

Meeting report

22nd Annual San Antonio Breast Cancer Symposium, 8–11 December 1999, San Antonio, Texas, USA

Robert B Clarke and Elizabeth Anderson

Christie Hospital NHS Trust, Manchester, UK

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Introduction

The 22nd Annual San Antonio Breast Cancer Symposium attracted over 3000 registrants, making it one of the largest regular conferences devoted to breast cancer research and treatment. In keeping with the wishes of its founder, the late William McGuire, there were no parallel sessions. Instead, there was a packed schedule of plenary speakers, general sessions and minisymposia, which all delegates were expected to attend and, more importantly, to participate in. This year the WL McGuire Memorial Lecture was given by Charles Coltman (University of Texas Health Science Center, San Antonio, TX, USA), who paid tribute to Bill McGuire's legacy of rigorously conducted clinical and translational research. The other plenary speakers were Walter Willett (Harvard School of Public Health, Boston, MA, USA), Martin Cheever (Corixa, Seattle, WA, USA), Richard Elledge (Baylor College of Medicine, Houston, TX, USA), Joseph Costantino (NSABP Biostatistics Center and University of Pittsburgh, Pittsburgh, PA, USA) and Marc Lippman (Georgetown University School of Medicine, Washington, WA, USA), whose topics ranged from the nutritional and behavioural causes of breast cancer through immunotherapy to risk assessment and the epidermal growth factor receptor (EGFR) superfamily. Areas such as micrometastases, premalignant and preinvasive disease, and high-dose chemotherapy were covered in minisymposia, whereas the general sessions comprised short communications of general interest, late breaking results or the results of particularly interesting or important clinical trials. Finally, there were nearly 500 posters spread over five early morning or evening sessions.

Breast development and premalignant disease

Barry Gusterson (Institute of Cancer Research, London, UK) outlined the current understanding of stem cells and the biology of human breast development. The location of

stem cells in the human breast remains uncertain, but extrapolation of the results of studies on the mouse mammary gland suggests that 1 in 1000 cells can be classed as progenitors and must be regarded as targets for neoplastic transformation. Ablation of stem cells is an important goal of breast cancer prevention and treatment strategies, and it was good to hear that this area has been prioritized for funding by the US National Cancer Institute. The mouse mammary gland is becoming increasingly important as a model in which the effects of altering single genes on the biology of breast and breast tumour development can be studied. Jeff Rosen (Baylor College of Medicine, Houston, USA) described experiments that showed important interactions between the *BRCA1* and *TP53* tumour suppressor genes in breast tumour formation. Conditional deletion of the *Brca1* gene from the mouse mammary gland resulted in developmental abnormalities and, eventually, the development of *p53*-null tumours. Crossing the conditional *Brca1*-knockout mice into a *p53*-null background greatly accelerated the formation of tumours that were strongly reminiscent of human ductal carcinoma *in situ* (DCIS). Other knockout studies described by Jeff Rosen have shown a key role for the transcription factor C/EBP β in mouse mammary gland differentiation. The mammary glands from mice lacking *c/ebp β* showed abnormalities in ductal morphogenesis and were unable to lactate. In another experiment, the introduction of a dominant-negative C/EBP β transgene, liver inhibitory protein, enhanced proliferation and the formation of preneoplastic lesions. Interestingly, liver inhibitory protein was overexpressed in 23% of human invasive ductal carcinomas, in which it was associated with a poorer prognosis.

Oestrogen receptor biology and biochemistry

The oestrogen receptor (ER) is a major target of current breast cancer prevention and treatment strategies, but our

understanding of this receptor is still expanding. Work by Robert Clarke (Christie Hospital NHS Trust, Manchester, UK) that showed that ER-containing epithelial cells express p27^{KIP1} and are growth-arrested suggests that these cells are a differentiated population that may control the activity of adjacent proliferation-competent cells via paracrine and/or juxtacrine factors. A novel ER coregulatory molecule, HET/SAF-B, described by Steffi Oesterrich (University of Texas Health Science Center, San Antonio, TX, USA) maps to human chromosome 19p13, an area frequently affected by loss of heterozygosity in human breast tumours. This new coregulator recognizes the ER when bound to tamoxifen and enhances antioestrogenic activity of this drug, and its expression is reduced in cultured breast cancer cells resistant to the inhibitory effects of antioestrogens. Finally, Adrian Lee (University of Texas Health Science Center, San Antonio, TX, USA) showed the complete interdependence of the insulin-like growth factor receptor and the ER signalling pathways in cultured human breast cancer cells, suggesting alternative targets for antitumour therapies.

