cognitive deficits in domains mainly involving memory, attention and concentration, psychomotor speed, executive functioning and multi-tasking. The focus of our study is not patients with primary brain pathology or secondary (metastatic) processes, but patients without clear existence of primary or secondary (focal) brain lesions, undergoing systemic chemotherapy. The pathophysiology of this impaired cognitive functioning is still unclear. So far, evaluation of the effects of adjuvant therapy on cognitive functioning has predominantly been done using neuropsychological tests and self-rated subjective questionnaires. Only a limited number of studies have used brain imaging techniques to investigate potential physical changes in the brain, induced by the therapy. These studies suggest both functional and structural changes in the brain1-3. A potential mechanism by which systemic adjuvant treatment could impair cognitive functioning is direct neurotoxicity, causing toxic injury to brain parenchyma, producing demyelination and/or altered water content, resulting in alterations of the white matter (WM) integrity of the brain. The purpose of this diffusion tensor imaging (DTI) study is to evaluate changes in WM fractional anisotropy (FA) and mean diffusivity (MD) in a group of breast cancer patients compared to age-matched healthy controls and correlate FA with possible cognitive impairment using voxel-based analyses. We hypothesize that FA is lower and MD higher in patients relative to controls in important WM tracts that are related to cognitive functioning.

Methods and materials

Seventeen postchemotherapy (2-4 months), early-stage breast cancer patients (age 45.4 ±4.2), and 19 matched controls (age 45.2 ±3.9) were imaged on a 3T scanner (Intera, Phillips, Best, the Netherlands) with an 8 channel phased array head coil. A whole brain DTI SE-EPI with 45 non-collinear directions and a b-value of 800 s/mm², was acquired, together with 3D-TFE, FLAIR and T2w TSE scans. The latter 3 scans were used to search for primary brain pathology as an exclusion criterion. Three subjects with excessive WM lesions and three subjects with inferior DTI image quality were excluded for further analysis, resulting in 14 patients and 16 controls included in the study. Subjects were evaluated with a comprehensive battery of cognitive tests, covering domains of attention, concentration, memory, executive functioning and psychomotor speed. Self-reported cognitive function, anxiety and depressive symptoms were assessed using the Cognitive Failure Questionnaire (CQF), the Spielberger State-Trait Anxiety Inventory and the Beck Depression Inventory. Statistically significant differences on test scores between patients and controls were assessed with two-tailed two-sample t-tests. Tests that showed significant difference between the groups (p<0.05) were subsequently selected for the voxel-based correlation analysis, namely: attention/concentration tests (Bourdon Wiersma Dot cancellation test; Test of Every Day Attention, auditory elevator with reversal (TEA_ST5)) and psychomotor/processing speed (Nine-hole Peg (9HPT); WAIS Digit Symbol; Trail Making Test A (TMTA)).

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Results

Compared to normal controls, the patient group demonstrated significantly decreased FA in frontal (superior fronto-occipital fasciculus, superior corona radiata: cluster extent 947, pvoxel<0.001) and temporal (sagittal stratum including inferior longitudinal fasciculus, cluster extent 273, pvoxel=0.004) WM tracts and cerebellum (inferior and middle cerebellar peduncle, cluster extent 261, pvoxel=0.003) (Fig. 1 & 2). Additionally, a significant increase of MD in patients compared to controls was demonstrated in frontal (cluster extent = 1189, pvoxel<0.001) and parietal (pvoxel=0.006) subgyral WM.

Conclusion

In this study, we demonstrated changes in cerebral WM integrity in breast cancer patients (without primary brain lesions or metastasis) after systemic chemotherapy by means of DTI. WM tracts that are affected are the superior fronto-occipital fasciculus, inferior longitudinal fasciculus, corona radiata, and cerebellum. Several recent studies have linked these WM tracts to cognitive processing speed3, to executive function, attention and cognition in general. These results therefore suggest a link between impaired cognition after systemic chemotherapy and WM integrity. Furthermore, significant correlations between neuropsychological tests and WM FA values seem to corroborate our findings.

References