480 Poster

Prediction of brain relapse by gene expression analysis in HER2-positive metastatic breast cancer patients

R. Duchnowska[1], J. Jassem[2], C. Szczylik[1], G.W. Sledge Jr.[3], L. Li[4], B. Czartoryska-Arlukowicz[5], B. Radecka[6], K. Sosinska[2], P. Steeg[7], S. Badve[8]. *[1]Military Institute of Medicine, Department of Oncology, Warsaw, Poland; [2]Medical University, Department of Oncology and Radiotherapy, Gdansk, Poland; [3]Indiana University, Department of Medicine, Indianapolis, USA; [4]Indiana University, Division of Biostatistics, Indianapolis, USA; [5]Regional Cancer Center, Department of Oncology, Bialystok, Poland; [6]Regional Cancer Center, Department of Oncology, Opole, Poland; [7]National Cancer Institute, Laboratory of Molecular Pharmacology, Bethesda, USA; [8]School of Medicine, Department of Pathology and Laboratory Medicine, Indianapolis, USA*

Background: Brain relapse is a common occurrence in HER2 positive breast cancer patients. We earlier demonstrated that clinical and pathological factors may select HER2 positive metastatic breast cancer patient categories with particularly high risk of brain relapse (*EJC Suppl* 2006;4,165−6). In the present study we explored whether early occurrence of brain relapse in HER2 positive metastatic breast cancer patients may be predicted by gene expression analysis.

Materials and Methods: Study group included 90 HER2 positive metastatic breast cancer patients, 43 of whom developed brain relapse after a median of 3 years from diagnosis: 22 and 21 patients with brain relapse at <3 vs >3 years from diagnosis, respectively. Expression of 502 known cancer genes was investigated with cDNA-mediated annealing, selection, extension and ligation (DASL) assay (Illumina Corp). RNA (200 ng) was extracted using HighPure RNA Paraffin Kit (Roche Applied Bioscience) from archived formalin-fixed, paraffin-embedded tumor tissues. RNA was pre-qualified using iScript (Bio-Rad) to reverse transcribe. Quantitative PCR was performed using SYBR Green Master Mix (Applied Biosystems). T-test with unequal variances was applied after sample median normalization. Differentially expressed genes were analyzed using Ingenuity Pathway Analysis.

Results: Among the analyzed genes, 95 were differentially expressed with a p-value <0.05. (false discovery rate = 0.25) and 48 with a p value <0.01 (false discovery rate = 0.1) in patients who developed brain relapse at <3 vs >3 years from diagnosis.

Conclusions: Occurrence of early brain relapse in HER2-positive metastatic breast cancer patients is associated with expression of numerous genes in tumor tissue. Analyses are ongoing to generate a gene-expression signature allowing prediction of brain relapse.

481 Poster

The Genomic Grade Index (GGI) – a potential predictor of relapse for endocrine-treated breast cancer patients in the BIG 1-98 trial

C. Desmedt[1], A. Giobbie-Hurder[2], P. Neven[3], R. Paridaens[3], M.R. Christiaens[3], A. Smeets[3], F. Lallemand[1], M. Piccart[1], R. Gelber[2], C. Sotiriou[1]. *[1]Institut Jules Bordet, Medical Oncology, Brussels, Belgium; [2]Harvard School of Public Health, IBCSG Statistical Center, Boston, USA; [3]Katholieke Universiteit Leuven-Gasthuisberg, Multidisciplinairy Breast Center, Leuven, Belgium*

Background: We have previously shown that the GGI was able to identify two subtypes of ER-positive tumors that were associated with statistically distinct clinical outcomes in tamoxifen-treated patients. Here, we aim to investigate the ability of the GGI to predict relapses in postmenopausal women with hormone receptor-positive breast cancer who were treated with tamoxifen (T) or letrozole (L) within the BIG 1-98 trial.

Methods: We generated gene expression profiles using Affymetrix and computed the GGI for a matched, case-control sample of frozen tissue specimens of patients participating in the BIG 1-98 trial from the two Belgian hospitals where frozen samples were available. All relapses (cases) were identified from patients randomized to receive either monotherapy or from the switching treatment arms for whom relapse occurred before the switch. Each case was randomly matched with four controls based upon nodal status and treatment (T or L). The prognostic value of GGI upon relapse was assessed using Cox models with GGI as a continuous predictor and divided at the median. Predictive accuracy of GGI was estimated using time-dependent area under the curve (AUC) of the ROC curves (100% = perfect classification, 50% = no discrimination).

