Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning in breast cancer patients

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Introduction

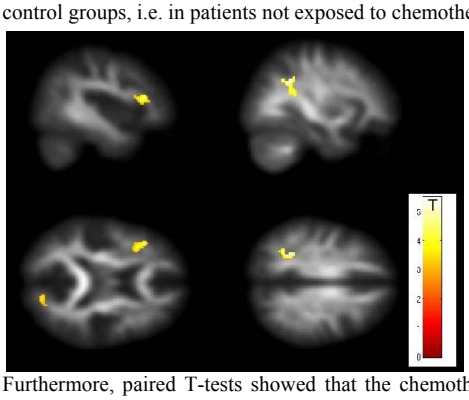
Impaired cognitive functioning has been recognized as a potential adverse effect of adjuvant systemic treatment in breast cancer patients. A subgroup of patients with breast cancer (10-40%) experiences mild cognitive deficits in domains mainly involving memory, attention and concentration, psychomotor speed, executive functioning and multi-tasking. The pathophysiology of this impaired cognitive functioning is still unclear. 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) organization of the brain. Systemic treatment with 5-FU, a frequently used chemotherapeutic agent, in mice has been shown to cause damage to myelinated WM tracts of the central nervous system[1]. 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 brain[2,3,4] In our cross-sectional pilot study, we have previously found significant differences between chemotherapy-treated patients and healthy controls in FA values of important WM tracts that are involved in cognition[5]. The purpose of the present *longitudinal* diffusion tensor imaging (DTI) study is to assess patients before and after chemotherapy and evaluate possible changes in WM fractional anisotropy (FA) in combination with detailed cognitive assessment. We hypothesize that FA would be lower after chemotherapy treatment and that such changes would be associated with cognitive impairment.

Methods and materials

Three groups of young active premenopauzal women were recruited: a group of early-stage breast cancer patients exposed to chemotherapy (n=34) (age 43.7 ±6.1y), a group of early-stage breast cancer patients not exposed to chemotherapy (n=16) (age 43.1 ±5.7y), and a group of age-matched healthy controls (n=19) (age 43.8 ±4.9y). The chemotherapy-treated patients underwent neuropsychological testing and MR imaging on a 3T scanner (Intera, Philips) before the start of the therapy (t1) and 3-4 months after treatment (t2). The two control groups underwent the same assessment at matched intervals. For each participant a whole brain DTI SE-EPI with 45 non-collinear directions and a b-value of 800 s/mm^2 was acquired. 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. DTI processing was performed using *ExploreDTI*[6] consisting of (i) motion and distortion correction with the required reorientation of the b-matrix and (ii) an iterative nonlinear tensor estimation process with outlier rejection. The individual DTI datasets were non-rigidly registered to a population-based DTI atlas generated from all subjects DTI-images as described by Van Hecke et al[7]. SPM8 voxel-based paired T-tests were used to assess differences in FA values between time points in each group. Paired T-tests were used to assess changes in neuropsychological test performance between time points within groups. Tests that showed significant performance changes between the groups (Two-sampled student's T-test, $p<0.05$) were subsequently selected for a correlation analysis with differences in FA.

Results

The voxel-based paired T-test revealed significantly decreased FA in the chemotherapy-treated patient group after treatment versus baseline in frontal (superior longitudinal fasciculus, pFWE = 0.003), parietal (superior longitudinal fasciculus, pFWE = 0.01) and occipital (forceps major, pFWE =0.01) WM tracts (Fig 1.). In both control groups, i.e. in patients not exposed to chemotherapy and in healthy controls, no significant changes in FA were found between t1 and t2.



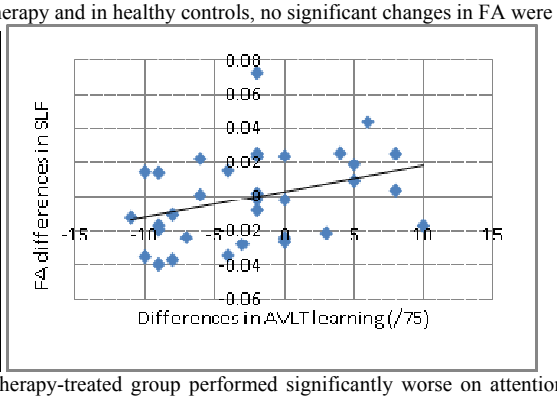


Fig 1 (left): Regions showing significant decrease in FA in chemotherapy-treated patients at t2 vs t1. (Height threshold at $p< 0.001$, cluster size > 50)

Fig 2 (right): Scatter plot of differences in AVLT learning score versus FA differences between t2 and t1 in the longitudinal superior fasciculus.

Furthermore, paired T-tests showed that the chemotherapy-treated group performed significantly worse on attention and concentration tests ($p<0.01$), psychomotor speed ($p<0.04$) and verbal memory ($p<0.03$) at t2 when compared to t1. Both control groups however, showed significant increased performance in those domains at t2 vs t1 ($p<0.01$, $p<0.04$ and $p<0.006$ respectively). Correlation analysis of differences in FA in the superior longitudinal fasciculus with differences in neuropsychological test scores in the attention and verbal memory domain revealed significant correlations ($p<0.05$). (Fig 2.)

Conclusion

In this longitudinal DTI study, we demonstrated for the first time changes in cerebral WM integrity in chemotherapy-treated breast cancer patients (without primary brain lesions or metastasis) by comparing DTI images taken before and after chemotherapy. We have shown significant differences in WM integrity parameters derived from DTI in important WM tracts involved in cognition after chemotherapy while this effect was not present in both control groups assessed at matched intervals. This suggests that there is a link between WM integrity and chemotherapy-induced impaired cognition. Furthermore, significant correlations between neuropsychological tests and WM FA values seem to corroborate our findings.

References

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