199 Proffered paper oral

Efficacy of Cognitive Behavioral Therapy and Physical Exercise in Alleviating Treatment-induced Menopausal Symptoms in Patients with Breast Cancer − Results of a Randomized Controlled Multi-center Trial

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Background: To evaluate the effect of cognitive behavioral therapy (CBT), physical exercise (PE) and of these two program elements combined (CBT/PE) on menopausal symptoms (primary outcome), body image, sexual functioning, psychological well-being and health-related quality of life (secondary outcomes) in breast cancer patients experiencing treatment-induced menopause.

Patients and Methods: Four hundred twenty-two breast cancer patients were randomly assigned to a CBT (N = 109), a PE (N = 104), a CBT/PE (N = 106) or a waiting list control group (N = 103). Self-report questionnaires were completed at baseline, 12 weeks (T1) and 6 months (T2) post-study entry. To compare the intervention groups with the control group over time, multilevel procedures were used to model the series of repeated measurements.

Results: Compared to the control group, intervention groups (intention-to-treat) showed overall decrease in levels of menopausal symptoms (FACT-ES; $p < 0.001$), hot flushes (Hfrs; $p < 0.001$), urinary symptoms (Bfluts; $p = 0.002$), and an increase in sexuality (habit; $p = 0.027$) and physical functioning (SF36 PF; $p = 0.002$). Positive effects of the interventions were found at both short- and long-term follow-up.

Conclusions: This multicenter trial demonstrates that cognitive behavioral therapy and physical exercise can have salutary effects on endocrine symptoms, and to a lesser degree on sexuality and HRQoL-related functioning, among breast cancer patients experiencing treatment-induced menopause. Future work is needed to improve the design and the planning of these interventions with an eye toward improving program adherence.

200 Proffered paper oral

TACT2 Trial in Early Breast Cancer (EBC): Differential Rates of Amenorrhoea in Premenopausal Women Following Adjuvant Epirubicin (E) or Accelerated Epirubicin (aE) Followed by Capecitabine (X) or CMF (CRUK/05/019)

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Background: TACT2, a multicentre randomised phase III trial with E-CMF as control (Poole NEJM 2006), tests 2 hypotheses in a 2x2 factorial design: A) accelerated chemotherapy (CT) improves outcomes: (B) capecitabine (X) gives similar efficacy but preferential side-effect profile to CMF. Here we focus on impact of treatment on menstruation in premenopausal women (⩽50 years old).

Materials and Methods: Between Dec 2005−08, 4391 pts (4371 women, 20 men) with node +ve or high risk node -ve invasive EBC were randomised to receive either E (100 mg/m^2 x 4) q3wk or aE (100 mg/m^2 x 4 plus pegfilgrastim, 6 mg d2) q2wk followed by classical CMF q4wk x 4 or X (2500 mg/m^2/day x 14) q3wk x 4. Impact on menstruation was assessed 18 months post-randomisation for premenopausal women ⩽50 years old (n = 1622). Use of elective ovarian ablation was taken as evidence of continuing menses, and data analysed by multiple logistic regression.

Results: Data describing menstruation at 18 months were received for 1333 premenopausal pts (Table).

In adjusted analyses, independent predictors of the continuation of periods included treatment with X over CMF and lower age (continuous) (both $p < 0.001$). Epirubicin schedule and ER status were not significant. A significant interaction was seen between age and X ($p < 0.001$), with a protective effect of X on continuation of menses greatest in older pts. aE rather than E resulted in fewer patients menstruating at the end of chemotherapy but this effect was lost by 18 months.

Menstruation at 18 months, by age	E-CMF (N = 348)		aE-CMF (N = 305)		E-X (N = 346)		aE-X (N = 334)	
	n	%	n	%	n	%	n	%
Continuing	82	*24*	76	*25*	202	*58*	196	*59*
⩽35	19	*63*	22	*67*	13	*62*	20	*80*
36−40	33	*47*	26	*39*	53	*72*	45	*68*
41−45	23	*19*	23	*21*	92	*62*	80	*63*
46−50	7	*6*	5	*5*	44	*43*	51	*44*
Stopped	**241**	***69***	**204**	***67***	**98**	***28***	**96**	***29***
⩽35	5	*17*	5	*15*	2	*10*	1	*4*
36−40	28	*40*	29	*44*	12	*16*	9	*14*
41−45	91	*75*	82	*75*	32	*22*	32	*25*
46−50	117	*92*	88	*92*	52	*50*	54	*47*
Stopped & had ovarian ablation	**25**	***7***	**25**	***8***	**46**	***13***	**42**	***13***
⩽35	6	*20*	6	*18*	6	*29*	4	*16*
36−40	9	*13*	11	*17*	9	*12*	12	*18*
41−45	7	*6*	5	*5*	24	*16*	16	*13*
46−50	3	*2*	3	*3*	7	*7*	10	*9*