Molecular analyses

Recently, important new methods of analyzing large numbers of molecular and chromosomal changes in small samples have been developed and a number of groups reported preliminary results from their use of such methods. For example, DM Euhus (University of Texas Southwestern Medical Center, Dallas, TX, USA) described an increased number of changes in microsatellite sequences in fine-needle aspirate samples of normal tissue taken from women at very high risk for breast cancer. FM Waldman (University of California, San Francisco, CA, USA) used comparative genome hybridization (CGH) to show that nearly all DCIS recurrences were closely related to their primary lesions. The use of complementary DNA microarrays to find changes in gene expression common to hereditary but not sporadic tumours was reported by EMJJ Berns (Josephine Nefkens Institute, Rotterdam, The Netherlands). Another use of microarray technology was demonstrated by L Assersohn (Royal Marsden Hospital, London, UK), who used it to examine fine-needle aspirates taken from tumours before, during and after presurgical tamoxifen treatment. In all, the expression of 190 genes was changed significantly by antioestrogen treatment, but several interesting clusters of genes emerged, some of which were common to all tumours. RA Baldocchi (University of California at San Francisco Cancer Center, San Francisco, CA, USA) described an oligonucleotide array-based CGH technique to assess gene loss or amplification. In this technique amplified tumour complementary DNA is hybridized to an array of oligonucleotides corresponding to sequences from the genes of interest. Thus, information regarding genetic loss or amplification is obtained and, it is claimed, the technique has greater resolution and is more quantitative than

existing CGH methods based on hybridization to metaphase chromosome spreads. Methodologies such as this and the others described above have great potential in the study of human tissues (both normal and malignant), because often only a very small sample is required and the analysis of hundreds if not thousands of genes is possible.

New chemotherapeutic strategies

As ever, new strategies for treating advanced breast cancer and new targets for preventive or adjuvant treatment are needed, and an entire minisymposium was devoted to the subject of high-dose chemotherapy. The 'take home' message from this session was that high-dose regimens with or without blood stem-cell support offer no significant improvements in overall or relapse-free survival compared with more conventional schedules, and were associated with more serious adverse side effects. Several presentations confirmed the clinical efficacy of the Herceptin (Genentech, San Francisco, CA, USA) antibody against the c-erbB2/HER2 cell-surface receptor when administered in combination with cytotoxics such as paclitaxel or vinorelbine. The HER2 receptor was also the target of immunotherapy strategies described by Martin Cheever (Corixa, Seattle, WA, USA). HER2 may not be an ideal antigen, however, so differential display was used to identify two new antigens, one or the other of which was overexpressed in 90% of breast tumours examined. Inhibitors of receptor tyrosine kinases such as the EGFR or HER2 receptors have been developed recently. Kai Chan (University Hospital of South Manchester, Manchester, UK) showed that the compound Iressa (AstraZeneca, Macclesfield, Cheshire, UK) decreased the proliferative activity of normal human breast epithelium and DCIS when implanted into athymic nude mice, suggesting that this class of compounds might have a role in the management of preinvasive as well as advanced disease. In his plenary lecture, Marc Lippman (Georgetown University School of Medicine, Washington, WA, USA) revealed that a new target for receptor tyrosine kinase inhibition might be a variant of the EGFR, EGFRvIII, which appears to be overexpressed in a large proportion of human breast tumours.

New prognostic markers

An important aspect of managing breast cancer is predicting both the likely course of the disease and the likely response to specific treatments. Promising new prognostic markers include p27^{KIP1}, increased levels of which are associated with longer survival in young women with breast cancer. Conversely, low levels of a bcl-2 binding protein BAG-1, an antiapoptotic protein, are associated with a better outlook in early breast cancer. Bivariate flow cytometric analysis of cellular cytokeratin and DNA content improves detection of hypodiploidy and tetraploidy, both of which are associated with poorer prognosis. Cytokeratin immunohistochemistry was used to show that micrometastases in bone marrow were indepen-

dent markers of poor prognosis, as were micrometastases in lymph nodes removed from early-stage breast cancer patients. Several papers reported preliminary results of sentinel node mapping as an alternative to full axillary dissection in suitable patients, although the clinical usefulness of such techniques remains to be established.

Prevention and prediction of breast cancer risk

It seems likely that the most significant advances will be made in the areas of prevention and in prediction of breast cancer risk. Walter Willett (Harvard School of Public Health, Boston, MA, USA) reported that women with the lowest risk of breast cancer are those who have had an early first pregnancy, who have maintained the same body weight since they were 18 years old, who have a Mediterranean diet, who do not drink and who do not use hormone replacement therapy. The inter-relationships between these factors are complex, but a better understanding should suggest new ways of preventing breast cancer. Accurate prediction of risk is also important for women with a family history of breast cancer and Richard Elledge (Baylor College of Medicine, Houston, TX, USA) presented data that revise estimates of the penetrance of the *BRCA1* breast cancer susceptibility gene. It now seems likely that the incidence of breast cancer before the age of 70 years in *BRCA1* mutation carriers is 56%, with a range of 40–85% and a median age of 40–45 years at onset. This contrasts with the estimate of 87% described in earlier studies. Estimates of the incidence of ovarian cancer in these women may also have to be revised downwards and Elledge attributes the discrepancy to ascertainment bias in the earlier studies, to genotype influences, modifying factors and plain old chance. These revised figures should allow more appropriate counselling and application of risk management strategies, however, such as prophylactic mastectomy in women with a family history of breast cancer.

Conclusion

The 22nd Annual San Antonio Breast Cancer Symposium achieved its aim of promoting discussion and interactions between all sections of the breast cancer research and treatment community.

Authors' affiliation: Clinical Research Department, Christie Hospital NHS Trust, Manchester, UK

Correspondence: Elizabeth Anderson, Clinical Research Department, Christie Hospital NHS Trust, Wilmslow Road, Manchester M20 4BX, UK