improves the accuracy of noninvasive assessment of tumour dimensions. Ultrasound is the best predictor of size for axillary lymph nodes. Magnetic resonance imaging (MRI) is the most accurate imaging modality for the assessment of tumour response (size), the detection of multifocal or multicentric disease, and residual tumours after NC. Flattening of the contrast uptake time-intensity curve after the first chemotherapy cycle and complete absence of contrast uptake after the fourth cycle are observed in the responders. The patients with a concentric shrinkage pattern are good candidates for breast conserving surgery. H1 MR spectroscopy and nuclear imaging are very promising for identifying good responders early in the course of therapy (after one cycle). A low ratio of metabolic rate (18FDG-PET) relative to blood flow is a predictor of complete response. Nevertheless, all modalities are restricted in the imaging of very small residual tumour foci.

16 Proffered Paper Oral

Screening women with a familial or genetic predisposition to breast cancer: costs and effects of alternative screening policies

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Background: For the substantial proportion of women that have a more than average risk for breast cancer due to a familial or genetic predisposition, magnetic resonance imaging (MRI) is a promising screening tool. Estimates on breast cancer mortality reduction of screening these women are lacking, and randomized controlled trials are practically impossible.

Methods: In a prospective cohort study in 1952 women with increased breast cancer risk we estimated stage-specific sensitivity of different screening tests and resulting stage-shift by screen detection. Benefit of early detection was based on modeling estimates and pooled analyses of randomized mammography screening trials. We explored the effectiveness and cost-effectiveness of alternative screening policies for three cumulative lifetime (CLTR) risk categories: *BRCA1/2* mutation carriers (50–85% CLTR), a high-risk (30–50% CLTR) and a moderate-risk group (15–30% CLTR).

Results: Intensive surveillance including MRI in *BRCA1/2* mutation carriers is estimated to reduce breast cancer mortality by 50%, compared to 41% by mammography and clinical breast examination (CBE) only. Its effectiveness is almost twice as high compared to mammographic screening in women with population risk at 50. Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI from age 30 to 60 is at a cost of * 4314 per life-year gained (3% discounting). Offering MRI and mammography alternately at a 6 months interval is even more cost-effective. For the moderate-risk group, screening regimes with only mammography, alternating in combination with CBE, from age 40 to 50 years are most favorable in terms of cost-effectiveness (range * 3080–4764), and may lead to 25–31% breast cancer mortality reduction. Observed breast cancer incidence in the high-risk group did not differ substantially from the moderate-risk group. Waar zijn de low risks?

Conclusions: Addition of MRI in *BRCA1/2* mutation carrier surveillance is a very cost-effective screening policy, and should therefore be offered. For the moderate-risk category, intensive surveillance without MRI is defendable. Longer study follow-up is needed to advise a screening regime for the high-risk category.

Wednesday, 22 March 2006 14:15–16:00

SCIENTIFIC SESSION

How should we do phase II/III trials in the age of molecular biology?

17 Invited

When is a biological marker (or multimarker) ready to be tested in a clinical trial?

P.E. Lønning. *Haukeland University Hospital, Dept. of Medicine, Bergen, Norway*

Implementation of molecular biological parameters to test for therapy sensitivity may influence the way we are conducting clinical studies. So far the problem has been our limited knowledge about the mechanism controlling drug sensitivity in vivo. At this moment, only 2 predictive factors are used for therapy selection in breast cancer (BC); the estrogen receptor alpha (ER), and HER-2 amplification. Notably, these markers are also associated with breast cancer classification based on gene profiling in general [1], suggesting they both have a critical importance controlling tumor growth and behavior.

Yet while lack of ER and HER-2 expression signals non-responsiveness to hormonal manipulation and trastuzumab therapy respectively, patients expressing these parameters may still relapse despite optimal therapy, suggesting additional mechanisms of resistance to be involved. Considering chemoresistance in general, different attempts, including use of microarray techniques, have revealed gene profiles correlating to but not predictive of therapy responsiveness [2]. Considering individual markers, mutations in the TP53 gene as well as HER-2 amplifications have been associated with response to chemotoxics; however, none of these factors have revealed a sensitivity and predictivity sufficient for clinical implementations.

