299 Poster

Breast cancer patients with negative hormone receptor tumours are less likely to relapse after 5 years of follow-up

R. Largillier[1], M. Prieto[1], J. Ferrero[1], M. Lallement[2], F. Ettore[3], C. Maestro[4], C. Chapellier[4], J. Hannoun-Levi[5], J. Machiavello[2], A. Courdi[5]. [1]*Centre Antoine-Lacassagne, Medical Oncology, Nice, France;* [2]*Centre Antoine-Lacassagne, Surgery, Nice, France;* [3]*Centre Antoine-Lacassagne, Pathology, Nice, France;* [4]*Centre Antoine-Lacassagne, Radiology, Nice, France;* [5]*Centre Antoine-Lacassagne, Radiotherapy, Nice, France*

Purpose: To identify subgroups of breast cancer patients who are less prone to relapse after 5 years of follow-up with no evidence of disease (NED), in order to consider less frequent examinations.

Patients and Methods: Out of 4404 breast cancer patients operated in our institution between June 1973 and December 2003, 2678 patients who were free of disease 5 years after surgery were included in this study. Almost half the patients had conservative surgery. Radiotherapy was given to all patients after conservative surgery and to high risk patients after mastectomy. Adjuvant medical and hormonal treatment was given according to the policy of the institution at the time of patient presentation. The endpoint was local, regional or distant relapse. The median follow-up was 110 months. Patient age, tumour grade and size at operation, axillary lymph node (ALN) status and hormone receptors (HR) were considered.

Results: Compared to the whole population, patients with NED at 5 years had negative HR tumours in a lower percent: 17.1% vs 19.1% (p = 0.048), had less frequent positive ALN: 35.1% vs 40.0% ($p < 10^{-4}$), and less grade 3 tumours: 11.8% vs 14.3% (p = 0.003). The 10-year actuarial disease-free survival (DFS) was 84%. Significantly better 10-year DFS was observed in patients aged above 40 (84.6% vs 77.5% for younger patients), in ALN negative tumours (87.4% vs 78.4% for positive ALN), in patients with pT1 tumours (87.0% vs 79.9% for bigger tumours) and in HR-negative tumours (86.8% vs 83.3% in HR-positive). The multivariate analysis yielded a hazard ratio of 0.50 for HR-negative tumours (p = 0.0002), a value of 0.70 for ALN-negative tumours (p = 0.0003) and 0.72 for pT1 tumours (p = 0.0007).

Conclusion: Breast cancer patients with negative HR tumours and with NED at 5 years have 50% less risk to relapse later on than patients with HR-positive tumours, suggesting that this factor is of concern only in the early years of follow-up, thus raising the possibility of loosening long-term follow-up in these patients. Moreover, extension of hormonal therapy beyond 5 years could be an option for patients with HR positive pT2 tumours or bigger, or positive ALN.

Thursday, 23 March 2006 16:00–16:45

POSTER SESSION

Molecular biology, markers

300 Poster

Robust identification of novel prognostic gene-signatures in breast cancer

A. Naderi[1], A.E. Teschendorff[1], N.L. Barbosa-Morais[1], J.F.R. Robertson[3], I.O. Ellis[2], J.D. Brenton[1], C. Caldas[1]. [1]*Hutchison/MRC Research Centre, Oncology, Cambridge, United Kingdom;* [2]*Nottingham City Hospital NHS Trust and University of Nottingham, Histopathology, Nottingham, United Kingdom;* [3]*Nottingham City Hospital NHS Trust and University of Nottingham, Medical and Surgical Sciences, Nottingham, United Kingdom*

Background: Breast cancer predictive signatures derived from microarray expression profiling have been reported by two independent groups. Surprisingly there were only three overlapping genes between these signatures, making immediate clinical application problematic.

Methods: We performed microarray expression profiling of 135 early-stage breast tumors, from a cohort representative of the demographics of breast cancer seen in clinical practice and with a median follow-up of 11 years.

Results: Using Cox-clustering and a genetic algorithm method we identified prognostic signatures of 70 and 90 genes that correlated with survival with hazard ratios of 5.97 (95% CI: 3.00–11.89, p = 2.7e-07) and 12.49 (95% CI: 6.22–25.07, p = 9.6e-12), respectively. In multivariate analysis the signatures were powerful independent predictors and performed significantly better than standard prognostic classifiers such as the Nottingham Prognostic Index and the "Adjuvant!" software. The derived signatures also predicted outcome in all clinical subgroups including post-menopausal women. Crucially using two independent methods the signatures performed well in predicting outcome in two large external datasets despite differences in methodology (Table). Moreover there was a subset of 29 genes associated with survival (Cox p value <0.05) in both our cohort and the two external datasets (representing a total of 715 patients).

