Wednesday, 21 March 2012 13:15–15:15

OPENING SYMPOSIUM

8th European Breast Cancer Conference − Opening

1 Invited

The EBCTCG Oxford Overview, 1984–2012

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In 1984–1985 the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) was established. Its aims, then as now, were to bring together, about every 5 years, results from all randomised trials of any type of adjuvant treatment for early breast cancer, so as to assess the effects on long-term outcome more reliably than any single trial could do. Until this collaboration began there was still widespread scepticism as to whether any such treatments would have any material effect on survival, and even though the 1985 collaboration found small but definite effects on 5-year survival, fears remained that these gains would prove evanescent, and that few, or no, patients would be cured. Those fears were largely dispelled by the next cycle of the collaboration, which found in 1990 that the effects of adjuvant therapy were about twice as great for 10-year survival as for 5-year survival, but still in 1990 many investigators were concerned that no evidence had yet emerged of a reduction in national breast cancer mortality rates.

During the 1990s, however, decreases in breast cancer mortality in middle age (35−69 years) emerged in one country after another that were too large to be plausibly ascribed to artefact or just to earlier detection and better local control. By 2005 the 15-year results from the trials suggested that widely practicable regimens of adjuvant chemo-endocrine therapy in estrogen-receptor-positive (ER+) disease could approximately halve breast cancer mortality, and national mortality trends at ages 35−69 suggested that in many countries breast cancer mortality rates during the 2010s would be only about half what they had been in the 1980s. The EBCTCG was fortunate to have existed while such progress was being made; it did not discover new drugs or conduct any trials itself, but it did bring forward by a few years the time when the importance of the discoveries and trials of others would be generally recognized, and it has helped avoid exaggeratedly positive or false negative results for particular types of patient.

In 2011 selected findings for hormonal therapy in ER+ disease, radiotherapy to a conserved breast and chemotherapy that does not require stem cell rescue were reported in the Lancet (each based on more than 99% of all randomized patients), and in 2012 another cycle of the collaboration will begin. Again it may well take a few years to get final data on all relevant trials and to get reports agreed and published, but so far every cycle of this collaboration has yielded some new, practicable findings, and this one should be no exception. Selected results from the current cycle will be presented.

2 Invited

The Biology of Breast Cancer − The New Super Highway to the Clinic

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It is now appreciated that breast cancer is not a single disease, but instead is a spectrum of tumor subtypes with distinct cellular origins, somatic changes and somewhat predictable clinical behaviors. Prognostic factors such as stage and grade, and predictive factors such as hormone receptors and HER2 status are the main features upon which clinical decision-making has traditionally been based. Gene expression data coming from DNA microarrays, and now sequencing-based technologies, has provided additional insights into the biology of breast cancer which has resulted in the development of a number of clinically useful assays. Our work on breast tumors using genomic analyses has led to a new molecular taxonomy that identifies at least five subtypes of breast cancers (Luminal A, Luminal B, HER2-enriched, Basal-like and Claudin-low) and a normal breast group. Known as the 'intrinsic subtypes', these groups have revealed critical differences in incidence, survival, metastatic site specificity, and response to treatment. Importantly, the information provided by the intrinsic subtypes complements the information provided by classical clinical-pathological markers, and adds value beyond estrogen receptor (ER) status, HER2 status, and stage.

In addition to the intrinsic subtypes, many other important prognostic and predictive gene expression-based profiles have been identified including the two most widely used clinical assays that are OncotypeDX and Mammaprint. Comparative genomic analyses have shown a significant level of concordance between the intrinsic subtypes, OncotypeDX and Mammaprint; however, recent analyses have also highlighted that these tests are in fact distinct and should not be considered to be three versions of the same assay. These tests and data have lead to the identification of a subset of ER−positive patients that have an extremely good outcome, and thus, for whom adjuvant endocrine therapy alone appears sufficient. Alternatively, the remaining patients/subtypes including Luminal B, HER2-enriched and Basal-like, show significantly worse prognoses, although targeted therapies for HER2+ patients have greatly improved their outcomes. Analysis of adjuvant and neoadjuvant trials also suggests that not all chemotherapeutics are equally effective on each of these high risk subtypes; therefore, further individualization of chemotherapy choices may be possible. Lastly, genome-based sequencing studies of genomic DNA and mRNA is providing a whole new level of tumor characterization including the ability to identify all somatic alterations occurring within a given tumor. These newest approaches, and the ability to detect all somatic coding sequence variants, are providing a possible biomarker of therapeutic responsiveness especially to targeted therapies, but for which there will certainly be a learning curve of how to integrate these biomarkers into validated clinical assays. The era of personalized medicine is upon us, but we must be cautious and thorough in our evaluation of these many new and promising biomarkers.

Wednesday, 21 March 2012 15:45–17:15

CLINICAL SCIENCE SYMPOSIUM

Neoadjuvant Therapy in Breast Cancer

3 Invited

Pathology of Neoadjuvant Chemotherapy in Breast Cancer

Abstract not received.

4 Invited

Neoadjuvant Therapy: What, When and Why

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Neoadjuvant chemotherapy achieves clinical responses in around 75% of patients with large breast primaries. It is clearly indicated to downstage and avoid mastectomy in patients with triple negative and HER2 positive breast cancers where pathCR rates (which predict well for long-term outcome) are 25% or more. Recent data suggest that chemotherapy in combination with anti-HER2 agents can increase pathCR to around 50%.

Neoadjuvant endocrine therapy in patients with ER positive tumours achieves downstaging to avoid mastectomy in up to 50% of patients (particularly with aromatase inhibitors). PathCRs are very uncommon and other endpoints are required to predict outcome.

A key issue in modern breast cancer medicine is to determine which patients with ER positive, HER2 negative cancers require adjuvant/neoadjuvant chemotherapy in addition to endocrine therapy. The neoadjuvant (or better the short-term preoperative approach) gives the opportunity to determine this using molecular markers. The neoadjuvant endocrine therapy trial IMPACT showed that the proliferation factor, Ki67, measured by core biopsy two weeks after starting endocrine therapy is a significantly better predictor of long-term outcome than pre-treatment Ki67. The UK POETIC trial is a large national Phase III trial involving 4,000 patients with the aim of determining whether Ki67 two weeks after starting preoperative endocrine therapy in standard practice can be used to predict which patients will do well with adjuvant endocrine therapy alone and which will require additional treatments.

Ki67 at the completion of neoadjuvant chemotherapy has also been shown to be a better predictor of long-term outcome than pre-treatment Ki67 and trials are currenlty underway to determine whether Ki67 after a single course of chemotherapy will likewise predicti for long-term outcome. If so, then this could be used to predict for example, which individual patients with triple negative breast cancer will fall into the 25% who achieve pathCR, and which would benefit from additional adjuvant/neoadjuvant therapies.

In summary, short-term neoadjuvant/pre-operative medical treatments prior to surgery offers greast potential for the selection of appropriate adjuvant therapy in the individual patient.

5 Invited

Local Treatment

Abstract not received.