Of these, 8 had inoperable or metastatic disease at presentation and a further 17 developed locally advanced or metastatic disease.

16 received an aromatase inhibitor. (9 anastrazole, 5 letrozole, and 2 exemestane).

13 patients received tamoxifen prior to an aromatase inhibitor. 15 patients received AI as either a first or second line therapy.

Duration of AI therapy was assessable in 14 patients. The median duration of aromatase inhibitor therapy was 17 weeks (1−90 weeks) and 6 patients (43%) remained on therapy beyond 24 weeks.

7 patients (47%) on AI had no documented clinical or radiological benefit and had therapy discontinued at the first review.

When comparing those who had a documented response to AI compared with those who never responded, responders were older (median age of 72.5 years (95% CI 69.9–75.1) vs. 64 years (95% CI 59.3–68.7)) and more likely to have recived prior anthracycline based chemotherapy (37.5% vs 14%).

Conclusions: Response rates to aromatase inhibitors in men are lower than would be expected in a similar population of women. Women receiving anastrazole after tamoxifen had a median time to progression is reported as 21 weeks compared to 17 weeks in our cohort (Buzdar 2001). 43% of patients were felt never to have had a clinical or radiological response to AI.

More clinical studies are required to establish why some male breast cancer patients respond to AI but the differences between responders and non-responders suggest testicular function may play a role.

Testicular function is known to decrease with age and patients responding to AI were older on average and a greater percentage of patients responding to AI had prior anthracycline chemotherapy. This case series supports the use of aromatase inhibitors in selected male breast cancer patients but there is still a need for further research into the cellular mechanisms of male breast cancer and the role of testicular steroid hormone production in AI resistance.

References

Buzdar, et al 2001 Phase III, Multicenter, Double-Blind, Randomized Study of Letrozole, an Aromatase Inhibitor, for Advanced Breast Cancer Versus Megestrol Acetate. Journal of Clinical Oncology 19(14): 3357−66.

Thursday, 22 March 2012 12:30–13:30

POSTER SESSION

Molecular Biology, Tumour Biology and Immunology

262 Poster discussion

MMP11 Expression Increases During Progression of Breast Cancer

T. Fehm[1], S. Schultz[1], K. Sotlar[2], K. Petat-Dutter[2], M. Bonin[3], S. Poths[3], H. Seeger[1], D. Wallwiener[1], H. Neubauer[1]. [1]*University of Tuebingen, Department for Gynecology and Obstetrics, Tuebingen, Germany;* [2]*Ludwig-Maximilians-University Munich, Institute for Pathology, Munich, Germany;* [3]*University of Tuebingen, Microarray Facility Tuebingen, Tuebingen, Germany*

Background: The ductal carcinoma *in situ* (DCIS) of the breast is considered to be the pre-invasive form of the invasive duct carcinoma (IDC). The aim of this project is (1) the identification and validation of potential progression markers and (2) to identify markers for high risk DCIS with aggressive potential. MMP11 (matrix-metalloproteinase 11) is a marker for the transition from DCIS to IDC. It is associated with tumour cell invasion and a poor clinical outcome.

Material and Methods: 15 formalin fixed and in paraffin embedded (FFPE) tissue samples with a 'pure' DCIS without IDC component (patients were at least five years free of cancer), and 15 paraffin tissue samples with DCIS/IDC tumours were selected. Tissue sections were prepared, stained with hematoxylin-eosin and the epithelial cells were isolated by laser capture microdissection (LCM). 200 ng RNA were extracted, hybridized to the Whole Genome DASL Array (Illumina) and bioinformatically evaluated. The RNA was linear amplified using the Ribo-SPIA® technology (WT-Ovation™ FFPE System, NuGen™) and the validation was done by qRT-PCR using the LightCycler® 480 System (Roche).

Results: We were able to identify 993 transcripts that are differentially expressed between DCIS and IDC of the same tumour and 1138 transcripts which are differentially expressed between 'pure' DCIS and DCIS/IDC tumours. Differential expression was validated for 9 transcripts using two sample sets, the technical validation sample set (15 DCIS/IDC tumours, 15 'pure' DCIS) and an independent validation sample set (26 DCIS/IDC tumours, 17 'pure' DCIS). MMP11 is highly expressed in IDC and moderately expressed in DCIS with IDC component. In 'pure' DCIS less or no expression of MMP11 was determined.