Performance of gene-signatures across different data sets.

Signature	Naderi *et al.*	Vijver *et al.*	Wang *et al.*
Cox-ranked	5.8 (p = 9e-9)	3.98 (p = 2e-9)	1.76 (p = 0.005)
GA-ranked	12.5 (p = 9e-12)	3.82 (p = 5e-8)	2.45 (p = 4e-6)
Wang 76g	2.2 (p = 0.02)	2.18 (p = 0.001)	2.19 (p = 6e-5)
Veer 70g	1.02 (p = 0.94)	11.4 (p = 8e-10)	1.6 (p = 0.03)

Hazard Ratios and p values for each signature are given. GA: Genetic Algorithm

Conclusions: The expression-signatures reported here are significant predictors of outcome in breast cancer and for the first time external validation supports the reliability of the results. The majority of genes in the signature are involved in proliferation and mitotic regulation and are candidates for testing in prospective studies to confirm their predictive value. Discovery of further prognostic gene signatures will require prospective studies and robust gene expression platforms that can be used in confirmatory trials.

301 Poster

Ki67 values measured at 2 weeks post treatment predict relapse free survival in a randomized trial of neo-adjuvant endocrine therapy (IMPACT)

M. Dowsett[1], R. A'Hern[2], G. Walsh[3], I. Smith[4]. [1]*Royal Marsden NHS Trust, Academic Department of Biochemistry and Breast Un, London, United Kingdom;* [2]*Institute of Cancer Research, Clinical Trials and Statistics Unit, Sutton, United Kingdom;* [3]*Royal Marsden NHS Trust, Breast Unit, London, United Kingdom;* [4]*Royal Marsden NHS Trust, Medicine, London, United Kingdom*

A short term biological marker that can predict long-term outcome on a particular therapy for early breast cancer could markedly speed drug development and possibly help select individualised patient treatment. We have shown in the IMPACT trial that Ki67 after 2 weeks was significantly lower in patients treated with anastrozole (A) than with tamoxifen (T) or the combination (C), a result that was parallel to the greater recurrence free survival (RFS) with A in the large ATAC adjuvant trial, but 2-week Ki67 was only poorly associated with clinical response. We therefore assessed whether 2-week Ki67 was associated with RFS in the IMPACT trial.

Methods: The IMPACT trial was a randomized double-blind multicentre neoadjuvant trial of 12 weeks A vs T vs C in 330 postmenopausal women with ER/PgR+ve primary operable breast cancer. Ki67 measurements were available baseline (n = 231), 2 weeks (n = 158) and 12 weeks (n = 208). Response rate was the primary endpoint of this trial, the current study of RFS was therefore an exploratory analysis. Median follow-up was 37 months and nearly all patients received the same treatment as adjuvant therapy post-surgery for an estimated median duration of 31 months.

Results: A total of 26 relapses were observed in the patients with Ki67 measured at 2 weeks. On univariate analysis 2 week Ki67 was significantly associated with RFS (hazard ratio 2.13; 95%CI: 1.45–3.13, p < 0.001) for log(2 week Ki67). The corresponding hazard ratio at baseline was 1.94 (CI: 1.17–3.24, p = 0.01), and for response (vs none) at 12 weeks it was 0.34 (CI:0.15–0.80, p = 0.01). The following factors were considered for inclusion in a multivariate analysis incorporating the 2 week Ki67 value: Ki67 at baseline; clinical tumour size at baseline; clinical nodal status at baseline; ER status at baseline and 2 weeks and apoptosis score at baseline and 2 weeks. Significant independent predictive factors were Ki67 at 2 weeks, clinical tumour size at baseline and ER status at 2 weeks. If Ki67 at 2 weeks was replaced by Ki67 change (log(Ki67:2 weeks/baseline)) in this analysis the multivariate hazard ratio for the latter was 1.40 (95%CI: 0.95–2.09, p = 0.09).

Conclusion: Despite the small number of relapses so far, 2 week Ki67 was a significant predictor of relapse free survival in this exploratory analysis. This provides further support for Ki67 being a marker of treatment benefit after short-term pre-surgical endocrine therapy.