336 Poster

Retrospective CYPTAM-BRUT 1 Study Shows Association Between the Genetic Variants Rs1800716 and Rs727479 in Tamoxifen Metabolisation and Tamoxifen-induced Increase in Double Endometrial Thickness

A.S. Dieudonné[1], D. Lambrechts[2], D. Smeets[2], A. Belmans[3], H. Wildiers[4], C. Hyonil[1], D. Timmerman[1], M.R. Christiaens[4], I. Vergote[1], P. Neven[4]. *[1]University Hospitals Leuven, Gynaecology and Obstetrics and the Leuven Cancer Institute, Leuven, Belgium; [2]Catholic University Leuven, Vesalius Research Center and VIB, Leuven, Belgium; [3]University Hospitals Leuven, Interuniversity Center for Biostatistics and Statistical Bioinformatics, Leuven, Belgium; [4]University Hospitals Leuven, Multidisciplinary Breast Center, Leuven, Belgium*

Background: Tamoxifen remains an important treatment in breast cancer. Its endometrial effect after menopause is estrogen-like, leading to hyperplasia, cysts, polyps and an increased endometrial cancer risk. Tamoxifen is metabolized to the more active endoxifen through cytochromeP450 enzymes. Genetic variants that affect the metabolisation and lead to lower endoxifen levels have been identified. Prospective studies are ongoing to elucidate their role on efficacy. We here assessed the influence of variants on the tamoxifen-induced increase in double endometrial thickness (DET).

Materials and Methods: Postmenopausal women at least 3 months on tamoxifen 20 mg daily were selected if there was at least 1 DET measurement registered in the gynaecology ultrasound database between 01/2000 and 08/2009. Germline DNA samples were analyzed using the Sequenom® platform. A total of 32 variants for CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A5 and CYP19 were genotyped. According to the present alleles, a phenotype was assigned. The association between variants and outcome (DET >5 mm) was assessed by means of a proportional hazards regression for interval censored data, whereby DET >5 mm was assumed to have occurred in the interval between the last ultrasound with DET <5 mm and the first with DET >5 mm.

Results: Of the 298 women retained from the database, DNA was available for 168 women; 42 with DET <5 mm on all ultrasounds and 126 with DET >5 mm on at least 1 ultrasound.

Rs1800716 (CYP2D6) and rs727479 (CYP19) showed a statistically significant association with DET. For rs1800716, hazard ratios were 2.750 (95% CI 0.970;7.827) and 1.724 (95% CI 1.151;2.581) for homozygous mutant (HM) vs homozygous wildtype (HW) women and heterozygous (HET) vs HW women respectively, with HM and HET women having an increased chance of having DET >5 mm. The p-value for the overall association was 0.01, however the false discovery rate (FDR) was 0.181. For rs727479, hazard ratios were 1.942 (95% CI 0.964; 3.906) and 0.773 (95% CI 0.515; 1.161) for HM vs HW women and HET vs HW women respectively, with HW and HET women showing a decreased chance of having DET >5 mm. The p-value for the overall association was 0.03, however FDR was 0.279. There was no statistical evidence that any of the phenotypes was associated with an increased DET.

Conclusions: Rs1800716 (CYP2D6) and rs727479 (CYP19) are associated with an increased chance of having DET >5 mm in women on tamoxifen. However FDR are high and the findings will be validated in a prospective study.

337 Poster

The Relationships of Lymph Node Ratio to Recurrence and Survival According to Molecular Subtypes of Breast Cancer

M.Y. Choi[1], S.K. Lee[1], S. Kim[1], J.Y. Kim[1], J.H. Lee[1], S.P. Jung[1], W.H. Kil[1], Y.L. Choi[2], J.E. Lee[1], S.J. Nam[1]. *[1]Samsung Medical Center Sungkyunkwan University School of Medicine, Surgery, Seoul, Korea; [2]Samsung Medical Center Sungkyunkwan University School of Medicine, Pathology, Seoul, Korea*

Background: Previous studies suggest that nodal ratio (metastatic/excised lymph nodes) may have prognostic value in breast cancer. In this study, we evaluated cutoff values of the lymph node ratio (LNR) and compared the impact of LNR on disease-free survival (DFS) and overall survival (OS) in each molecular subtype of patients with that of N stage.

Materials and Methods: We reviewed the medical records and pathological slides of 666 breast cancer patients with metastatic axillary lymph nodes who underwent surgical treatment at the Samsung Medical Center in Korea, from January 1995 to December 2003. Molecular subtypes were defined by estrogen receptors (ER), progesterone receptors (PR) and HER2 expression status.

