

Meeting report

25th Annual San Antonio Breast Cancer Symposium, San Antonio, Texas, USA, 10–14 December 2002 Update on preclinical and translational research

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See *clinical report*, page 113

Abstract

The Annual San Antonio Breast Cancer Symposium is one of the largest regular conferences devoted to breast cancer research and treatment. In particular, it provides a forum in which to discuss the more translational aspects of current basic research, and the 2002 meeting was no exception. Growth factor pathways and endocrine resistance, cancer genomics and the clinical applications of proteomics were three of the major topics for discussion. Presentations on genetic susceptibility and the development of prognostic and predictive markers also created much interest.

Keywords: BRCA 1/2, cDNA microarray, growth factor pathways, prognostic and predictive markers, proteomics

Introduction

The 25th Annual San Antonio Breast Cancer Symposium attracted nearly 5000 physicians and researchers in breast oncology, as well as other health care professionals and patient advocates with an interest in breast cancer. This meeting has become a key forum for the presentation and discussion of scientific, translational and clinical aspects of breast cancer care. The present report will focus on the preclinical and translational highlights of the meeting. The clinical research presented at the meeting is discussed in another report, also published in the present issue of *Breast Cancer Research* [1].

The work presented, as ever, was diverse and stimulating. Three plenary lectures were given addressing growth factor signalling, cancer genomics and proteomics, while two minisymposia were devoted to epithelial–stromal interactions and cancer genetics: 'BRAC1 and 2 and beyond'. There were also general presentations of original research, and a large number of posters covering other topics of interest such as protein arrays and the development of novel prognostic and predictive markers.

Growth factor pathways and signalling

Elucidation of the signal transduction cascade downstream from growth factors and receptor tyrosine kinases has revealed several key proteins that promote cell proliferation and cell survival. Interest in the field of signalling continues to grow, and this year's meeting was launched by a lecture from Robert Nicholson (Tenovus Centre for Cancer Research, Cardiff, UK). Nicholson focused on the complex signalling pathways of the oestrogen receptor (ER) and, in particular, the development of endocrine-resistant disease. Inappropriate activation of growth factors, such as epidermal growth factor (EGF), insulin-like growth factor (IGF) and heregulins, and the subsequent upregulation of downstream signalling cascades, results in a sustained induction of cell proliferation and survival mechanisms that ultimately override the antitumour effect of endocrine treatments. Several growth factor-induced protein kinases such as protein kinase B (AKT) and mitogen-activated protein kinase (MAPK/ERK) can target and phosphorylate key regulatory sites on the ER. There is also evidence of a positive feedback loop as the phosphorylated ER is able to increase the levels of growth factors

AKT = protein kinase B; EGF = epidermal growth factor; ELISA = enzyme-linked immunosorbent assay; ER = oestrogen receptor; IGF = insulin-like growth factor; HER-2 = human epidermal growth factor receptor related gene 2; MAPK/ERK = mitogen-activated protein kinase; PAI-1 = plasminogen activator inhibitor-1; uPA = urokinase-type plasminogen activator.

such as EGF, in an independent fashion. Robert Nicholson went on to demonstrate that it is possible to block the EGF/HER-2/MAPK pathways *in vitro*, with novel agents such as ZD 1839 (Iressa), and to consequently inhibit the growth of anti-oestrogen-resistant cells.

These findings were supported by some data presented by Jiang Shou (Bayer College of Medicine, Houston, TX, USA), who showed that, in a xenograft model of breast cancer, the combination of Iressa and tamoxifen results in greater antitumour effect compared with either drug alone, and that the combination can delay the development of acquired endocrine resistance [2]. Studies in tumour models of breast cancer to date indicate that increased growth factor signalling clearly represents a mechanism for the development of endocrine resistance. If we are to design better treatments, then we must not consider ER signalling in isolation from the rest of the complex biology of cancer cells.

Proteomics in cancer prevention and treatment

As the human genome project progresses, the next challenge facing biologists is to understand the functional significance of the genes identified. The phenotype of a given cell is ultimately determined by the composition and the activation status of its proteins. The study of the proteome and protein expression is a rapidly expanding area of research that provides us with novel data on functional cellular content, and thus complements genomic DNA and gene expression analyses.

