right patient, as well as the probable need to make use of multiple "targeted" drugs. This talk with discuss traditional drug development strategies in metastatic breast cancer as well as the lessons learned from such strategies. The use of predictive biomarkers in completed trials will illustrate the need for upfront incorporation of biomarkers in patient selection. Integration of newer technologies, such as proteomics and genomics, in drug discovery and accelerated drug development in metastatic breast cancer will be outlined. Genomic signaling signatures exist for a number of dysregulated pathways including ras, src, myc, Her2, and Hif-1α, and strategies to include such signatures in rational trial design and patient selection will be presented. Finally, utilization of new technologies in order to optimally combine targeted therapies in metastatic breast cancer will be discussed.

224 Proffered Paper Oral

Breast carcinomas with basal phenotype: An appraisal of morphology and prognostic significance

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The aim of this study was to assess the morphological and immunophenotypical characteristics and prognostic significance of breast carcinomas with basal differentiation. We have examined a well-characterised series of invasive breast carcinomas (1944 cases) with a long term follow-up (median 58 months), using tissue microarray technology and immunohistochemistry, to identify those tumours that have a basal phenotype. Their immunophenotype profile was characterized using a variety of markers including basal cytokeratins and myoepithelial markers. In addition, hematoxylin & eosin stained sections of these tumours were studied for several morphological parameters. For the purposes of this study basal phenotype [BP] was defined by the expression of one or both basal cytokeratin markers CK5/6 and CK14) in >10% of the tumour cells. This was identified in 18.6% of the whole series (347 cases). The commonest histological types were ductal/no specific type, tubular mixed and medullary like carcinomas; the majority of these tumours were grade 3. There were positive association with larger size, adenoid cystic growth pattern, loss of tubule formation, marked cellular pleomorphism, high-grade comedo-type necrosis, poorer Nottingham Prognostic Index (NPI) and development of distant metastasis and tumour recurrence. Positive associations were found with loss of expression of steroid hormone receptors, BCL2 and FHIT proteins and positive expression of p53 and EGFR. Univariate and multivariate analyses showed that BP is associated with poor prognosis and shorter outcome in terms of shorter overall survival and disease free interval in the whole series as well as in both LN negative and LN positive groups. However, when we stratified the cases into different grades, we found that BP has a prognostic value in grade 3 tumours but not in grade 1 or 2. In a subgroup comprised LN negative, grade 3 tumours (30% of cases), it was the only prognostic marker identified in our series compared to other markers (NPI, VI, ER, p53, cerbB-2, EGFR, E-cadherin or P-cadherin). These results demonstrate that BP is a distinct group of tumours that can provide significant prognostic information particularly in grade 3 tumours. We recommend routine staining of breast cancer for basal CK expression.

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Comparison of IHC and FISH techniques to determine HER2 status of metastatic breast cancer in France: interim analysis of the FISH 2002 study

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Introduction: Immunohistochemistry (IHC) and fluorescence *in situ* hybridisation (FISH) can be used to assess HER2 status and identify metastatic breast cancer patients for treatment with trastuzumab (Herceptin®). The FISH 2002 study was designed to investigate the concordance between IHC and FISH, and between the regional reference and peripheral pathology laboratories across a large number of centres in France.

Methods: Following diagnosis of a patient with metastatic breast cancer, IHC was performed on primary breast tumours according to the IHC HER2 protocols of each centre. For peripheral centres, the tissue sample and initial IHC result were also sent to a reference centre, where IHC was repeated to assess peripheral/reference concordance and FISH performed on all samples to determine concordance with IHC. Assessments of concordance between techniques and centres excluded samples with ambiguous scores (IHC 2+). Statistical analysis was performed using SAS® version 8.

