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?

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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