be pro-active in price adjustment and regulations so that new therapies introduced are economically viable for health systems.

As breast cancer treatments become more complex, more targeted and more tailored to each woman's particular needs, patient advocates need to be vigilant in seeing that new, potentially effective treatments are studied and made available to patients. We cannot walk away from health economics but effectiveness must remain the criterion for introducing new treatments. Breast cancer advocates need to keep a close watch on the economic decision making process utilised in each country setting.

6 Invited

The doctor's view

E. Winer[1]. [1]*Dana Farber Cancer Center, Harvard Medical School, Boston, USA*

The cost of cancer treatment continues to escalate and is a major problem around the world. In less developed countries, the cost of new treatments, such as monoclonal antibodies and targeted small molecules, is simply prohibitive. In other countries, these new treatments have been embraced but have placed a major strain on health care budgets and have led to unprecedented increases in medical expenditures for breast cancer. What is the role of the physician in this ever more complex and frequently frustrating economic environment? At a minimum, the physician plays three distinct and very important parts. First, on an individual level, the physician must be his own patient's advocate, attempting, whenever possible, to provide the best available evidence-based care. When one is sitting in the examining room with a patient, societal costs should not affect the treatment recommendation. Second, and on a broader scale, the physician must actively participate in a societal process that determines whether a particular treatment should be available to patients. The decision may well differ across countries and will be highly dependent on both resources and competing demands, but in all cases, physicians must play a pivotal role. Third, the physician must be a spokesperson for the development of cost-effective strategies to care for individuals with breast cancer. Breast cancer clinicians, working with scientists, advocates, and others, need to speak against costly and ineffective strategies, as well as excess profits. If, as doctors, we walk away from economics, we walk away from a set of responsibilities and increase the likelihood that both our patients and we will become the victims of the economic realities that lie ahead.

Wednesday, 16 April 2008 16:00–17:30

CLINICAL SCIENCE SYMPOSIUM

Towards a rational endocrine therapy treatment

7 Invited

Biomarkers to guide rational endocrine therapy of breast cancer

M. Dowsett[1]. [1]*Royal Marsden Hospital – NHS Trust, Academic Department of Biochemistry, London, United Kingdom*

Approximately 75−80% of breast cancer patients have oestrogen receptor positive (ER+) disease and all such patients should receive some form of endocrine therapy. Tamoxifen may be used in both pre and postmenopausal patients while GnRH agonists and aromatase inhibitors are confined to pre and postmenopausal women, respectively. Overall aromatase inhibitors show greater efficacy than tamoxifen but the difference is not so substantial to exclude the possibility that some patients derive equal benefit from tamoxifen. Despite major efforts being directed at identifying such patients at present there are no markers are usable with confidence. HER2 positive disease shows impeded response to tamoxifen in the neoadjuvant setting and aromatase inhibitors do not show this effect but in the adjuvant setting no distinction has been shown. The presurgical setting provides the opportunity to determine the biological response of individual patients to endocrine therapy based on molecular markers and to consider additional treatments to be considered in relation to this response.

8 Invited

Endocrine treatment of premenopausal breast cancer patients

M. Gnant[1]. [1]*Medical University Vienna, Department of Surgery, Vienna, Austria*

Premenopausal breast cancer patients face a particular challenge for the interdisciplinary team: The prognosis of breas young breast cancer patients is often considered worse due to the increased agressiveness of the tumor. In fact, young age is an independent risk factor in most epidemiologic studies. Also, the special social situation of young patients need to be taken into account for treatment planning. Younger patients have also different tolerabilities for treatment side effects. Chemotherapy is considered the mainstay of the advuvant treatment, even for endocrine responsive disease. This may not me necessarily true. Several trials have shown that adjuvant endocrine intervention alone can yield comparable or even improved results for premenopausal patients with endocrine responsive breast cancer. Tamoxifen is effective in premenopausal breast cancer patients, and several combinations of aromatase inhibitorswith ovarian function suppression (OFS) using GnRH analogues are tested in clinical trials.

9 Invited

Are there any difference between third-generation aromatase inhibitors?

