neo-adjuvant chemotherapy. To improve cosmetic outcome, oncoplastic techniques should be applied whenever possible to achieve best margin width, optimal breast shape and no dead space to minimize boost dose volume; all to improve cosmetic outcome and diminish late side effects. In case mastectomy is indicated (either for oncological reasons or the wish of the patient), immediate breast shape reconstruction according to the form of the breast, the body shape of the patient or her desires, should be discussed and applied whenever possible.

Another option to diminish side-effects is the possibility of minimal invasive ablative surgery by radiofrequency ablation. So. far, the disadvantage of this procedure is the lack of sufficient tumor tissue to stage the tumor and to estimate the extent of the tumor with great certainty. Further follow-up after necrotizing the tumor will be difficult since necrotic tissue will be in place for a long time.

All this requires an experienced breast surgeon who applies his/her technical skills only after multidisciplinary consultation and discussion of every individual patient.

Thursday, 25 March 2010 15:30–17:00

CLINICAL SCIENCE SYMPOSIUM

Is tailored chemotherapy becoming a reality?

209 Invited

Can we select patients for adjuvant therapy based on the presence of micro-metastatic disease?

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Adjuvant therapy targets minimal residual disease. However, the presence of minimal residual disease is presumed not measured. Our current approach for determining adjuvant systemic therapy is to assess the primary tumour, using traditional clinicopathological features or multigene signatures, and estimate an individual's recurrence risk. Subsequent treatment decisions are based on characteristics of the primary tumour (eg. ER, HER2) with the presumption of biological homogeneity between the primary lesion and micrometastases. However, biological discrepancy between a primary tumour and corresponding micrometastases may have significant therapeutic consequences.

An alternative approach is to identify micrometastatic disease postoperatively. Disseminated tumour cells (DTC) in the bone marrow and circulating tumour cells (CTC) from peripheral blood collection may offer quantification and biocharacterisation of residual disease. Detection at the single cell level with high sensitivity and specificity is facilitated by immunocytochemical and molecular enrichment assays. Detection of DTC at the time of surgery for the primary tumour is not currently a routine procedure. Standardised DTC detection and implementation in clinical trials are required. CTCs offer a less invasive potential alternative. New tools, such as a recently described anti-EpCAM and flow based microchip technology, 'CTC-chip', offer greater efficiency in cell capture. The biological role and clinical significance of CTC in early breast cancer remain unclear.

Some CTC and DTC remain dormant with patients never developing overt metastases. Detection of micrometastatic disease alone may not be enough. Favourable host features, including conducive stromal microenvironment and evasion of host immunity, appear critical for the switch from this dormant state to evolution of metastatic disease. New tools are required to assess this dynamic multifactorial interaction between tumour and host. A potential novel tool may be metabolomics, a science of metabolites and small molecules. As metabolomic analysis of systemic biofluids incorporates both tumour and host signal, a dynamic portrait of metabolic status may identify individuals at risk of relapse due to presence of both residual disease and favourable host features.

210 Invited

Anthracyclines and topoisomerase II alpha − what is beyond?

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Anthracycline-based regimens are among the most active chemotherapies in breast cancer (BC). However, their use is associated with rare but significant toxicities and their efficacy may be restricted to a subset of BC patients. Topoisomerase IIa (TOP2A) is arguably a promising marker for predicting the efficacy of anthracycline-based chemotherapy for BC patients. However, several groups have reported conflicting results with regard to its predictive value.

We recently reported the results of the first neo-adjuvant trial − called TOP (NCT00162812) − designed to prospectively evaluate the predictive value of TOP2A and to identify biomarkers of response/resistance to anthracyclines. This trial was specifically designed to identify markers of efficacy to preoperative single-agent epirubicin (100 mg/m^2 q2 or q3wks) in 149 estrogen receptor (ER)-negative patients.

The results support TOP2A gene amplification, but not protein overexpression, as predictive marker of pathological complete response (pCR). However, it has recently been suggested that TOP2A might actually be a surrogate for CEP17 since an increased CEP17 copy number predicts for enhanced benefit of anthracyclines compared to CMF (Bartlett et al. *Cancer Res 2009*). Increased CEP17 was evident in 68% of the TOP trial cases. Interestingly, samples with TOP2A aberrations had a higher proportion of increased CEP17 than TOP2A normal samples but CEP17 status was not associated with pCR.

We further hypothesized that TOP2A gene amplification might be a surrogate for other genes that are co-amplified with TOP2A. To this end, we built and validated a TOP2A index that was made of genes located close to TOP2A.

Next, we investigated the predictive value of the biological gene expression modules (Desmedt et al. Clin Can Res 2008). We found that high levels of the tumor invasion module were associated with the presence of residual disease. This observation is consistent with the results reported recently by Farmer et al. (Nat Med 2009), which demonstrated that their stroma-related gene signature predicts resistance to neoadjuvant anthracycline-based chemotherapy. We also showed that high levels of the immune response module were associated with increased pCR rate.

Altogether, these results suggest that sensitivity to anthracyclines is likely multifactorial and that the cohort of patients who derive the largest benefit is not necessarily confined to the HER2/TOP2A co-amplified subgroup.

211 Invited

Predictive signatures for chemosensitivity and new targeted therapies − dream or reality?

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To date, predictive markers have been analyzed either as single markers (for example, proliferation markers, hormone receptors, HER2 and p53) or in groups, commonly referred to as gene signatures, metagenes, multigene biomarkers, multigene predictors or multigene classifiers. I will concentrate in my lecture on signatures and address an important practical question: are these signatures ready for routine clinical use?

1. Predictive signatures for chemosensitivity [1]: They must address two questions: (a) which tumours are more likely to respond to chemotherapy? (b) what is the optimal chemotherapy regimen for a specific tumour or group of tumours? The signatures which answer these questions are likely to be different; for the sake of simplicity I will describe them in two categories: those predicting general chemosensitivity (meaning that a tumour is sensitive to any chemotherapy or to a wide range of chemotherapeutic drugs) and those predicting drug-specific chemosensitivity (meaning that a tumour is sensitive to a specific class of agents). I will review retrospective trials that have reported promising chemotherapy signatures, presenting in a comprehensive manner for the non bio-informatician the different methods used so far.

2. Signatures for targeted therapies (oncogenic pathways signatures [2]): I will briefly explain how these signatures have been identified and discuss the value of DNA based and RNA based technics.

3. Integrated approach [3]: Unsupervised gene expression analyses have allowed to develop a molecular classification of breast cancer and to identify at least 5 subtypes (Luminal A, Luminal B, HER2 enriched, Basal and normal like). A group has tried to further dissect this classification using oncogenic and chemosensitivity signatures. Concentrating on the Luminal B and Basal subtypes, they found a high variability of specific oncogenic pathways (MYC, E2F3, SRC) within these subtypes. Similarly they found a clear heterogeneity of chemosensitivity signatures within these two subtypes. These findings may have important implications when designing a trial tailoring the treatment based on oncogenic pathways and/or chemosensitivity signatures.

In addition, I will briefly summarize prospective trials (either ongoing or under development). Of note, these trials will be presented and discussed in more details in my Friday lecture "Incorporating multigene signatures into the design of adjuvant clinical trials".

References

[1] Bonnefoi H, Underhill C, Iggo R, Cameron D. Predictive signatures for chemotherapy sensitivity in breast cancer: Are they ready for use in the clinic? Eur J Cancer 2009; 45(10): 1733−43.

[2] Bild AH, Yao G, Chang JT, Wang Q, Potti A, Chasse D, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 2006; 439(7074): 353−7.