Does Chemotherapy for Breast Cancer cause MRS detectable Oxidative Stress in the Brain? A 1H-MEGA-PRESS glutathione pilot study at 3T

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Introduction

Cognitive dysfunction is a common side effect of anti-cancer chemotherapy (15-45% [1]) with a significant impact on quality of life. Deficits have been most commonly reported in the domains of attention, executive function, verbal and visual memory, and processing speed [2]. Candidate mechanisms include direct neurotoxic effects, oxidative stress and DNA damage, induced hormonal changes, immune dysregulation and/or release of cytokines, and blood clotting in small CNS vessels. At present, there are no effective treatments to prevent these cognitive symptoms following chemotherapy with current management being focused on psychoeducation. A better understanding of the underlying mechanism and noninvasive biomarkers to monitor the effects are needed to optimise neuroprotective drugs that may prevent or mitigate cognitive dysfunction. Therefore, in this pilot study we test whether cerebral glutathione (GSH), a marker of antioxidative capacity, can provide a marker of chemotherapy related oxidative stress.

Methods

10 patients diagnosed with breast cancer undergoing chemotherapy treatment were recruited into this study. MRI and MRS in the precuneus region were taken pre-treatment (within one week prior to first cycle) and post treatment (10 days following start of the first cycle). The imaging scan consisted of T1weighted imaging and single voxel MRS (MEGA-PRESS, TR=1800ms, TE=131ms, Nx=128 off, 128 On, voxel: 35x 25x20mm^3). MRS was analysed via inhouse Matlab algorithm, to phase shift and remove outliers via NAA correlation [3]. LCMODEL was used to fit the off and difference spectra. LCMODEL outputs were used to provide GSH/Cr ratios and concentration measures. Segmentation of the MRS ROI was done in an inhouse Matlab algorithm and SPM12, with relaxation correction as described in Gasparovic 2006 [4]. Spectra were removed if water linewidths >15Hz, difference spectra SNR<3 and lipid contamination or artefacts were in the off spectra. Paired student t-tests were used to assess significance between groups, $p<0.05$.

Results and Discussion

Three patients did not return for their second scan and two patients spectra failed quality control, leaving five pre and post treatment spectra in this cohort. GSH peak fit quality in the difference spectra was high (CRLB < 20%). While mean(sd) GSH concentrations differed between pre 7.76 (0.76)mM and post treatment condition 7.28 (1.21)mM, it wasn't significant ($p>0.05$, Fig 1a). Mean(sd) GSH/Cr ratio values were 0.077 (0.007) and 0.066 (0.013) revealing a trend for reduction ($0.05<p<0.10$, Fig 1b). The mean values of both measures were lower in the post treatment group, which is consistent with previous preclinical measures [5] and GSH may be an indication of redox imbalance or oxidative stress [6]. Individual patient changes for GSH concentrations (Fig 1c) and GSH/Cr (Fig 1d) in patients 1, 2 and 4 the GSH decreases, which is consistent across both measures. In this study using ratios against creatine may provide a more representative measure. Chemotherapy patients can suffer from dehydration, this may overestimate the water content in some cases, artificially increasing the concentration, e.g. patient 3 and 5. The lack of significance in the GSH measure across pre and post treatment is certainly due to sample size and should be investigated further.

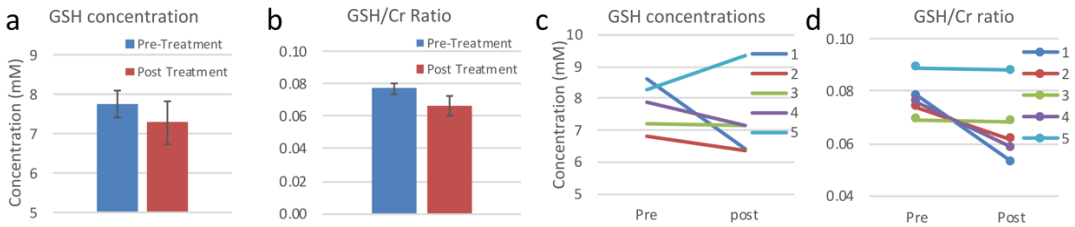

Figure 1: Mean (standard error) of GSH concentrations (a) and GSH/Cr ratios (b) of pre and post chemotherapy scans. Individual patient GSH concentrations (c) and GSH/Cr ratios (d) of pre and post chemotherapy scans.

Conclusions

In this preliminary study we observed that GSH estimates decreased with chemotherapy treatment in three out of five patients in keeping with increased oxidative stress and warrants further examination.

Acknowledgements

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References: [1] Vardy J, Tannock I. Critical Reviews in Oncology/Hematology 2007;63:183-202. [2] Falleti MG et al. Brain and Cognition 2005;59:60-70. [3] Raschke et al. AJNR 2018;39:375-379. [4] Gasparovic et al. Magn Reson Med. 2006 Jun;55(6):1219-26. [5] G. Joshi et al. / Neuroscience 166 (2010) 796–807. [6] Watson et al., FEBS Letters 543 (2003) 144-147. 2003