Conclusions: We identified progression-specific candidate transcripts using LCM and microarray analysis from FFPE breast cancer tissues. MMP11 is a progression marker which differentiates between high and low risk DCIS.

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Computational Prioritization of NsSNP's Involved in Causing Breast Cancer in Human

A. Kumar[1]. [1]*VIT University, School of Biosciences and Technology, Vellore, India*

Breast cancer is counted among the most common invasive and fatal cancer's in women. It has been reported to cause 458,503 deaths worldwide in year 2008. Therefore the in-depth scientific research is important to gain complete information regarding the molecular pathway related to this disease and to discover the effective pharmacological treatment. We used computational approach to identify the SNPs involved in causing breast cancer. In order to identify the possible locus of tumorigenic mutations we analyzed 535 nsSNPs in 20 candidate genes (BRCA1, BRCA2, CDH1, CHEK2, DIRAS3, ERBB2, MYC, CCND1, TRIM37, APPBP2, TRAP240, RAD51C, BCAS3, PTEN, STK11, TP53, AR, ATM, RB1CC1, AKT1, BARD1, PALB2, RAD51L1, NQO1, NQO2, RAF1, ZNF217, TGFB1, TOX3, CYP1A1, CASP8, HMMR, LSP1, RAD51 and MAP3K1) taken from journals and publications based on the case control studies. Using evolutionary conservation analysis and statistical potential energy function evaluation algorithm we prioritized 171 SNPs that were predicted to be damaging. Further using Support Vector Machine based classifier we selected 63 nsSNP's that were reported to be extremely deleterious and could be the possible cause of inducing cancers in human breast region. Among these 63 variants 12 were reported to distrupt the lignad binding site and 7 lead to the overpacking at the burried regions. Molecular Dynamic Simulation of native and mutant proteins were carried out to analyze the structural dependency of the mutants tumorigenic property. The clear variation in the RMSD (Root Mean Square Deviation) values were observed in all the 19 variants which accounts for the loss of proper signal transdution in the cellular pathways which may induce the oncogenicity leading to Cancer. To study the pathway based dependencies of these mutations we used Ordinary Differential Equation and Boolean Algebra to understand the mutation induced relative variation in the rate of activation of phosphorylases and kinases mediated cell divisons. Genetic algorithm is used to predict the unknown concentration of the involved proteins, ligands and enzymes in the native and mutant pathway conditions. These findings will facilitate the understanding of the involvement of nsSNP's in causing breast cancer in human.

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Mitochondrial DNa Mutations and Copy Number Alteration in Breast Cancer Patients From Romania

C. Rusanu[1], A. Botezatu[1], I. Iancu[1], I. Huica[1], A. Plesa[1], G. Anton[1]. [1]*"Stefan S. Nicolau" Institute of Virology, Molecular Biology, Bucharest, Romania*

Background: Breast carcinoma is one of the most common types of malignancy worldwide and the leading cause of mortality from cancer among Romanian women. Mutations in mitochondrial DNA (mtDNA) as well as alterations in mtDNA content have been reported in numerous cancers examined. However, it still remains unclear whether the alterations in mtDNA are related to the clinicopathological features and/or the prognosis in breast cancer.

Material and Methods: Total DNA (nuclear and mitochondrial) was isolated (High Pure PCR Template, Roche Diagnostics) from breast cancer and paired normal breast tissues originating from 40 Romanian patients. Somatic mutations in the D-loop region (4,977-bp deletions) were investigated using Mutector mtDNA kit (TrimGen Corporation). MtDNA copy number was quantified using a one-step quantitative multiplex real-time PCR. A FAM labeled probe and primers were used to amplify the mtDNA sequence of the ATP 8 gene, and a VIC labeled probe and primers were designed to amplify the beta-globine gene.

Results: MtDNA copy number in stage I breast cancer patients was significantly lower than in other stages ($P = 0.0015$). A reduced mtDNA copy number was found often in post menopausal cancer group ($P = 0.024$). The study revealed no difference in mtDNA content related to age ($p = 0.255$) or lymph node involvement ($p = 0.173$).

We failed to detect any mtDNA mutations in normal breast tissue specimens. 16.66% of stage I breast cancer patients presented mutations in D-loop region whereas 28.57% of stage II cases showed mutations in mtDNA. 4,977-bp deletions were detected in 66.66% cases of stage III cancer cases.