The plenary lecture by Emanuel Petricoin (Food and Drug Administration, Bethesda, MD, USA) gave insight into how emerging proteomic technology might, in the future, be used as a clinical tool in the diagnosis of cancer. The serum proteome consists of multiple proteins and peptides that are too numerous to identify individually. It is possible, however, to look at emerging patterns of proteome expression using a novel informatic tool, which can distinguish the malignant phenotype from benign conditions. Proteins from blood samples bind to the surface of a mass spectroscopy chip and patterns of protein expression can then be mined using an artificial intelligence-based software package. The state of signalling pathways in an individual patient's tumour can be demonstrated using these protein arrays and, hence, the most susceptible targets for treatment may be identified.

This technology has future clinical applications in a variety of tumours including lung, prostate and ovarian carcinoma. In breast cancer, one of the first applications would be as an adjunct to mammography in detecting early disease. An example of this was illustrated by LLL Wilson (Eastern Virginia Medical School, Norfolk, VA, USA), who described the use of proteomics technology to create a simple test

for breast cancer detection [3]. A specific mass spectrometry technique was used to generate protein profiles from the sera of women with breast cancer and from controls. Serum profiles were thereby identified that were consistent with a diagnosis with breast cancer. Crossvalidation studies demonstrated high levels of sensitivity and specificity. If validated in larger studies, techniques such as this could prove to be powerful adjuncts to existing methods of breast cancer detection.

The ultimate goal is to apply proteomic technology to the treatment of cancer and to the development of patient-tailored therapy.

Prognostic and predictive factors

The delivery of adjuvant systemic therapy inevitably involves the overtreatment of some patients (who would be cured by local therapy alone), and the undertreatment of others. In his plenary lecture, Stephen Friend (Rosetta Inpharmatics/Merck Research, Westpoint, PA, USA) outlined the need to identify molecular profiles that could predict which patients have a high risk of relapse. Adjuvant therapy could in this way be reserved for those most likely to benefit, maximising therapeutic effects while minimising unnecessary toxicity. It may be possible not only to identify profiles predicting relapse (prognostic profiles), but also to predict which treatments are most likely to be effective (predictive profiles). The expansion of molecular oncology, and in particular the development of cDNA microarrays, has made this a clinical reality.

Jonas Bergh (Karolinska Institute and Hospital, Stockholm, Sweden) presented results of a microarray analysis of a cohort of 186 patients treated for breast cancer between 1994 and 1996, and from whom stored frozen tissue was available [4]. The RNA from the tissue was extracted and examined using two different gene chips of 39,000 and 10,000 genes, respectively. By comparing the gene expression profiles with outcome, a set of 100 genes were identified that were thought to have the greatest prognostic importance in this cohort. Twenty-one per cent of the patients in this series had received adjuvant chemotherapy, however, and it is therefore important to stratify for treatment effects. In addition, the training profiles generated require further validation using independent data sets. Nonetheless, gene expression profiling using cDNA microarrays represents a major advance in estimating prognosis and predicting responses to therapy.

Friend emphasised that molecular profiling should not be viewed in isolation, but should be regarded as complementary to, and used in parallel with, existing pathological parameters. When putative prognostic or predictive genes are proposed by molecular profiling, it may be desirable to compare gene expression with expression of downstream proteins. The construction of tissue microarrays may

enhance our ability to do this [5]. Tissue microarrays consist of cores of tumour taken from multiple patients and arranged on a single array. These cohorts of patients can then be rapidly screened for proposed prognostic or predictive markers using immunohistochemical techniques. Because these arrays are constructed prospectively, they represent an important biological resource. Novel markers of interest not initially identified at the time of trial design may be retrospectively investigated.