Conclusions: E followed by X has much lower risk of rate of permanent loss of menstrual function in pre-menopausal EBC women than CMF after E, particularly for those >40 years old. Whilst comparable efficacy data on these regimens are awaited, these data could be important when interpreting future analyses in TACT2.

Thursday, 22 March 2012 13:30–15:00

KEYNOTE SYMPOSIUM

The Biology of Metastasis in Breast Cancer

201 Invited

Mouse Models of Metastatic Breast Cancer

J. Jonkers[1]. [1]*The Netherlands Cancer Institute, Amsterdam, The Netherlands*

Metastatic disease is the major cause of death in cancer patients. Metastasis is the result of a complex set of molecular events whose outcome is eventually disseminated disease. Moreover, metastasis development is influenced by a number of host factors, including stromal cells as well as innate and adaptive immune cells. This complexity has made it difficult to identify the molecular mechanisms driving the metastatic process and has confounded our understanding of how and when therapeutic intervention can be effectively used. Delineation of the mechanisms and tumor-host interactions underlying metastasis formation requires realistic animal models for de novo spontaneous tumor development and metastasis.

To establish GEM models of metastatic breast cancer, we have used the Cre/loxP system for time- and tissue-restricted switching of multiple tumor suppressor genes within cells in vivo. This technology enables the induction of defined tumors within a narrow time window, and the correlation of specific genetic lesions with phenotypic characteristics of the tumor. Using this approach, we have established several mouse models for for E-cadherin mutated lobular breast cancer. These mice develop mammary tumors that closely resemble the lobular morphology and the metastatic spectrum of the cognate tumors in humans. These mouse mammary tumor models can be effectively used to study therapy response and acquired drug resistance of primary tumors and their metastases in a physiologically relevant setting.

202 Invited

Imaging and targeting the drivers of invasion and metastasis

M. Frame[1], A. Serrels[1], B. Serrels[1], M. Canel[1], E. Sandilands[1], H. Patel[1], V. Brunton[1]. [1]*Edinburgh Cancer Research Centre, Edinburgh, United Kingdom*

One of the hallmarks of cancer cells is their ability to invade into adjacent tissue and spread to distant sites within the body. We have been studying invasion, metastasis and ingression of host vasculature into tumours, leading to findings that will take forward development of small molecule

inhibitors for clinical use. Our basic work focuses on the role of the non-receptor tyrosine kinases Src and its substrate focal adhesion kinase (FAK). Src is the prototypical oncoprotein with an important role in controlling the actin cytoskeleton, as well as the cell interaction networks regulating cadherin-mediated cell-cell contacts and integrin-dependent cell-matrix adhesions. Indeed the Src/FAK pathway is at the heart of adhesion crosstalk that is perturbed in cancer during the epithelial to mesenchymal transition (EMT). Elevated pathway throughput commonly promotes cancer invasion and metastasis by perturbing cancer cell adhesions and polarity. Hence, we are now combining new technologies of dynamic intra-vital imaging and cell tracking to address whether interventions that target adhesion/actin regulators have anti-invasive, anti-metastatic and/or anti-angiogenic activities, and/or affect tumor/host interactions. We strive to determine how best these can be monitored in cancer models in vivo and used for clinical tests. We seek a more complete understanding of a) the molecular mechanisms by which cell interaction networks promote the malignant phenotype, b) how the biological properties they perturb can be imaged in the pre-clinical setting, and c) how best these can be targeted therapeutically.

