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Generalizability of survival estimates for patients with breast cancer – a comparison across two population-based series

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Background: Recently, attempts have been made to develop tools that generate more individualized and quantitative outcome estimates to aid in decision-making on adjuvant therapy in breast cancer. This is in line with a more general trend in many areas of medicine, where similar approaches for personalized and absolute, instead of relative risk assessments have been proposed.

Objective: The purpose of this study was to analyze the accuracy and transportability of survival estimates for patients with breast cancer by a comparison of outcome data in two population-based series.

Methods: We compared the influence of tumor size, grade, axillary nodal status, estrogen and progesterone receptor contents, and two prognostication schemes (the Nottingham Prognostic Index and St. Gallen's criteria) on outcome between two nationwide cohorts of breast cancer patients diagnosed in 1991–2, the FinProg (n = 2923, Finland) and the SEER series (n = 43,249, the United States).

Results: Eight-year estimates of breast cancer-specific (84% vs. 80%), relative (86% vs. 83%), and overall (70% vs. 69%) survival were slightly better in the SEER than in the FinProg series, respectively. However, after adjustment for the prognostic factors available, no signficant difference between the series remained. Despite differences in demographic variables, adjuvant therapies and mammography screening between the series, the prognostic factors examined produced close to overlapping survival curves with similar shapes between the series, and both prognostication schemes predicted outcome in a roughly similar fashion.

Conclusion: We conclude that quantitative survival estimates based on currently used prognostic factors and prognostication schemes are generalizable and transportable between large, unselected cohorts of breast cancer patients.

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Importance of HER2 and receptor status on the response to adjuvant radiotherapy in high-risk breast cancer – Results from the DBCG82 b&c randomized study

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The study was conducted on behalf of the Danish Breast Cancer Cooperative Group DBCG

Purpose: The DBCG82bc study showed that adjuvant radiotherapy (RT) improved survival in high-risk pts treated with mastectomy and systemic therapy. So far, pts and tumors have been described by classical clinical factors only (e.g. nodal status, tumor size) not by biological markers. However, the disease is heterogeneous and biological markers might describe the response to RT more precisely. The aim of this study was to evaluate the importance of adding information on markers such as estrogen receptor (ER), progesterone receptor (PR), and HER2.

Material: DBCG82bc included 3083 high-risk breast cancer pts, characterized by positive nodes and/or tumor size > 5 cm and/or invasion to skin or fascia. The present analysis included 1241 pts with 8+ lymph nodes removed. Based on paraffin embedded tumor samples, tissue microarrays have been constructed for 918 pts, so far. Successful immunohistochemical staining for ER was obtained in 892 pts, PR in 894 pts and HER2 in 870 pts. Endpoints were loco-regional recurrence as first event (LR), distant metastases (DM) and survival.

Results: Of the 918 pts, 468 pts were randomized to no RT and 450 to RT. LR was found in 134 pts and DM in 516 pts. Overall, RT resulted in a significant reduction in LR (Odds Ratio 0.14 (0.08–0.22, 95% cf.l.)), in DM (OR 0.73 (0.56–0.94)), and death (OR: 0.73 (0.55–0.97)). When combining ER and PR, 658 pts were either ER or PR positive (receptor positive) and 245 pts were both ER and PR negative (receptor negative). HER2 positivity (3+) was observed in 149 pts. Significantly fewer DM were found in pts randomized to RT as compared to no RT, for receptor positive pts (OR: 0.66 (0.49–0.90)) and HER2 negative pts (OR: 0.68 (0.51–0.92)). No difference in DM as a function of RT was seen for the receptor negative pts (OR: 0.97 (0.58–1.63)) and the HER2 positive pts (OR: 1.02 (0.52–2.02)). Cox multivariate analyses of the separate prognostic subgroups showed that RT was not significant for survival in pts with HER2 positive and/or receptor negative tumors, whereas it was important in pts with HER2 negative and receptor positive tumors (P = 0.03).

Conclusion: Postmastectomy RT caused a significant reduction in DM for pts with HER2 negative and receptor positive tumors. This reduction was, however, not found for pts with the poorest prognosis i.e. receptor negative and/or HER2 positive. More exploration in other biologically markers is needed to confine the indication for RT in high-risk breast cancer.

Thursday, 23 March 2006 14:15–16:00

SCIENTIFIC SESSION

Best use of targeted treatment

222 Invited

Overview of biotherapies: standards and new orientations

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In the last decade a new class of compounds targeting critical pathways for breast cancer cell proliferation, migration and survival, has been identified and tested in clinical trials.

Presently, one of these compounds (trastuzumab) has already taken a definite place in the practical management of breast cancer patients, while others have shown promising activity in phase II and phase III (bevacizumab) clinical trials.

This first generation of studies has also been useful to learn some "take home" messages for the development of future biotherapy trials:

1. the identification of molecular predictors of response would certainly help in defining the activity of these compounds. Trastuzumab has so far been the most successful compound because HER-2 gene evaluation allows for the characterization of the molecular profile of responding patients. A similar strategy could lead to the identification of molecular markers predicting the activity of other biotherapies. This would ultimately translate into a more targeted and cost-effective approach to breast cancer treatment;
2. molecular predictors of response to biotherapies are most frequently evaluated on primary tumor samples although biotherapies are first tested in clinical trials for metastatic breast cancer patients. The assumption is that tumor phenotype does not change over time, although tumor clone selection might occur under selective pressures played by systemic therapies administered for metastatic disease. The evaluation of molecular markers in circulating tumor cells collected immediately before starting a new treatment for advanced disease might represent an interesting strategy to be explored in the attempt to properly identify molecular predictors of response to biotherapies;
3. the first proof of clinical activity for biotherapies is still based on the assessment of objective response rates in phase II clinical trials, although tumor shrinkage might not be the most sensitive indicator of clinical activity for this new class of compunds. Additional methods defining the activity of biotherapies might complement the response rate information and might avoid the potential risk of underestimating the worth of new biotherapies. Positron Emission Tomography based on the use of apoptotic markers and Metabolomics might represent new technologies to be introduced in clinical trials in the attempt to improve our current method of tumor response assessment.

The implementation of these concepts into the next generation of clinical trials might lead to new findings in the field of biotherapies and might translate into a more appropriate use of new biotherapies in daily practice.

223 Invited

Searching new active compounds for breast cancer – evolution or revolution?

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In the past decade, a number of therapeutic targets in human breast cancer have been identified, and although hundreds of potential therapies have been discovered, metastatic breast cancer remains an incurable problem. The pace at which targeted therapeutic drugs reach the clinical setting is frustratingly slow. The challenge is in matching the appropriate drug to the

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.

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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.

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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.