Friday, 26 March 2010 08:30–09:15

EUROPA DONNA TEACHING LECTURE

Breast unit implementation − A national response

422 Invited

Breast unit implementation − A national response

N. O'Higgins[1]. [1]*Medical University of Bahrain, Bahrain*

Many breast cancers, formerly fatal, are now curable because of (i) quality of diagnosis, combining increasing accuracy with minimizing error, (ii) advances in therapy, (iii) improved clinical audit and accountability and comparing outcomes with the international norms, (iv) better training of cancer specialists, (v) collaborative effort in research and (vi) appreciation that when specialists, working together as a team, care for a large number of patients, expertise is maintained, skills are enhanced and innovation and research are developed.

The only realistic way to deliver this type of care is in a small number of specialized breast cancer centres. Patients treated in these settings have better survival and quality of life compared with those treated elsewhere. The public is quick to appreciate the value of multidisciplinary and multiprofessional care. When such care is absent, the potential for errors in diagnosis and treatment increases. Mismanagement is nowadays frequently brought to public attention. Publication in the media of suboptimal care provides a further powerful stimulus for improvement.

Medical evidence, public pressure and support by health authorities and the body politic place the need for breast centres on the political agenda. To set them up properly with highly-trained staff, top-quality equipment and a system of audit often requires a more sustained campaign. Governments are always assailed by a myriad of demands, each clamouring for priority. Medical personnel, although always supporting the need, find it difficult to be in tune with an arrangement that may result in removal of services from the hospitals in which they operate. Politicians often see withdrawal of cancer facilities from their local hospital as a threat to the community. Local communities often perceive that centralization or regionalisation of breast cancer care will reduce the quality of personal, individual attention and cause inconvenience and economic loss because of the loss of time and the expense of travelling to the specialist centre.

The implementation of a national programme for breast cancer care requires collaboration of many groupings in a society:-medical profession, nursing profession, training bodies, universities, politicians, health authorities, hospital managers, advocacy groups, cancer societies, patients, the general public and the audio-visual and print media.

Representatives of each of these groups must operate with evidence, effort, education, explanation and enthusiasm. In addition, they must be patient, persuasive and persistent. When these combinations are in place, a high-quality national breast cancer service, both for screening and symptomatic women, can be established.

Friday, 26 March 2010 11:00–12:30

KEYNOTE SYMPOSIUM

Understanding progression of breast cancer and its clinical implications

423 Invited

Models to study breast cancer invasion and metastases: lessons from normal

M. Bissell[1]. [1]*Lawrence Berkeley National Laboratory, Division of Life Sciences, Berkeley, USA*

Our work in the last three decades has underscored the plasticity of both the differentiated state and tumors. I will discuss how we use the normal mammary gland to understand breast cancer. I will describe a number of recent and unpublished works shedding light on the importance of the microenvironment, context and the tissue architecture on gene expression and tissue behavior.

These will include description of a novel forward genetic screen which takes advantage of the 3-dimensional assays of malignant and 'reverted' human breast cells we have developed over the years. The screen has allowed identification of a number of previously undescribed genes that could provide new targets in the EGFR and PI3K pathways. Upon screening for resistance to reverting agents acting on the EGFR pathway, we identified FAM83A, a previously uncharacterized protein, as conferring resistance to EGFR-inhibitors that could otherwise revert the malignant cells in 3D matrices. I will describe in vivo and culture studies that provide evidence that this novel family of previously uncharacterized proteins plays an important role in the EGFR/PI3K pathways, that it can cause malignant transformation, and that it can possibly explain some forms of resistance to EGFR therapies.

Other studies will highlight the importance of nuclear actin in growth regulation of epithelial cells by both growth factors and by extracellular matrix components. I will also describe an unexpected role for 14-3-3 sigma in malignant progressions. Finally, I will highlight how glucose transport and metabolism themselves constitute an axis of transformation with the ability to not only transform but also to modulate the classical oncogenic pathways such as EGFR, MAPK, PI3K and others.

425 Invited

Stem cells and cancer: treatment resistance, markers and novel therapeutic targets

R. Clarke[1]. [1]*Breast Biology Group, Paterson Institute for Cancer Research, University of Manchester, Manchester, UK*

There is emerging evidence that cancer stem cells (CSCs) are resistant to current therapies suggesting that CSC-specific treatments are needed. Due to their relative insensitivity to treatment, we and others have demonstrated that CSCs are enriched by radio, chemo and endocrine therapy. Increases in the proportion of CSCs after therapy is measured using cell surface markers and mammosphere colony assays of stem cell activity. DNA repair, survival and stem cell signalling pathways are strong emerging candidates for the underlying mechanisms of resistance. However, CSCs still respond to therapy-induced changes in microenvironmental signals. One candidate pathway known to regulate normal stem cells is Notch receptor signalling. We have evidence that activated Notch plays a key role in breast tumour initiation by CSCs and that therapies targeting Notch receptor are likely to be effective in preventing treatment resistance.

