378 Invited

Targeting ER and signalling pathway

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The last few years has seen a significant increase in the number of novel targeted therapeutic agents entering clinical development for breast cancer. These have followed in the footsteps of targeted endocrine therapies against ER which since the 1980's have contributed to significant gains in breast cancer survival. HER2 targeted therapies (ie trastuzumab) have delivered significant improvements in disease-free and overall survival in early breast cancer. However, not all HER2 positive cancers respond to this therapy, and several approaches are now being developed to enhance blockade of HER2 signalling and overcome trastuzumab resistance. Promising strategies include improved antibodies (ie. 2C4 or pertuzumab) that bind at different extracellular sites to disrupt HER2 hetero-dimerisation, HSP90 inhibitors (ie. 17-AAG) that interfere with client HER2 protein processing, or small molecule tyrosine kinase inhibitors (ie. lapatinib) that target both HER2 and EGFR. Another important area of translational breast cancer research has been the use of various signal transduction inhibitors (STIs) to enhance the benefit of endocrine therapy that targets ER, specifically by overcoming and/or preventing de-novo/acquired resistance. The recognition of the role played by EGFR and HER2 in cross-talk activation of ER signalling has been confirmed by pre-clinical studies showing that various STIs give additive or synergistic effects when combined with endocrine agents. Activation of the PI3-K/Akt pathway has also been associated with resistance to either estrogen deprivation or tamoxifen, and inhibitors of mTOR (a downstream target of Akt) can restore tamoxifen sensitivity in breast cancer cells. Inhibitors of IGFR which activates Akt cell survival pathways are also in early stage development for breast cancer. Strategies to combine endocrine agents with various targeted therapies are being explored in both early stage (neoadjuvant) and metastatic settings. The EGFR tyrosine kinase inhibitor gefitinib combined with the aromatase inhibitor anastrozole for 4−6 weeks induced greater inhibition of Ki-67 than with gefitinib alone in a double-blind placebo controlled pre-operative study in 56 women with ER+ve and EGFR+ve primary breast cancer. In metastatic disease a randomised phase II study (TAnDEM) has reported that the addition of trastuzumab to the aromatase inhibitors anastrozole significantly improved time to disease progression in ER+ve HER+ve advanced breast cancer. A phase III study of the mTOR inhibitor temsirolimus with letrozole in metastatic disease was stopped early due to lack of efficacy over letrozole alone, although a neoadjuvant study of RAD-001 (everolimus) with/without letrozole recently reported some additional benefit for the combination. Biomarker studies associated with these trials remain important in attempting to select appropriate patients for these novel targeted agents, especially for the combination of STIs with ER targeting. Ongoing studies in both advanced breast cancer and in the pre-operative setting continue to study the pharmacodynamic effects of these novel agents, in particular trying to define molecular signatures that may predict response.

379 Invited

Targeting HER family

Abstract not received.

380 Invited

Synthetic lethal approaches to the treatment of cancers with DNA repair defects

A. Ashworth[1]. [1]*The Institute of Cancer Research, The Breakthrough Breast Cancer Research Centre, London, United Kingdom*

About one in nine women in the Western world develop cancer of the breast and at least 5% of these cases are thought to result from a hereditary predisposition to the disease. Two breast cancer susceptibility (BRCA) genes have been identified and mutations in these genes account for most families with four or more cases of breast cancer diagnosed before the age of 60. Women who inherit loss-of-function mutations in either of these genes have an up to 85% risk of breast cancer by age 70. As well as breast cancer, carriers of mutations in BRCA1 and BRCA2 are at elevated risk of cancer of the ovary, prostate and pancreas. The genes are thought to be tumour suppressor genes as the wild-type allele of the gene is observed to be lost in tumours of heterozygous carriers. Both BRCA1 and BRCA2 have significant roles in the maintenance of genome integrity via roles in the repair of DNA damage via homologous recombination. The specific DNA repair defect in BRCA-mutant cells provides opportunities for novel therapeutic approaches based on selective inhibition of functionally interacting repair pathways, in particular by inhibition of the enzyme PARP. Here I will describe recent work defining determinants of sensitivity and resistance to PARP inhibitors, as well as the application of the synthetic lethal approach to other cancer types.

Selected publications

Turner N, Tutt A, Ashworth A (2004) Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 4: 814–819.

Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A (2005) Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434: 917–921

Lord, C.J., Garrett, M.D. and Ashworth, A. (2006) Targeting the double-strand DNA break repair pathway as a therapeutic strategy. Clin Cancer Res, 12, 4463–4468.

Iorns, E., Lord, C.J., Turner, N. and Ashworth, A. (2007) Utilizing RNA interference to enhance cancer drug development. Nat Rev Drug Disc, 6, 556–568.

Edwards, S., Brough, R., Lord, C.J., Natrajan, R., Vatcheva, R., Levine, D.A., Boyd, J., Reis-Filho, J.S. and Ashworth, A. (2007) Resistance to Therapy caused by Intragenic Deletion in BRCA2. Nature, In press.

