Feasibility study to examine underlying mechanisms for "chemo-cog"

Jenkins V[1], Harder H[1], Cercingani M[2], Whiteley-Jones H[2], Thwaites R[2],
Mullen L[2], Harrison N[2], Davies KA[2], Zammit C[3], Sacre S[2]
[1]SHORE-C, [2]Brighton & Sussex Medical School, University of Sussex, [3]Brighton University Hospitals Trust

Background: Many women treated with chemotherapy for breast cancer report memory & attention problems.[1] The mechanisms underlying "chemo-cog" are not clear but include stress and coping styles.[2] Research suggests that elevated levels of peripheral inflammatory cytokines may be involved.[3] Our feasibility study examined relationships between cognitive performance, quality of life (QoL), fatigue, blood factors and Magnetic Resonance Imaging (MRI) in two groups of women with Early Breast Cancer (EBC). One group received chemotherapy (CG) and the other did not (NCG).

Aims & Methods: 1) to investigate the association of reports of "foggy" thinking following EBC treatments with levels of inflammatory blood factors & changes on brain scans **2)** examine the feasibility of invasive testing especially in the pre surgical period. Women with EBC were assessed at 3 time points:-

- **T1** pre (breast) surgery
- **T2** post surgery
- **T3** within 2 weeks of completing chemo (or at 6mths)

Objective and subjective cognitive performance, quality of life (QoL), level of fatigue and blood factors were assessed 3 times, brain imaging at T1 &T3 only.

Cognitive tests: 7 tasks of attention, learning, memory & planning based on ICCTF[4] plus pre-morbid estimation of Full Scale Intelligence Quotient (FSIQ)
Patient reported outcomes: QoL (FACT B), fatigue (Fn subscale), cognitive failures (FACT-Cog), Traumatic Stress Questionnaire (TS-Q).
Cytokine analysis: Serum measurement of Tumour Necrosis Factor(TNF), Interleukin(IL)-6, IL-10, soluble TNF receptor II (sTNFRII), monocyte chemotactic protein-1 & vascular endothelial growth factor(VEGF).
MRI Acquisition: 1.5T scanner (32-channel head coil)

- T1-weighted high-resolution volumetric scan(VBM)
- Diffusion-tensor imaging (DTI) sequence
- Serial gradient echo-planar imaging
- fMRI data (iv) 3D gradient echo sequence
- T1& B1-mapping sequence

Cognitive, PRO & Blood Factor Results

- 14/52 (27%) women participated (8 CG; 6 NCG)
- Main reason for refusal was lack of time pre-surgery
- Table 1 participants' characteristics; NCG sig. higher FSIQ (p=0.015)*
- 5/14 women experienced traumatic stress at T1
- Two women (1 from each group) were impaired on ≥ 1 cognitive measure at or below 2.0 SDs from norms[4]
- Minimally Clinical Important Difference for FACT B is a change of ≥7 points, for Fn is ≥3 points (Table 2)

Table 2	Minimally Clinical Important Difference			
T1 toT3	**No. pts improved**		**No. pts worsened**	
	CG	**NCG**	**CG**	**NCG**
FACTB	2	2	5	1
Fn	2	1	6	2

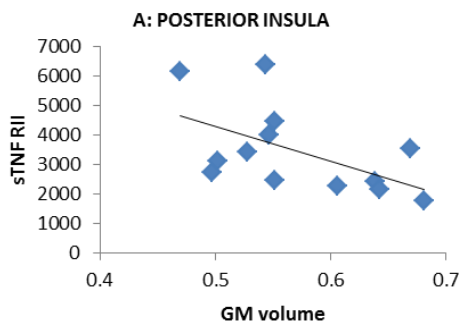
- Levels of fatigue correlated with perceived cognitive impairment on the FACT Cog (r =0.718; p=0.01)
- At T3 sig. increase in CG of sTNFRII (p=0.01) & IL-6 (p=0.03)

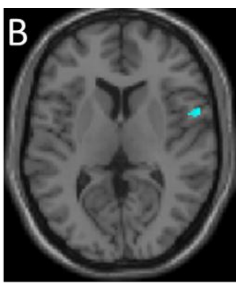
Table 1	CG n=8	NCG n=6
Age: mean (sd)	52.63 (3.82)	50.27 (2.09)
Range	50-61	47-53
Partner: yes	4	5
Education: higher/further	6	5
Employed: F/T	5	4
Mastectomy: yes	2	1
Chemo:		
AC	1	
FEC 75	2	
FEC-T + GCSF	5	
Herceptin: yes	1	
Endocrine therapy: yes	3	6
Radiotherapy: yes	7	5
Post-menopausal: yes	3	2
HRT: used previously	2	1
Pre- morbid FSIQ: mean (sd)	111.13 (7.41)	120.83 (4.44)*

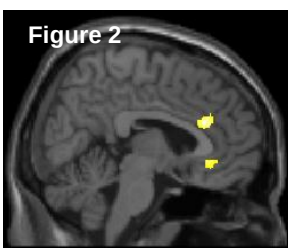
MRI Results

Figure 1 shows that across the whole group, levels of sTNFRII were inversely correlated with grey matter volume of the right posterior insula. A shows the scatterplot, while B shows the anatomical location (in light blue).

Figure 1







The VBM analysis showed a significant group-by-time interaction, with CG showing a larger reduction in volume of the subgenual and dorsal anterior cingulate and in the inferior temporal gyrus (ITG) compared to NCG (Fig. 2)

Summary

- Hypothesis that chemotherapy induced fatigue is mediated by changes in inflammatory factors is supported by our data
- Imaging data are suggestive of changes in circuits targeted by cytokines
- Proved difficult to recruit women to undergo a battery of tests and investigations in the pre operative period
- Minimal objective cognitive changes across time but women in CG reported more fatigue, and lower scores on measures of QoL

References
1. Shilling V, Jenkins VA. Eur J Oncol Nurs. 2007, 11(1) : 6-15
2. Reid-Arndt SA, Cox CR. J Clin Psychol MedSet. 2012, 19(2) :127-37
3. Janelsins M et al. Supp Care Cancer. 2012, 20 (4): 831-839
4. Wefel J et al. International Cancer and Cognition Task Force Lancet Oncol. 2011,12 (7):703-708

Acknowledgements: Breast Cancer Campaign funded the study. Grateful thanks to participants, clinical staff and L Matthews for co-ordinating the study.