426 Invited

Resistance to anti-angiogenic therapy induced by hypoxia and notch signalling

A. Harris[1]. [1]*University of Oxford, Weatherall Institute of Molecular Medicine, Oxford, UK*

Hypoxia is a major driver to tumour angiogenesis, inducing vascular endothelial growth factor, VEGF, and many other growth factors. Bevacizumab has shown activity in early and late recurrent breast cancer, enhancing the effectiveness of chemotherapy in delaying disease progression but resistance is common. This may be either de novo with failure to respond at all to initial therapy or may be induced during treatment, and they are likely to have different mechanisms.

We have started a clinical trial of neoadjuvant Bevacizumab in a window study before neoadjuvant chemotherapy and this shows three patterns of response to Bevacizumab; a clear reduction in tumour vascularity, permeability and perfusion evenly across the tumour, a pattern of reduction of perfusion and permeability but increase in central necrosis and thirdly no response at all. We think these may mimic the major types of resistance. We have developed in vivo models for each type and show that upregulation of notch ligands, such as delta-like 4 in the tumour, can change the biology of the endothelial cells making them resistant to anti-VEGF therapy. This can be reversed with notch inhibitors and more recently we have shown that this is true with Ephrin B2 blockade. The study highlights the importance of understanding the vasculature in detail in a patient entering such studies.

We have also shown that after Avastin, although initially inhibiting tumour growth, tumours can carry on growing through treatment and they have marked changes in their biology. Amongst these changes is upregulation of the pH regulating protein, Carbonic Anhydrase 9, which we have previously shown is prognostic in of breast cancer and other tumour types. We inhibited Carbonic Anhydrase 9 expression in two tumour types and showed that in vivo the knockdown of Carbonic Anhydrase 9 was associated with much greater effect of Bevacizumab, a potentially turning a drug that had no effect at all on a tumour to one where the survival could be prolonged two-fold. This will support development of inhibitors against this target. We further investigated other mechanisms of adaptation to acid pH and found that bicarbonate transport is a key pathway and we are currently evaluating inhibitors developed for cardiac disease in this role.

In conclusion, resistance to anti-angiogenic therapy is complex, we need to profile patients for the mechanisms, and we can enhance the effectiveness through several different routes. It is likely, therefore, that anti-angiogenic therapy will increase in effectiveness as we target resistance

mechanisms. It is important also to be able to classify hypoxia in tumours, t as this is likely to affect response to therapy and we have shown that a specific microRNA regulated by hypoxia, miR-210, is associated with prognosis, strongly associated with tumour hypoxia and provides a ready method to assess hypoxia.

Friday, 26 March 2010 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Long term sequelae of breast cancer management

427 Invited

Late sequelae of breast cancer surgery

M. Dixon[1]. [1]*Western General Hospital, Breast Unit, Edinburgh, United Kingdom*

Approximately ¾ of patients who have breast conserving surgery have excellent to good results. Patients who get excellent to good results have less anxiety and depression, better body image, less problems with sexuality and better self esteem. Between 25% and 30% of patients, however, get poor cosmetic results. For these women there are options to achieve symmetry. In the long term patients who have breast conserving surgery when young even if they have an initial good result, report that the treated breast remains the same size or even gets smaller whereas the opposite breast usually increases in size with age.

For long term asymmetry there is the option of reducing the opposite breast or augmenting the treated breast. Options for augmenting the treated breast include local flaps, inserting a breast implant and lipo-filling. A combination of techniques is often needed. With distortion or skin loss, implants alone are unlikely to be effective and local flaps are usually required most commonly an LD flap, although other local flaps or rarely a TRAM flap are an option. If the breast shape is satisfactory but the breast is of smaller volume then one option is to use an implant and/or lipo-filling or to reduce one or both breasts.

We have reviewed 23 patients who had augmentation after breast conserving surgery and radiotherapy performed by a single surgeon. The median weight of excision in this series was 71 grams. The mean age of wide local excision was 42 and the mean age of augmentation was 46. The mean follow up since augmentation was 46 months and six patients had bilateral augmentations. None of the patients were dissatisfied when dressed and none of the patients felt their body was less whole. 27% changed clothes occasionally although 73% hadn't changed their clothes at all. 18% felt a little less attractive, although 82% did not feel at all less attractive. 18% were a little self conscious but 82% were not at all self conscious. The mean score out of ten was happiness with size 8.8, (SD 0.9), happiness with shape 8.6, (SD 1), happiness with the texture of the breast 8.7, (SD 1.3) and overall appearance score was 8.5, (SD 0.9).

The more recent trend is to use lipo-filling to improve long term cosmetic outcomes after breast conserving surgery. Lipo-filling brings in fat which contains mesenchymal stem cells which help rejuvenate irradiated tissue. Results suggest that this is a real option for many patients with asymmetry following previous breast surgery. Debate continues whether new devices which concentrate these stem cells from fat improve cosmetic outcomes compared to less sophisticated centrifuges which separate whole cells from fluid and disrupted cells.