P.E. Lønning[1]. [1]*Section of Oncology Institute of Medicine, University of Bergen, Bergen, Norway*

Third-generation aromatase inhibitors (anastrozole, letrozole and exemestane) have been successfully implemented for treatment of early breast cancer. These drugs all inhibit in vivo aromatization effectively (>98%). Based on head-to-head comparison, letrozole (2.5 mg daily) was found superior to anastrozole (1 mg daily) inhibiting in vivo aromatization. While each compound has been revealed to improve relapse-free survival in early breast cancer, we are awaiting the results of head-to-head comparisons between individual compounds regarding clinical efficacy. Steroidal (exemestane) and non-steroidal (anastrozole and letrozole) compounds differ with respect to several important aspects.

First, steroidal compounds like exemestane binds to the substrate pocket of the aromatase enzyme while the non-steroidal compounds (anastrozole and letrozole) bind to the heme part. Second, steroidal compounds bind irreversibly, destroying the aromatase protein. Third, and probably of most importance to the clinic, steroidal compounds express light androgen agonistic activity, revealed by a significant suppression of sex hormone binding globulin, an androgen parameter in vivo. Notably, most breast cancers which express the estrogen receptor will express the androgen receptor in concert, and androgens may cause anti-tumour effects in experimental system as well as in clinical breast cancer. Clinically, several studies now confirm lack of cross-resistance between steroidal and non-steroidal compounds, in as much as patients progressing on non-steroidal compounds including anastrozole and letrozole may subsequently benefit from treatment with exemestane. In addition, a large randomized study recently confirmed for metastatic breast cancer exemestane to be as effective as faslodex among patients failing anastrozole therapy. While anecdotic evidence suggest patients becoming resistant to steroidal compounds may subsequently respond to a non-steroidal third-generation inhibitor, more data are needed to address this issue.

10 Proffered Paper Oral

A randomised study of the impact of endocrine therapy for breast cancer on bone turnover and quality of life

F.M. McCaig[1], L. Renshaw[1], R. Hannon[2], L. Williams[3], L. Fallowfied[4], O. Young[1], J. Murray[1], E.J. Macaskill[1], M. McHugh[1], J.M. Dixon[1]. [1]*Western General Hospital, Edinburgh Breast Unit, Edinburgh, United Kingdom;* [2]*Metabolic Bone Centre, Northern General Hospital, Unit of Bone Metabolism, Sheffield, United Kingdom;* [3]*Edinburgh University Medical School, Medical Statistics Unit, Edinburgh, United Kingdom;* [4]*Brighton and Sussex Medical School, Cancer Research UK Psychosocial Oncology Group, Falmer, Sussex, United Kingdom*

Background: Letrozole (L) decreases circulating oestrogen levels to a greater degree than anastrozole (A). The aim of this study was to compare the effects of L and A on musculoskeletal symptoms and bone turnover.

Patients and Methods: 182 postmenopausal women with invasive oestrogen receptor (ER) positive breast cancer were randomised as part of their adjuvant hormone therapy to receive: "12 weeks of L followed by 12 weeks of A or" 12 weeks of A followed by 12 weeks of L as initial upfront adjuvant or delayed adjuvant therapy after 5 years of tamoxifen (T). 84 had fasting blood and urine samples for the markers N-terminal telopeptides (NTx), C-terminal telopeptides (CTx), bone alkaline phosphatase (ALP) and parathyroid hormone (PTH). 170 patients had sufficient data on musculoskeletal side effects collected by a nurse after 4, 8 and 12 weeks of each drug for analysis.

