A combined use of goserelin and anastrozole produces CB with long duration in significant proportion of premenopausal women with ER+ ABC when used as first-line therapy. Further studies with more patients and longer follow-up are warranted.

O-83. Inhibition of haematogenous micrometastasis using Tinzaparin small oligosaccharides of heparin

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Chemokines are small proteins important in the metastasis of breast cancer cells. Binding of the chemokine CXCL12 to its receptor CXCR4 stimulates cells to migrate out of the vasculature and establish metastases. Glycosaminoglycans (GAGs – complex sugars) on the cell surface are vital for presentation of chemokine to its receptor. We aim to prevent haematogenous spread of breast cancer cells using Tinzaparin (a GAG-like drug) and short heparin molecules – oligosaccharides.

Radioligand competition binding assays were performed using a range of the oligosaccharides to compete against GAG for binding of I^{125} CXCLI2. A dp12 (degrees of polymerization) oligosaccharide was the smallest heparin derivative to compete efficiently (71% inhibition; $p < 0.001$) at low concentrations.

Mammalian cells transfected with CXCR4 (KI-CXCR4) and MDA-MB-231, a CXCR4-expressing metastatic breast cancer cell line were used in chemotaxis assays. Chemotaxis was assessed in response to CXCL12 and heparins including Tinzaparin and dp12. An *in vivo* model evaluated the effect of dp12 and a therapeutic dose of Tinzaparin upon haematological metastasis. SCID mice were injected daily from Days 0 to 28 with s/c Tinzaparin, dp12 or control salt solution, on Day 1 mice received i.v. injection of 200,000 MDA-MB-231 cells. On day 28, mice were examined microscopically to assess tumour load.

KI-CXCR4 and MDA-MB-231 migrated significantly in response to CXCLI2. Tinzaparin and dp12 inhibited CXCL12 induced migration and activation of CXCR4 ($p < 0.001$). *In vivo*, Tinzaparin decreased the number of metastases by 23% ($p < 0.004$) and decreased tumour area by 46% ($p < 0.0001$).

Heparins inhibit migration and activation of CXCR4-expressing breast cancer cells. Peri-operatively, it is known that up to 85% of patients have cancer cells within the vasculature. Low Molecular Weight Heparins prevent haematological metastasis of breast cancer *in vivo* and may have a role in cancer therapy, over and above the benefit gained from thromboprophylaxis.

O-84. Primary Taxotere versus doxorubicin for breast cancer. Five year survival analysis

Ogston KN, Hutcheon AW, Sarkar TK, Chaturvedi S, Heys SD. *University of Aberdeen*

We have previously reported that taxotere primary chemotherapy has a survival advantage at 3 years compared to doxorubicin based chemotherapy for breast cancer. These findings were not reproduced in the NSABP B-27 trial. We report survival data over 5 years of follow up.

160 patients with large primary breast cancers (>4 cms) were treated with 4 cycles of doxorubicin based primary chemotherapy. Those who initially responded were randomised to receive either 4 further cycles of doxorubicin or 4 further cycles of taxotere. 96 patients were available for randomisation – 46 to doxorubicin and 50 to taxotere. All patients proceeded to surgery and standard adjuvant treatments. Survival data is now available for a median follow up time of 72 months.

Overall survival at 6 years is 82%. In patients randomised to taxotere survival is 86% and in those randomised to doxorubicin 78%. There is however no significant difference in survival between taxotere and doxorubicin (log rank $p = 0.24$).

These results have shown a non-significant improvement in survival between patients treated with taxotere and doxorubicin for breast cancer and compare to the NSABP B-27 results.

O-85. Definition of the evolutionary pathway to acquired Docetaxel resistance

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Background: Docetaxel is one of the most active agents used in the treatment of breast cancer. However, tumours may be inherently resistant or develop resistance to docetaxel during treatment. The mechanisms of resistance to docetaxel, whether inherent or acquired, are poorly understood. We have developed an *in vitro* model of docetaxel resistance in breast cancer cells to understand the genetic pathways of resistance. The aim of this study was to define the genetic changes that occur in breast cancer cells as they acquire resistance to docetaxel.

Methods: MDA-MB-231 and MCF-7 breast cancer cells were made resistant to docetaxel by exposure to increasing docetaxel concentrations (from 1 μM to 30 μM). By using cell lines with increasing levels of docetaxel resistance, we were able to identify changes associated with resistance to lower concentrations of docetaxel (early resistance) and those associated with resistance to high concentrations of docetaxel (late resistance). Microarray analysis, RT-PCR and western analysis were used to identify and validate candidate genes and proteins associated with resistance. In order to establish whether a candidate was involved in resistance we aimed to modulate expression by either gene transfection or siRNA modulation and then to re-assess chemosensitivity.

Results: Microarray analysis identified several changes in gene expression associated with early and late resistance including reduced expression of the p27 protein. Expression of exogenous p27 protein by gene transfection resulted in increased chemosensitivity to docetaxel.

Conclusions: We have used a global analysis technique to identify candidate genes involved in docetaxel resistance. We have demonstrated that p27 plays a role in resistance to lower levels of docetaxel (<1 μM). Identification of genes involved in resistance offers the possibility of targeted therapy for patients breast cancer.