Friday, 18 April 2008 14:00–16:00

SENONETWORK MEETING

Breast units: Time to define the standards

381 Invited

The pathology report: what do we really need to know?

C. Wells[1]. [1]*St. Bartholomew's Hospital, Dept of Pathology, London, United Kingdom*

Background: It is not so long ago that a pathology report on a breast cancer read "Adenocarcinoma of the breast" or "Spheroidal cell carcinoma of the breast" with no reference to prognostic factors and no report on margins. Surgeons did not request this information or dissect the axilla to assess nodal status. In the UK, one could still see occasional reports like this in the early 1980's although more enlightened clinicians were beginning to realise that cancers were not all the same and that tailored treatment might be more effective.

The advent of breast cancer screening made the assessment of prognostic factors mandatory and increasing use of anti-oestrogenic therapy lead to the assessment of receptors. Today there are many factors which are required for prognostic and therapeutic planning. Pathology data are essential for entry into decision making systems which are used by many oncologists to decide on chemotherapy.

Mandatory Information: Standard factors have been used now for a number of years to predict prognosis. The most useful are tumour size, tumour grade (Elston & Ellis), tumour type and nodal status. These factors have been combined into prognostic indices such as the Nottingham Prognostic Index (NPI) and have been used since the 1980's. Other factors which may not be as important for prognosis, may have an effect on local recurrence. These are margin status, vascular invasion and the presence of an extensive in-situ component.

Breast cancer was one of the first cancers to have targeted therapy for some tumours and assessment of the hormone receptor status is necessary to avoid unnecessary anti-oestrogen therapy. This was originally the preserve of biochemists but the advent of immunohistochemistry and the production of high quality antibodies for the assessment of receptor status moved the test into the routine pathology laboratory and the oestrogen receptor status also became an essential part of the pathology report. Due to the known increase in hormone sensitivity with tumours which are oestrogen and progesterone receptor positive, many laboratories assess both of these receptors routinely.

More recent development of humanised antibodies to the human epidermal growth factor receptor type 2 (HER-2) has made the assessment of HER-2 status an essential part of the pathology report. While some units assess this on all cancers, others only perform the test on the patients who may be eligible for trastuzumab (Herceptin) therapy.

Other markers: Other prognostic markers have been assessed in the past and are assessed in some units today. Examples of these are proliferation markers such as S-phase fraction, or MiB1, markers of invasiveness such as urokinase (uPA), uPA inhibitors such as plasminogen activator inhibitor (PAI-1), angiogenesis and angiogenic factors and other growth factor receptors such as epidermal growth factor receptor (EGFR). None of these are regarded as front line markers necessary to predict

therapy although the development of tyrosine kinase growth factor inhibitors may lead to a requirement to measure EGFR or possibly vascular endothelial growth factor receptors (VEGFR).

Molecular signatures: The development of molecular techniques to classify breast tumours, may in the future become a necessary test as these become more advanced and further markers are discovered which may predict response of tumours to various agents.

Conclusion: Pathology reports should contain a number of mandatory facts about a tumour. These are tumour size, tumour type, tumour grade, axillary nodal status, lymphovascular invasion, presence or absence of an extensive in-situ component and the status of the resection margins. Other mandatory tests are oestrogen receptor status and HER-2 status. Many laboratories would also include progesterone receptor status in this list.

382 Invited

The tumour board: how to prepare it properly

A. Awada[1], G. Tomasello[1]. [1]*Jules Bordet Institute, Medical Oncology Clinic, Brussels, Belgium*

Tumor board is a treatment planning approach in which experts in different specialties (oncologists, radiologists, pathologists, surgeons, radiation oncologists, geneticists and psychologists) review and discuss the medical condition and treatment options of a breast cancer (BC) patient (pt).

A multidisciplinary (MD) approach tailored to the stage of disease, estimation of risk of recurrence and mortality and assessment of the benefits and toxicities of adjuvant therapies can deliver the best possible overall care to BC pts. There is evidence that MD care for BC pts has the potential to reduce mortality, improve quality of life and reduce health care costs. MD meetings have been widely recommended as the preferred approach to managing BC in the USA and Europe.

They must be held at least weekly and the following should be discussed:

– cases in which the diagnosis is as yet uncertain;
– cases in whom the diagnosis of cancer is confirmed and who may be considered for primary medical therapy;
– all cases following surgery on receipt of the histopathology for discussion of further care;
– cases in follow-up who recently have undergone diagnostic investigations for possible symptoms of recurrent or advanced disease

For this purpose, an appropriate report of a BC case should be presented collegially in electronic format and include: a complete medical history, a clear histological description including tumor's main characteristics as well as all pathological biomarkers and gene expression profile if available, estimation of recurrence risk according to online prediction models, such as the validated "Adjuvant! Online" tool, instrumental exams and a genetic counseling when requested.