Results: Tamoxifen Effect: Baseline PINP 37.5 (32.1−42.9) vs. 46.2 (41.0−51.3 and serum CTx 0.49 (0.42−0.57) vs. 0.62 (0.55−0.70), both $p < 0.025$ were lower in the prior T group. Letrozole vs. Anastrozole: L and A had similar effects on markers at all time point (all $p > 0.10$). 131 had

joint pain – no difference in frequency between L and A. Joint stiffness reported by 10 patients was more common with A than L ($p = 0.014$). 56% reporting joint symptoms on L did not have the same problems on A and 55% with problems on A did not report joint symptoms on L. Change over time: By 3 months all bone markers had significantly increased from baseline. Further increases were seen at 6 months in PINP, serum CTx, bone ALP (all $p < 0.00001$) and urinary NTx ($p = 0.04$) but not in PTH. Patients with prior T had significantly greater increases than no prior T group at both 3 and 6 months (all $p < 0.002$). The fall in PTH was less in the prior T group ($p = 0.0004$). Joint problems increased over time irrespective of drug sequence ($p = 0.0009$). Joint symptoms comparing Letrozole and Anastrozole vs Tamoxifen 57% with joint symptoms on T did not have these on A. Conversely 74% with joint symptoms on L and (85%) with joint symptoms of A did not have these on T.

Conclusions: A and L cause similar significant increase in bone turnover which increases at least to 6 months. Prior T has a major effect on how AIs affect bone. Over half of patients with joint symptoms on L or A do not have the same problems on the other drug. Three quarters with joint symptoms on A or L did not have these problems on T.

12 Proffered Paper Oral

Aktivation of the Akt and MAPK pathways in relation to survival for patients with estrogen receptor positive breast cancer subjected to adjuvant tamoxifen

B. Linderholm[1], P. Karlsson[2], M. Sundqvist[3], L.G. Arnesson[4], B. Nordenskjöld[2], O. Stål[2]. [1]*Karolinska Biomic Center (KBC), Karolinska University Hospital, Stockholm, Sweden;* [2]*Department of Oncology, Linköping University Hospital, Linköping, Sweden;* [3]*Department of Surgery, Kalmar Hospital, Kalmar, Sweden;* [4]*Department of Surgery, Linköping University Hospital, Linköping, Sweden*

Background: Resistance to endocrine therapy is a clinical problem also in some patients with an endocrine sensitive breast cancer (BC), expressing significant levels of ER and/or PgR. Cross-talk between the ER and receptor tyrosine kinases (RTK) as the EGFR family and downstream intracellular kinases such as Akt, extra cellular signal related kinase (ERK), c-Jun-terminal kinase (JNK) and p38 has been suggested as one reason for resistance.

The aims of the study was to investigate the expression of phosphorylated MAPK's (pJNK, pERK, pp38) and pAkt in primary BC and to relate expression to survival after adjuvant tamoxifen (tam).

Patients and Methods: A total of 449 patients with operable ER pos. breast cancer, stage I-III diagnosed 1991−96 and treated with tam for 2 or 5 years were included. The median age was 63 years (range 30 to 96). The median follow up time is 9.8 years. Quantification was done by use of a flow cytometry based analyser unit with fluorescent dyed microspheres bound to antibodies.

Results: All four kinases showed a significant reciprocal correlation where pERK/pp38 showed the strongest correlation ($r = 0.6$) ($p < 0.05$). All kinases but pp38 were related to better clinical factors; pAkt with few lymph node metastasis ($p = 0.036$), pERK with smaller tumour size ($p = 0.022$), pJNK with smaller tumour size ($p < 0.01$) and lymph node metastasis ($p = 0.001$). All three were significantly correlated with low S-phase fraction (SPF). Low levels of pAkt was significantly correlated with lover recurrence-free survival (RFS) ($p = 0.007$), a similar tendency not reaching statistical significance was seen for pJNK and pERK. Contrary pat with extreme high levels of at least one kinase (20% of patients) did not benefit from 5 years tam (HR = 1.06; 95% CI = 0.4−2.5, $p = 0.9$) compared to those without extreme levels of any kinase (HR = 0.58; 95% CI = 0.4−0.9, $p = 0.01$).

Discussion: Intracellular signalling of phosphorylated kinases may function differently i.e. to both promote cell survival and apoptosis due to different pathways, iso-forms and co-activators. Both JNK and p38 is reported necessary for tam induced apoptosis (Pearson et. al. 2001, Kyriakis et. al. 2001), while higher levels of p38 has been reported as correlated to less efficacy of neo-adjuvant endocrine therapy (Gutierrez et al. 2005). This rise the hypothesis that modest activated kinases may be a marker of a functional ER thus responding to tam treatment.