203 Invited

A Clinician's Perspective on Metastatic Breast Cancer: Many Diseases − We Need to Understand the Biology

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Breast cancer represents the paradigm of clinically important inter-tumor heterogeneity. The observation by Beatson more than 100 years ago that only two of three women on whom he performed ovariectomy experienced benefit was later followed by Jensen, McGuire and others that estrogen receptor (ER) is not universally expressed in all breast cancers, and that ER negative cancers do not respond to endocrine therapy. Likewise, in the 1980s, King and colleagues reported heterogenous expression of HER2 in breast cancers, and Slamon and others demonstrated differences in prognosis related to HER2 expression, and of course the predictive role of HER2 for endocrine, chemo, and more importantly anti-HER2 therapies. More recently, genomic expression profiling has identified at least 5 major biological categories of breast cancers, which are not surprisingly strongly influenced by ER and HER2. These have been designated Luminal A & B, HER2-like, basal, and claudin-low. A 6th category, initially described as 'normal-like' may be a technical artifact. These terms have become useful 'shorthand' for relatively crude categorization of groups of patients, but as of yet have no obvious role beyond knowledge of ER and HER2 for caring for individual patients. However, they have been helpful in driving translational and clinical research by raising the following, and many more, questions:

- Why do serial endocrine therapies work and what are the mechanisms for resistance to individual endocrine strategies and for ultimate resistance to all?
- Are there additional molecular pathways in each category that can serve as targets for novel therapies?
- Are these categories fixed or are they plastic, with both genetic evolution and ongoing fluidic changes in response to therapeutic pressures?
- What is the role of intra-tumor heterogeneity in driving both the biology and therapeutic response?
- Is the cancer stem cell theory correct, and if so how do we target these cells as well as the symptom-causing bulk cells?
- Answers to all of these questions will be essential to improving care for patients in both the metastatic and adjuvant settings.

Thursday, 22 March 2012 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

When to Add Chemotherapy to Endocrine Therapy and Endocrine Sensitivity

204 Invited

How Much Genetic Sequencing can Help?

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The implementation of molecular technologies in cancer research has helped in elucidating the complexity and heterogeneity of breast cancer. On the basis of their expression profiles, breast cancers have been classified in several subtypes with different biology, response to treatment and clinical behaviors. Moreover, gene expression signatures have been developed with the main aim to support clinicians in their treatment decision making. Among estrogen receptor positive (ER+) breast cancers, these signatures could help in identifying either patients al lower risk that might be spared the side effects of chemotherapy and be treated with the sole hormone therapy or, at the contrary, patients at higher risk that can benefit from a combined treatment. While the prospective validation of these signatures is ongoing, new evidences have shown that breast cancers subtypes carry specific genetic aberrations (i.e. chromosomal copy number variation and/or chromosomal translocations), and that disruption of cancer associated pathways (e.g. PI3K/AKT/mTOR and RAS/MEK/ERK) could influence the response to treatment. This underlines the importance of exploring the breast cancer genome and suggests that combining the analysis at both the transcriptome and genome level could provide a more complete and clinically useful tumor characterization. The use of next generation sequencing technologies allow to obtain genomic information at many levels, including point mutations, insertions/deletions, copy number variation and translocation. Being both the cost of the technology and the amount of the needed biological material progressively diminishing, its future implementation in the clinical setting could be envisaged. This could help in refining breast cancer classification and in identifying genomic aberrations with prognostic and predictive value to be implemented in clinical practice as a guide for patients' management.

205 Invited

Added Value Tools

Abstract not received.

206 Invited

What I Need to Know in the Clinic

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Based on the results of the Oxford overviews published in 2005 and 2012, all subgroups of hormone receptor-positive (HR+ve) breast cancers seem to benefit in average from the addition of adjuvant chemotherapy irrespective of age or nodal status. We believe that despite this observation clinicians should not underestimate the heterogeneity of this population and its therapeutic impact.

First, we should remember that the prognosis of patients with HR+ve tumours treated with hormonal therapy without chemotherapy is often excellent including in recently published trials [1].

Second, clinicians should be aware that even in trials with a statistically demonstrated survival benefit due to the addition of chemotherapy, subpopulations that do not benefit have been identified [2−4]. These retrospective analyses from prospective trials used either simple single markers (for example estrogen level with STEPP analysis) [2, 3] or more sophisticated signatures [5]. We will discuss these trials and their consequences in daily practice.

Lastly, we will present recently completed or ongoing studies using innovative designs (including preoperative studies) both in node negative and positive tumours which may allow to better identify subpopulations of HR+ve tumours who are extremely sensitive to endocrine therapy (and don't need additional chemotherapy) and/or don't benefit from chemotherapy.

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