Results: This interim analysis was performed after 15 reference and 56 peripheral centres had collected data from 874 patients. The HER2 overexpression rate (IHC 3+ according to HercepTest® scoring system) was 206/874 (23.6%) in the reference centres and 87/424 (20.5%) in the peripheral centres. The comparison of IHC tests performed by both reference and peripheral centres (n = 424) showed a low discordance rate (4.4%). High HER2 gene amplification (≥8 copies/cell) was found in 192/874 (22%) of samples when tested by FISH, with a further 58/874 (6.6%) showing moderate amplification (6–7 copies/cell). Overall, 250/874 (28.6%) of samples were FISH+. Considering IHC 0, 1+ and 3+ cases (n = 759) the rate of discordance between IHC and FISH was 2.9% for the reference centres and 6.7% for the peripheral centres. The IHC false positive rate (4.9% for the reference centres; 13.8% for the peripheral centres) and false negative rate (respectively, 2.2% and 4.5%) were slightly higher for the peripheral centres.

Conclusion: The preliminary results of this study show that concordance was high between the reference and peripheral centres as well as between IHC and FISH. Whereas the rate of false negatives for IHC was low, the higher rate of false positives emphasises the need and the importance of IHC calibration with FISH, and quality assurance programmes such as this, to achieve high-quality HER2 testing, ensuring patients receive the most suitable treatment.

226 Proffered Paper Oral

Radiotherapy concurrent with trastuzumab is well tolerated in the adjuvant treatment of women with HER2-positive breast cancer: cardiac safety data from the NCCTG N9831 study

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Introduction: Trastuzumab (Herceptin®) [H] targets HER2 and is an effective treatment option for women with early and advanced HER2-positive breast cancer (BC). A large proportion of women will receive radiotherapy (RT) after surgery. Preclinical data suggest that H may have a radiosensitizing effect on breast tumor cells.[1] In the clinical setting it is important to ensure that this potential effect does not cause unexpected tolerability problems. In particular, because BC patients may receive RT to the chest, it is necessary to determine whether combining H and RT affects cardiac safety.

Methods: The NCCTG N9831 study enrolled 3505 women with invasive HER2-positive early BC who had undergone surgery. The study aimed to evaluate the benefit of doxorubicin (A) and cyclophosphamide (C) followed by paclitaxel (T), with sequential (AC → T → H) or concurrent H (AC → TH → H). RT was recommended for patients who had undergone lumpectomy or had >3 involved axillary lymph nodes, and was given concurrently with H (after completing chemotherapy).

Results: The most recent interim analysis was after 1.5 years' follow-up and showed that H provides significant disease-free survival benefit, with a hazard ratio of 0.57 (p = 0.0009) for AC → T vs AC → TH (further follow-up is needed to accurately compare AC → TH with AC → T → H) [2]. Around 80% of patients received RT concurrent with H. Therapy was well tolerated and associated with a low incidence of cardiac events (CEs), with a 3-year cumulative incidence of 0.3% (AC → T), 2.5% (AC → T → H), and 3.3% (AC → TH) of patients experiencing CEs. For patients receiving AC → T → H, incidence of CEs was 2% (4/164) for those who did not receive RT, 2% (5/259) for left-sided RT, and 2% (6/260) for right-sided RT. For patients receiving AC → TH, incidence of CEs was 4% (6/136) for those who did not receive RT, 2% (5/201) for left-sided RT, and 2% (4/219) for right-sided RT. Thus, no marked differences in CEs were noted between patients receiving right- or left-sided RT, or those who did and did not receive RT. Data on asymptomatic cardiac function changes will be presented.

Conclusion: The results suggest that H does not lead to an increase in RT-induced clinical CEs at a median follow-up of 1.5 years, indicating that patients should be able to receive concurrent H and RT. Further follow-up will provide more insight into the efficacy and safety of this approach.

References

[1] Liang et al. Mol Cancer Ther 2003;2:1113–20.
[2] Perez et al. J Clin Oncol (Meeting Abstracts) 2005; 23: 17 abs 556.