Conclusions: Activated kinases are correlated to each other, and all but pp38 to less aggressive BC (smaller tumours, fewer lymph-node metastasis and low SPF). Only lower levels of pAkt were significantly correlated to shorter RFS.

Wednesday, 16 April 2008 16:00–17:25

CLINICAL SCIENCE SYMPOSIUM

Breast cancer surgery: Quo Vadis?

13 Invited

The key role of the surgeon in translational research

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The surgeon is in an ideal position to co-ordinate translational research in breast cancer. The first doctor to see the patient is the surgeon and in patients with a mass the surgeon performs a core biopsy to establish diagnosis. This provides an opportunity to obtain fresh tissue which can then be stored for subsequent research purposes. Most patients with breast cancer come to surgery. The period of time between diagnosis and surgery provides an opportunity to give patients a variety of agents and investigate the effects of these agents on the breast cancer. These pre-operative or window studies have already provided valuable information on the effects of aromatase inhibitors and novel biological agents. It is the ideal setting to investigate new drugs and specifically to establish the biological effects of the drugs and the appropriate dose. Furthermore the surgeon is in a good position to obtain further fresh tissue after drug treatment at surgery. Using micro array techniques to investigate the effects of drugs on cancers, it is possible to identify in much greater detail than was previously possible, the exact mechanisms of the action of a particular drug and the various targets it hits. Current data suggest that analysis of the tumour following a challenge with drugs, gives more useful information than an analysis of the primary tumour prior to any treatment.

The other active area of translational research which involves surgeons is neoadjuvant therapy. Work in our own Edinburgh Breast Unit demonstrated that aromatase inhibitors appeared to be of greater potential than tamoxifen and this was subsequently confirmed in a randomised clinical trial. By collecting tissue at diagnosis, during and after treatment, it has also been possible to identify patterns and early changes within tumours which predict for subsequent response. By conducting such studies, it should be possible to better delineate those patients who benefit from endocrine, chemotherapeutic, and biological agents. By investigation of those who are either primarily resistant or subsequently develop resistance to the different treatments, it should also be possible to investigate pathways to circumvent this resistance.

Obtaining high quality tissue specifically collected for research is pivotal to improving our understanding and obtaining better treatments for our patients. The surgeon is in an ideal position to collect such tissue and more surgeons should be involved in translational research.

14 Invited

Oncoplastic surgery: extending breast conservation possibilities

K.B. Clough[1], C. Nos[1], A. Fitoussi[1], I. Sarfati[1]. [1]*The Paris Breast Center, Parice, France*

The number of breast cancer patients treated with breast conservation is expanding. However, when proposing breast conserving therapy, one should be sure to leave a normal appearing breast, as secondary reconstruction of breast deformities is difficult: it requires further operations and often leads to disappointing results. The objectives for conservative breast cancer surgery are thus to develop surgical techniques that allow wide resections with free histologic margins, but do not distort the breast. However, in patients with large, ill-defined or poorly situated tumours, cosmetic results after conservative surgery can be poor and clear resection margins difficult to obtain. Oncoplastic surgery is a novel surgical approach, which integrates plastic surgery techniques at the time of the initial lumpectomy. Initially this approach was developed to allow wide breast excisions and prevent breast deformities. Oncoplastic surgery has furthermore allowed us to extend the indications of breast conserving surgery to tumours that would otherwise be treated by mastectomy.

Methods: All Oncoplastic techniques are based upon plastic surgery techniques that are used to immediately reshape the breast at the time of the initial conservative surgery. They can be unilateral or bilateral, as a contralateral symmetrization is often necessary to obtain breast symmetry. When indicated, this symmetrization is performed during the same initial operation as the lumpectomy. Over the years, we have developed a wide range of techniques, to be able to answer most clinical situations, depending on the breast volume and the tumour location. We present a prospective study of 300 patients who were operated on for breast carcinoma between July 1985 and December 2002. All patients had a wide tumor excision, with a remodelling mammoplasty and immediate