Results: Frozen samples were analyzable for 48 patients (10 cases and 38 controls). Seven of the 10 cases had been assigned to receive L at the time of trial enrollment. Cases and controls were comparable with respect to menopausal and nodal status, local therapy, HER2 over-expression, and adjuvant or neoadjuvant chemotherapy. Cases were slightly older than controls and had a larger proportion of large, poorly differentiated ER-positive/PgR-negative tumors. Higher values of GGI were associated with a significant increase in the hazard of relapse, with each 10-unit increase resulting in an 11% increase in the hazard rate (HR = 1.11, 95% CI 1.03 to 1.21). Within the subgroups of patients with node-positive disease or who were randomized to treatment with L, the hazard of relapse was significantly greater for patients with GGI at or above the median. AUC reached a maximum of 78% at 27 months.

Conclusions: This analysis supports the GGI as a good predictor of relapse, even among patients who receive L. Validation of these results, in a larger series from BIG 1-98, is planned using the simplified GGI represented by only four genes and tested by RT-PCR on paraffin-embedded formalin-fixed tissues.

482 Poster

Is it possible to identify parameters that predict nipple–areola complex involvement in breast cancer patients

N. Djordjevic[1], A. Karanikolic[1], L. Djordjevic[1], D. Budjevac[1], J. Paravina[1]. *[1]General surgery, Breast Surgery, Nis, Serbia*

Introduction: A clinically normal-appearing nipple in patients with breast cancer may contain unsuspected neoplastic cells. Preservation of a nipple containing occult malignancy could potentially increase local recurrence rates and affect disease-free survival. Consequently, patients considered for breast conservation operations with nipple preservation must be carefully selected.

Materials and Methods: Information available on 382 patients diagnosed and treated with breast cancer at the Clinical Center Nis from 2000 to 2003 were retrospectively reviewed. Multivariate hazard analyses was used to assess the association between potential risk factors of cancerous nipple involvement.

Results: The frequency of nipple involvement was 12.04%. Nearly half of the patients had disease stage III and IV. Most patients, 29 (63.04%), had a tumor to nipple distance of less then 2 cm. Twenty-five patients (54.34%) had more than four positive axillary nodes. A central/overlap tumor location was present in 28 (60.87%) patients. Cox multivariate analysis of prognostic factors showed that Stage III, central/overlap tumor location and nuclear grade III or greater had a statistically significant effect on malign nipple involvement.

Conclusions: The multivariable model used in this study showed a significant association between stage, centrally located tumors and nuclear grade III or greater in predicting the risk of cancerous nipple involvement. Preoperative magnetic resonance imaging or computed tomography scan examinations are recommended for treatment planning of breast cancer, in particular nipple preserving surgery in patients with central/overlap tumor localization and with a tumor to nipple distance of less than 2 cm.

Friday, 18 April 2008 12:30–14:30

POSTER SESSION

Response and outcome prediction

483 Poster Discussion

The influence of Lympho Vascular Invasion (LVI) on local (LR) and regional recurrences (RR) and survival: an ONCOPOOL study

M. Sundquist[1], R.W. Blamey[2], G.R. Ball[3], M. Blichert-Toft[4], L. Cataliotti[5], I.O. Ellis[6], R. Jakesz[7], M. Kerin[8], I. Monypenny[9], A. Oates[10], on behalf of the ONCOPOOL Consortium[11]. *[1]ONCOPOOL, Surgery, Kalmar, Sweden; [2]Nottingham City Hospital, Breast Institute, Nottingham, United Kingdom; [3]Nottingham University, Breast Institute, Nottingham, United Kingdom; [4]ONCOPOOL, Surgery, Copenhagen, Denmark; [5]ONCOPOOL, Surgery, Florence, Italy; [6]Nottingham City Hospital, Pathology, Nottingham, United Kingdom; [7]ONCOPOOL, Surgery, Vienna, Austria; [8]ONCOPOOL, Surgery, Dublin, Ireland; [9]ONCOPOOL, Surgery, Cardiff, United Kingdom; [10]Nottingham City Hospital, Data Managment, Nottingham, United Kingdom*

Introduction: This report is of the effect of Lympho Vascular Invasion (LVI) on Survival and on Local and Regional recurrences in 5997. LN neg and 1−3 pos cases from ONCOPOOL in which LVI data had been recorded.

Patients and Methods: ONCOPOOL is a dataset (n = 17,653) of primary breast cancers diagnoses in the 1990's from 12 European units. LVI measured on Histology has been recorded in 5997 of these and compared