In a few patients who survive many years after mastectomy or breast conserving surgery combined with radiotherapy, do develop radiation ulcers. Although excision and bringing in new tissue has been the main stay of treatment, there is some evidence that in these patients lipo-filling may have a role.

428 Invited

Long term toxicity of radiation therapy

S. Darby[1]. [1]*University of Oxford, Epidemiological Studies Unit, Oxford, United Kingdom*

Each year about a million women worldwide are diagnosed with breast cancer. In the majority of cases, the disease is diagnosed sufficiently early for surgery to be appropriate. For women with node-positive disease who receive mastectomy, and for women with either node-positive or node-negative disease who receive breast-conserving surgery, adjuvant radiotherapy has been shown to decrease the risk of dying from breast cancer [1].

Despite the beneficial effect of radiotherapy on breast cancer mortality, there was in the past little net benefit of radiotherapy on mortality from all causes, as the beneficial effect was largely offset by the risk from radiotherapy. The principal component of this risk was an increased risk of death from cardiovascular disease, although there was also an increased risk from second cancers [1].

In recent years radiotherapy techniques have changed, and in many countries incidental exposure to the heart and other organs is lower now than in the past, and risks may now also be lower [2]. It is, however, likely that many of the regimens that are in use today still carry some risk, although there is little information on the risk associated with any particular regimen. This creates a difficult situation for those planning radiotherapy treatments.

The talk will summarize the evidence that is presently available regarding the risks of cardiovascular disease and second cancer following radiotherapy for breast cancer. The talk will also describe work that is currently underway to enable the risk associated with any particular regimen to be characterized.

References

[1] Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687–1717.

[2] Darby SC, McGale P, Taylor CW and Peto R. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective study of about 300 000 women in US SEER cancer registries. Lancet Oncol 2005; 6: 557–65.

430 Proffered paper oral

Cross-sectional study of Quality of Life (QL) 6 years after start of treatment in the UK Taxotere as Adjuvant Chemotherapy Trial (TACT; CRUK01/001)

E. Hall[1], L. Johnson[1], N. Atkins[1], R. Waters[1], P. Barrett-Lee[2], P. Ellis[3], D. Cameron[4], J. Bliss[1], P. Hopwood[1], on behalf of the TACT Trial Management Group. [1]*The Institute of Cancer Research, ICR-CTSU, Sutton, United Kingdom;* [2]*Velindre NHS Trust, Velindre Cancer Centre, Cardiff, United Kingdom;* [3]*Guy's and St Thomas' NHS Trust, Guy's and St Thomas Hospital, London, United Kingdom;* [4]*University of Leeds, St James's University Hospital, London, United Kingdom*

Background: 4162 patients (pts) were randomised to FEC-docetaxel or anthracycline chemotherapy (control). No difference in disease-free survival was observed (Lancet 2009 373:1681), but QL findings at 2yrs prompted further investigation of breast cancer survivorship in a cross-sectional study.

Materials and Methods: At 5.0–7.9 (median 6.1) years after entry into TACT, relapse-free pts were asked to complete EORTC QLQ-C30/BR23 (general/breast QL), FACT-ES (endocrine effects), HADS (anxiety & depression), & report changes in work status & continuing treatment symptoms. Descriptive statistics were used for the 6-year cross-sectional data (between group comparisons will be reported separately); change over time was assessed for pts who had also completed a 2-year prospective QL study in the TACT trial (TACTQL). Associations between change in work status & known side effects/key aspects of QL were assessed.

Results: In participating centres, 1776/2335 (76%) pts responded by October 2009 (median age 49.5 (IQR 43.7–54.8)). Problems most commonly rated quite a bit/v much were loss of libido (38%), joint pain (38%), weight gain (36%), hot flashes (32%) & tiredness (22%). FACT-ES median endocrine symptom subscale score was worse for women aged <50 at trial entry compared to those aged ⩾50 (58 (IQR 49–67) vs. 62 (IQR 54–68) respectively; $p < 0.0001$). Median global health/QL, physical, role & social functioning were high (good). 54% pts still had symptoms/problems they attributed to prior chemo/endocrine therapy.

Of 1066 pts aged <60 at 6yrs who were employed at baseline, 17% had left employment; in ⩾60s this figure was 62%. In both age groups there was an association between leaving employment & higher levels of fatigue, pain, endocrine symptoms, anxiety & depression, & lower levels of physical, role & social functioning & global health/quality of life (<60yrs: all $p < 0.0001$; ⩾60yrs: $p < 0.05$ except anxiety $p = 0.06$).

20% (361) pts were TACTQL participants. Although median symptom & functional subscale scores were similar at 0 & 6 years, memory worsened for 32% & improved for 11% pts; for tiredness, 21% were worse & 26% better. Anxiety ratings improved for 28% & worsened for 11%; depression ratings improved for 5% & worsened for 9%.

Conclusions: Moderate/severe endocrine symptoms affect a significant minority of women at 6yrs. Despite good global QL, there is an association between leaving employment & patient reported late treatment effects.