This appointment represents a unique educational opportunity for all the attending physicians and a crucial moment of professional growth since it allows interflow of opinion, clarification of surgical and pathologic details and information from a collective expert opinion on individual case management.

The complexity of modern BC treatment and abundance of new clinical and basic research studies make it difficult for one specialty to stay abreast of the rapid evolving field of BC management.

Since BC management continues to evolve rapidly a MD approach is required to implement a comprehensive treatment plan for both the prevention and treatment of BC. It is in this setting that the ultimate goal of reducing the incidence, morbidity, and mortality of this disease is best achieved.

383 Invited

The breast unit database: mission impossible?

A. Ponti[1], M. Tomatis[1]. [1]*CPO-Piemonte, Unit of Cancer Epidemiology, Torino, Italy*

The final statement of the first Joint Breast Cancer Conference [1] states that quality assurance programmes should be mandatory for all clinical Units treating breast cancer. According to the final report of the European Society of Breast Cancer Specialists (EUSOMA) workshop in Leuven, Belgium, in May 1999 on "Breast Units: future standards and minimum requirements" [2], performance figures on precisely defined quality objectives and outcome measures must be produced by Breast Units yearly. Following these lines, EUSOMA is conducting a voluntary accreditation programme for breast units [3] in which audit is among the main criteria adopted for granting accreditation. Within this programme some 25 European breast units, using eight different databases, have been visited so far.

Audit requirements for breast units aiming at achieve EUSOMA Initial Accreditation include:

– perform audit regularly. Audit procedures, including audit meetings, must be described in detail and found satisfactory;
– employ a database which is rated as satisfactory by EUSOMA. To be considered satisfactory a database must be able to reliably transfer information on cancer detection, diagnosis, primary operative and adjuvant therapies, tumour pathology and biology, and follow up to the EUSOMA Network database.

In order to achieve and mantain Full Accreditation, breast units must transfer their data, including follow up, to the EUSOMA database for a minimum period of five years and the results of their quality objectives and outcome measures, calculated yearly, must be satisfactory.

References

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[2] Blamey R, Blichert-Toft M, Cataliotti L, et al. The requirements of a specialist breast unit. *Eur J Cancer* 2000;36:2288−93.
[3] Blamey R, Cataliotti L. EUSOMA Accreditation of Breast Units. *Eur J Cancer* 2006;42:1331−7.

384 Proffered Paper Oral

Actions of the Polish Forum of the European Brest Cancer Coalition EUROPA DONNA for propagating in Poland the idea of breast units

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Poland has participated in the actions of the European Breast Cancer Coalition EUROPA DONNA since the beginning of its operations, i.e. since 1993. Representatives of the Polish Forum of the European Breast Cancer Coalition EUROPA DONNA [EBCC ED] take part in all conferences concerning breast cancer organized or co-organized by EBCC ED. We keep trace of all information that may help to improve the fate of women at risk or suffering from breast cancer. What we value in particular is all the actions of the Management of EBCC ED in the European Parliament. We have great hopes for the creation of Breast Units in Poland. We have been propagating this idea in Poland since 2005. Government and self-government administration politicians participate in these conferences. We have also presented this topic at medical conferences.

The aim of this presentation is to show the calendar of our actions, suggestions for administrative solutions under Polish conditions and the role of the Polish Forum of EUROPA DONNA in propagating knowledge concerning the aim and organizational and financial principles of Breast Units. It should be stressed that it is a non-governmental organization – the Polish Forum EUROPA DONNA – to be the first in Poland to inform doctors, politicians and society about actions of an international research centre EUSOMA and European Parliament for breast cancer prevention and limiting mortality and disability rate due to breast cancer among women in the whole of Europe.

Friday, 18 April 2008 16:00–17:20

CLINICAL SCIENCE SYMPOSIUM

Triple negative breast cancer, one or several diseases?

385 Invited

Designing clinical trials for triple negative breast cancer: evidence and issues

A. Di Leo[1], E. Zafarana[1], M. De Stefanis[1], L. Biganzoli[1]. [1]*Hospital of Prato, "Sandro Pitigliani" medical oncology unit Istituto Toscano Tumori, Prato, Italy*

The basal-like breast cancer sub-type represents a new treatment challenge for clinicians. This presentation will focus on some issues that are of critical importance for designing basal-like breast cancer trials. The following controversial issues related to the design of trials for basal-like tumors will be reviewed and discussed: a) study population; b) treatment duration; c) treatment targets; d) tumor biology progression.

Key-messages: Basal-like tumors do not entirely overlap with the triple-negative (ER, PgR, and HER-2 negative) cohort of breast cancer. The selection of basal-like patients for a clinical trial seems to be feasible according to the expression of molecular markers correlated to the basal-like phenotype and evaluable by immunohistochemistry. It is still unclear what might be the most appropriate adjuvant treatment duration for basal-like tumors. An extended clinical follow-up of patients carrying a basal-like