Clearly, there is a need for better predictive factors. The way forward probably lies in phase II neoadjuvant studies, in which proper tissue collection are made upfront and responsiveness to therapy carefully classified. There is actually little need to upfront hypothesize about individual predictive factors or array gene profiles predicting responsiveness. Assuming a time interval between editing a protocol and completion of patient data may last 3–5 years; most likely there will be a panel of novel potential predictive factors identified within that time interval. In this way, different phase II trials may identify and cross-validate the predictive value of individual as well as gene profile markers. Assuming resistance may be due not due disturbances in individual factors but rather disturbances in "functional pathways" [3], identification of certain markers may suggest other parameters involved up-/down-stream in the same pathways should be studied as well.

When is a parameter ready to be evaluated in a phase III study, selecting patients for individual therapy based on molecular profiling? This should mean some patients would be allocated to an experimental arm based on molecular testing and, as such, allocated away from standard therapy. In an ethical perspective however this is a decision not different from the ones we have been taking with respect to designing phase III trials in general; recent examples in breast cancer include trials evaluating aromatase inhibitors for adjuvant therapy. Thus, as soon we have sufficient evidence from phase II studies indicating expression of a particular marker may signal an experimental treatment approach to be advantageous, its clinical use should be confirmed in the phase III setting.

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18 Invited

Surrogate end-points: thick or thin ice?

H. Bonnefoi. *University Hospital of Geneva, Department of Gynecology and Department of Medicine, Geneva 14, Switzerland*

There is a long history of using surrogates in breast cancer research. For decades disease-free survival has been used as a surrogate for overall survival in studies assessing the efficacy of adjuvant treatment modalities

and is now considered as "thick ice". However its obvious weakness is that it takes time to be assessed and therefore does not accelerate the median time required for a new drug to be implemented (or not) in daily practice. Nowadays we have new surrogates that can be assessed within a few month time or even less. We will review critically the potential clinical utility of a selection of these new surrogates and mention planned or ongoing trials using these surrogates.

1. Pathological complete response after neo-adjuvant chemotherapy is now considered as a surrogate for survival. During our lecture we will discuss whether there is enough evidence to say that an increase of the pathological complete response rate will translate in a survival advantage. Using examples we will explain why we consider that pathological complete response should be used as a mandatory checkpoint in randomised clinical trials comparing chemotherapy regimens or chemotherapy regimens combined with "targeted therapies".

2. The IMPACT neo-adjuvant trial mimicked the ATAC adjuvant trial design (tamoxifen alone versus tamoxifen + letrozole versus letrozole alone). This trial have shown that patients on letrozole alone have a higher Ki67% change from baseline at 2 weeks than patients treated with tamoxifen alone or tamoxifen + letrozole). This biological change suggests that early biomarker changes may predict for long-term outcome (DFS) in the ATAC trial. This hypothesis was recently reinforced by the latest results of the IMPACT trial showing that Ki67 changes after 2 weeks predict for relapse-free survival after multivariate analysis. However this provide further support for the activation of biomarker studies assessing early biological changes using the in vivo preoperative model which can predict for long-term outcome. Such trials should be considered as research priorities in the era of new "targeted therapies" including anti-EGFR molecules.

3. A recently published meta- and pooled analysis have confirmed with a long-term follow up the independent prognostic value of disseminated tumour cells in bone marrow (DTC) at initial diagnosis. The potential clinical utility of DTC as a surrogate marker of therapeutic efficacy will be tested in a randomised intergroup (CGBMM and ABCSG) phase 2 study comparing anastrozole versus anastrozole + fulvestrant in patients with positive DTC at diagnosis. A bone marrow aspiration will be repeated at 12 months and 24 months.