The importance of retrospective analysis of biological markers was illustrated by an update of the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial 24 given by Craig Allred (Baylor College of Medicine, Houston, TX, USA) [6]. In this trial, 1804 women with ductal carcinoma *in situ* (DCIS) treated by excision and radiotherapy had been randomised to tamoxifen or placebo. When first published in 1999, women in the tamoxifen-treated group were found to have fewer breast cancer-related deaths than those in the placebo group, but the findings were not stratified for ER status [7]. In this update, ER status was available for 676 patients (450 analysed centrally and 226 analysed externally). Tamoxifen reduced the risk of invasive breast cancer recurrence in ER-positive patients (relative risk=0.41, $P=0.0002$). There was also a reported benefit in ER-negative patients, but this was not statistically significant (relative risk=0.8, $P=0.51$). Allred pointed out that the trend to benefit in ER-negative patients was only seen in the externally tested samples where the rate of ER-negative tumours was higher. This raises the possibility of false-negative reporting in the externally tested cases, which would explain the apparent trend to benefit from tamoxifen in ER-negative patients.

The potential clinical utility of predictive biological markers was demonstrated in a study presented by Nadia Harbeck and colleagues (Technical University, Munich, Germany) concerning the invasion factors urokinase-type plasminogen activator (uPA) and plasminogen activator inhibitor-1 (PAI-1) [8]. These factors are recognised as having prognostic significance in breast cancer: patients with high tumour levels of either factor have a significantly worse prognosis than patients with low levels. The data presented, however, suggest that these factors may also have a predictive impact on responses to adjuvant chemotherapy and endocrine therapy. uPA and PAI-1 antigen levels were measured by enzyme-linked immunoadsorbent assay (ELISA) in 3424 primary tissue extracts, and were compared with subsequent disease-free survival. As previously shown, patients with high uPA/PAI-1 levels were found to have a worse disease-free survival than those with low levels. However, this study also demonstrated that high levels of these factors predicted an enhanced benefit from adjuvant chemotherapy in certain patient groups. In node-negative patients who have low levels of uPA/PAI-1, the

overall risk of relapse is low and it may be possible to avoid adjuvant systemic chemotherapy. Node-negative patients with high uPA/PAI-1 levels, however, are at significant risk of relapse, and systemic treatment in these cases is warranted. The elaboration of factors such as uPA/PAI-1 considered in conjunction with established pathological parameters will improve treatment decisions in the adjuvant setting.

Genetics

A minisymposium on breast cancer genetics provided a timely update on current understanding of breast cancer susceptibility genes. Ashok Venkitaraman (University of Cambridge, UK) reviewed the putative biological functions of BRCA1 and BRCA2, focusing particularly on the chromosomal instability that arises following gene mutations. When DNA double-strand breaks occur, repair is either by homologous recombination, which is error free, or by non-homologous end joining, which is error prone. BRCA1-deficient and BRCA2-deficient cells are not able to repair by homologous recombination, and therefore have to rely on error-prone nonhomologous end joining. This could explain the spontaneous chromosomal instability of BRCA-deficient cells, underpinning their mutability and propensity for neoplastic transformation. Under normal circumstances, however, a cell with such chromosomal instability would not be viable. It is therefore postulated that further mutations, particularly in genes crucial to the cell cycle checkpoints, must also be mutated to allow the continued proliferation and survival of these defective cells. One such gene is CHK2, and this was discussed further in a complimentary presentation given by Daniel Haber (Massachusetts General Hospital, Charlestown, MA, USA).

The clinical impact of susceptibility genes must not be underestimated. Judy Garber (Dana-Farber Cancer Institute, Boston, MA, USA) discussed the difficulties encountered when screening this patient group. The high rate of interval breast cancers seen with mammography continues to cause concern, and Garber presented data from some small studies suggesting that magnetic resonance imaging may be the screening modality of choice. Data published earlier in 2002 demonstrate that prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations may reduce the risk of both ovarian and breast cancer with hazard ratios of 0.04 and 0.47, respectively [9]. It was finally emphasised that, while bilateral prophylactic mastectomy may reduce the risk of breast cancer by approximately 90%, the risk reducing roles of tamoxifen and oral contraceptives remain less well studied.

Conclusion

The 25th San Antonio Breast Cancer Symposium was the largest meeting to date, and the range of scientific and translational research covered was impressive. Continued

advances in genetics, proteomics and cell signalling have increased our understanding of the pathogenesis of breast cancer and, in particular, the development of resistant disease. With ever-advancing technology this knowledge is readily translated into the clinical arena and, as novel targets for breast cancer detection and treatment are being identified, the concept of patient-tailored management is becoming a reality.

Competing interests

None declared.

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