Results: Out of the 666 patients, 55.3% were luminal A type (ER+ or PR+, HER2−); 12.9% were luminal B type (ER+ or PR+, HER2+); 11.3% were HER2 type (ER−, PR−, HER2+); and 20.6% were triple-negative (TNBC) type (ER−, PR−, HER2−). The median follow-up duration was 8.1 years. The significant LNR cutoff values that have an effect on the DFS and OS rates were different from in each group.

Conclusions: LNR may be a more significant factor for predicting of DFS and OS than N stage in each molecular subtype of breast cancer.

338 Poster

A Metabolomic Approach to Breast Cancer Prognostication

A. Sonkar[1], A. Raj[1], S. Srivastava[2], J.K. Kushwaha[1], R. Roy[2], N. Husain[3]. *[1]CSM Medical University (King George's Medical University), Surgery, Lucknow, India; [2]Center of Biomedical Magnetic Resonance, Center of Biomedical Magnetic Resonance, Lucknow, India; [3]RML Institute of Medical Sciences, Pathology, Lucknow, India*

Background: The poor prognostic factors in breast cancer identified on histopathology include perineural invasion, lymphovascular invasion, number of lymph nodes involved, size of tumour, involvement of skin, etc. In the present study an attempt has been made to identify metabolic changes discriminating in favour of malignancy by ^{1}H nuclear magnetic resonance(NMR) spectroscopy of malignant nerves, veins, skin and lymph nodes.

Material and Methods: The current study is a prospective correlation between ex-vivo HR MAS(High Resolution Magic Angle Spin) spectroscopy with histopathology in different breast cancer tissue specimens. Tissue specimens (n = 119) were obtained from 25 patients who were enrolled with a written consent to participate in the study. Tissue samples comprising of breast carcinoma, lymph nodes, veins, arteries, nerve, skin and corresponding non-involved tissues were sampled during surgical excision. All these tissue samples were stored at −80ºC till the NMR experiments were performed. The NMR experiments were performed at 80C on a Bruker Fallandan Switzerland 400 MHz FT NMR spectrometer equipped with a 4 mm 1H/13C HR-MAS dual probehead. After spectroscopic analysis, the tissue samples were initially fixed in 10% formalin, and were further embedded using paraffin. Tissue sections of 5 mm at 100 mm intervals were taken and stained using haematoxylin and eosin for assessment of malignancy. The NMR data from 25 patients (119 tissue specimens) were subjected to Principal Component Analysis(PCA) using (lsquo;The Unscrambler X' Software package.

Results: The NMR spectrum of various malignant tissues showed significantly increased levels of glycine, lactate, creatine, taurine, choline, glutamate, alanine and phosphocholine and decreased levels of fatty acids and lipids as compared to tissue found to benign on histopathology. The metabolic Nuclear Magnetic Resonance analysis could predict perineural invasion, lymphovascular tumour embolization and skin involvement.

Conclusions: In the present study ^{1}H NMR analysis could differentiate malignant from non invaded nerve, vein, skin and lymph node with high sensitivity and specificity. Present study has shown potential in prognosticating breast cancer hitherto done by histopathology with added advantage of being faster and without human and tissue processing error.

339 Poster

Participation in Clinical Trials is an Independent Prognostic Factor of Breast Cancer Treatment

N. Lukavetskyy[1], B. Bilynskyy[1], Y.A. Shparyk[2], T. Kachmar[2]. *[1]Lviv Medical University, Oncology Department, Lviv, Ukraine; [2]Lviv Cancer Center, Chemotherapy Department, Lviv, Ukraine*

Background: In addition to the classical clinical prognostic factors of breast cancer, participation in clinical trial has played a significant role in the prognosis of patients. These studies focused on influence of participation in clinical trials in patient's prognosis.

Methods: The present study is a retrospective review of the data of 7693 breast cancer patients treated in the Lviv Regional Cancer Centre within the period 1999 to 2010. Of these, 562 patients (7.3%) were included in 33 clinical trials (phases 1−3 randomised international clinical trials). Among all clinical trial we selected 1 finished trial (by the method of casual selection) for detailed analysis of patient's data. An additional prerequisite in trial selections was IV stage of breast cancer at the moment of screening.

Results: There were 42 women who formed population for the following analyses (had received supportive therapy treatment). The study group was divided into 23 women with history of previous clinical trial participation and 19 women without this history. Screen time was December 2006 and trial status is ongoing at this moment. By 1.12.2010 31 of the 42 patients had already died. 11 patients, survived for more 4 years. Among the 11 survivors eight have trial history and three haven't. In trial history subgroup the 3-year survival rates were higher than those seen in patients without trial history (study treatment is ongoing).

Conclusions: Participation in clinical trial is a independent prognostic factor of breast cancer treatment. Careful randomized prospective study will be required to validate these results in large population.