19 Invited

Study design in the age of molecular biology

I.F. Tannock. *Princess Margaret Hospital, Medical Oncology, Toronto ON, Canada*

The optimal design of clinical trials for evaluating molecular targeted agents differs from that for evaluating chemotherapy. A classical phase 1 trial seeks to find the maximum tolerated dose (MTD) for a new drug and evaluates toxicity and pharmacokinetics in patients with cancer (of various types) for whom there is no known effective treatment. Patients agree to participate because of possible therapeutic benefit, although the probability of benefit is low. For molecular targeted agents, a phase 1 trial should only include subjects with the target of interest (to maintain the possibility of benefit) and the target dose should be that which inhibits the target in the tumour, rather than the MTD. Classical phase 2 trials determine if there is sufficient evidence of efficacy in subjects with a given type of cancer to warrant further evaluation of the new drug, and tumour response is the most frequent endpoint. Phase 2 trials of targeted drugs should again include only those whose tumours express the target, and ideally should also require studies to evaluate inhibition of the target. Response rate has been criticised as an endpoint for trials evaluating cytostatic biological agents, but tumours do shrink (because cells undergo apoptosis) following treatment with effective drugs (e.g. hormones) and stable disease or time to progression are unreliable endpoints (unless prolonged) because of measurement error. Phase 3 trials should remain pragmatic, with endpoints of patient benefit such as duration and quality of survival. Again patients should be selected for presence of the target molecular marker (as in the trials of trastuzumab) and at least a subset should be evaluated for inhibition of the molecular target. The optimal translational studies will require frequent biopsies and for ethical reasons these can only be requested when discomfort and the risk of complications are low. Many molecular agents will be used in combination with chemotherapy, and such combinations must also be evaluated in trials. A design in which both agents are given concurrently may be suboptimal (as shown for adjuvant tamoxifen and chemotherapy). Rather one might schedule cytostatic molecular targeted agents between courses of chemotherapy to avoid inhibiting the activity of cycle-active chemotherapy, and to inhibit selectively the repopulation of surviving tumour cells between courses of chemotherapy.

20 Proffered Paper Oral

Identification and validation of a genomic predictor to distinguish classes of patients with distinct outcomes among poor prognosis breast tumors after anthracycline-based adjuvant therapy

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The significant genetic heterogeneity among breast cancer patients is a primary obstacle to effective clinical diagnosis and management. Emerging technologies based on gene expression profiling (GEP) may provide clinically useful information. GEP has been used to refine classification of previously undistinguishable tumor subgroups, and predict prognosis and response to anticancer agents. Here we report a multicentric GEP analysis to identify and validate a predictor in order to improve tumor classification and predict clinical outcome of patients after standard anthracycline-based adjuvant chemotherapy.

504 patients with early breast cancer treated with adjuvant anthracycline-based chemotherapy were selected from IPC, CLB, IB, and from two prospective randomized therapeutical trials of adjuvant chemotherapy (FNCLCC: arm A of PACS01, and arms A and B of PEGASE01). Tumor RNAs were analyzed on 10K nylon cDNA microarrays. Metagenes for tumor classification were identified based on adjusted t-test analysis and hierarchical clustering on an identification set (IPC). A Cox-based method was applied to metagenes on an identification set of 323 patients to find predictors able to discriminate patients with favorable outcome (no metastasis) after chemotherapy. The stability and robustness of the model were assessed on an independent validation set (n = 181).

A predictor was identified on 323 patients treated with chemotherapy (anthracyclines). This predictor was based on a linear combination involving different metagenes, and allowed the computing of a metastatic score = $\Sigma(a_i \times \text{metagene}_i)$. This score separated two groups of patients with different outcome with respective 5-year MFS of 79% and 52% ($p < 0.0001$, log-rank test). The robustness of this predictor was then confirmed on a validation set of 181 patients, with respective 5-year MFS of 80% and 60% in the so-defined good-prognosis and poor-prognosis groups ($p = 0.01$, log-rank test). In multivariate analysis, our multigenic predictor compared favorably with other classical prognostic parameters.

Our metagene-based predictor is highly efficient to discriminate patients with unfavorable outcome after adjuvant anthracycline-based chemotherapy. It uses a validated combination of genes known for their biological relevance, and is valid irrespective of the clinical centre. Additional clinical studies and technical developments are ongoing to translate this new tool into a test designed for routine clinical practice.

Wednesday, 22 March 2006 14:15–16:00

SCIENTIFIC SESSION

Specific issues of radiotherapy after breast conserving surgery

21 Invited

Radiotherapy in early breast cancer: who does not need it?

A. Fourquet. *Institut Curie, Dept. de Radiothérapie, Paris, France*

In early breast cancers treated with surgery, large randomised trials and meta-analyses provided evidence of the strong effects of radiotherapy on the reduction of locoregional recurrences and breast cancer mortality. These trials showed also that a large proportion of patients who did not receive radiotherapy never experienced locoregional recurrences, either because of distant failures occurring before local recurrences, or because they were cured by surgery alone. Therefore, identifying these patients is a challenge for the radiation oncologists.

Predictors of local failure after surgery for breast cancer include age at diagnosis, grade, lymphovascular extension, proliferation, hormone receptor status, extent of intraductal component, tumor size, and axillary node involvement. Many of these factors are related. In addition, margins involvement and the extent of such an involvement is a predictor of local failure. In theory, a combination of favourable prognostic factors would help to select groups of patients who would not need radiotherapy. Various attempts were made, which failed to identify such subgroups where radiotherapy would not add a significant benefit to surgery. As