Results: A total of 136 cases of MM were identified, with an overall incidence of 1.3/100,000. Men had a higher incidence rate compared to women (1.47/100,000 vs 0.2/100,000, respectively), and a higher median age at diagnosis (70 vs 64 years, respectively).69% of all patients had documented asbestos exposure and 78% had a positive smoking history. The distribution of MM per anatomical site was 87% pleural, 12% peritoneal and 1% unspecified (testicular). The most common presenting symptoms were shortness of breath (61%), chest pain (43%) and cough (27%). Of all cases reported, 62 had pathology evaluable for analysis. Histological type was epithelioid in 42 (68%); sarcomatoid in 12 (19%) and biphasic in 8 (13%). EGFR expression was seen in 44 (71%); VEGFR and SV40 in 14 (22%). A survival analysis for potential prognostic factors including EGFR, VEGFR, SV40, WBC, LDH, platelet count and hemoglobin level, will be presented.
Conclusion: In this large cohort, the majority of MM tumors expressed EGFR, while a small proportion expressed VEGFR or SV40. Survival analysis for prognostic factors, as well as the correlation between EGFR, VEGFR, SV40, and other variables will be presented.

550 POSTER

Demethylation of the human telomerase catalytic subunit gene promoter restored telomerase activity in tamoxifen-resistant breast cancer cells

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Background: Estrogen can activate telomerase activity (TA) of breast caner cells through direct or indirect mechanisms and TA is regulated by many transcriptional factors that actually regulate the expression of the human telomerase catalytic subunit (hTERT), the rate-limiting factor in TA. In the previous study with tamoxifen-resistant T47D:A18 breast caner cells (T47D:A18/4-OHT), we showed that the TA was highly increased and deregulated by estrogen not in parental cells but in tamoxifen-resistant cells. It is also reported by others that strong and positive correlation between hTERT promoter methylation, hTERT expression, and TA. We performed this study to see whether the methylation of hTERT gene promoter is associated with deregulated and highly increased TA in T47D:A18/4-OHT cells.
Materials and Methods: We established tamoxifen-resistant cells from parental T47D:A18 human breast cancer cells by long-term treatment with 1 μM of 4-hydroxytamoxifen. The genomic DNA was isolated from cells, and bisulfite modification and methylation-specific PCR was performed using primers specific for unmethylated and methylated alleles of hTERT. In case of detecting hypermethylation of hTERT in T47:DA18/4-OHT cells, we planed to treat with a demethylating agent, 2.5 μM of 5-aza-2′-deoxycytidine (5azadC). The semiquantitative TRAP assay was performed for measurement of TA.
Results: Methylation of hTERT gene promoter was not detected in parental T47D:A18 cells, but in tamoxifen resistant T47D:A18/4-OHT cells. The elevated and deregulated TA in T47D:A18/4-OHT cells were restored to basal level of parental T47D:A18 cells, and regulated by estrogen after the treatment of 5azadC.
Conclusions: In tamoxifen-resistant breast cancer cells (T47D:A18/4-OHT cells), deregulated TA is thought to be associated with the hypermethylation of hTERT gene and could be restored to basal level with demethylation of hTERT gene promoter. This epigenetic change could be considered not only as a mechanism of the development of tamoxifen resistance, but as a target to overcome tamoxifen resistance in breast cancer cells.

551 POSTER

Clinical significance of MDR1/ABCB1 single nucleotide polymorphism (SNP) in the breast cancer patients receiving neoadjuvant chemotherapy

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Background: Variations in the expression and activity levels of the multidrug-resistance MDR1/ABCB1 encoded P-glycoprotein (P-gp) have an impact on the therapeutic efficacy of many drugs. C3435T and G2677T polymorphisms of the MDR1/ABCB1 gene correlate with cellular expression levels of P-gp, a membrane-bound efflux pump which removes a chemotherapeutic drug including docetaxel and doxorubicin from the cells. The aim of this study was to investigate the clinical significance of SNPs in MDR1/ABCB1 genes in breast cancer treated with neoadjuvant chemotherapy (CTx).
Methods: One hundred stage II or III patients (pts.) (median age 45; range 25−63) were treated with 3 cycles of neoadjuvant CTx consisted of docetaxel 75 mg/m^2 iv and doxorubicin 50 mg/m^2 iv D1 every 3 wks before curative surgery. The objective tumor response was evaluated by RECIST. Pathologic CR (pCR) was defined as complete disappearance of invasive carcinoma in both breast and axillary lymph nodes after 3 cycles of CTx. Whole blood samples were obtained before CTx. DNA was extracted from the PB MNCs and C1236T, G2677T/A, C3435T polymorphisms of the MDR1 gene were genotyped by PCR-restriction fragment length polymorphism (RFLP). We evaluated the correlation between the clinico-pathologic prognostic factors, polymorphisms and clinical outcomes.
Results: Out of 100 pts, blood samples were available from 92 pts (ER− and PR−: 53.2%, HER2+: 27.2%). The overall radiologic response rate (RR) was 70.6% (CR 7.6%, PR 63.0%) and 8 patients (8.7%) achieved a pCR. Although statistically insignificant, clinical RR is higher in CT or TT allele than wild type CC allele on C1236T site (73.4% vs. 53.8%, $p = 0.17$). There was no significant difference of RR according to C3435T and G2677T/A SNPs. Genetic linkage was observed between C1236T and C3435T. No polymorphism predicted severe CTC toxicity. Two-year RFS rate was higher in CT or TT group compared with CC wild type (96% vs 48%, $p = 0.002$). Multivariate analysis will be presented.
Conclusions: The C1236T MDR1 polymorphism correlated with the prolongation of RFS in this study. More research is warranted to identify the molecular biological characteristics of C1236T that lead to altered P-gp.

552 POSTER

Identification of predictive markers for tumour response to neo-adjuvant chemotherapy (NCT) treatment for locally-advanced breast cancer (LABC)

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Background: The aim of this study was to use expression profiling to identify genes that are predictive for successful response to NCT in women with LABC.
Material and Methods: Following informed consent, 47 patients with locally advanced breast cancer suitable for NCT were recruited. Participants were randomly assigned to receive either sequential FEC100 (×4) and Docetaxel 100/m2 (×4), or the reverse sequence. Serial assessment of response was performed with Physical Exam, Mammography, U/S, Serial Tumour biopsy and PET scans. A total of 39 Affymetrix arrays (U133 Plus 2.0) were performed on RNA isolated from core biopsies taken pre-chemotherapy. Analysis of array data was undertaken with R language and Bioconductor using an empirical Bayes linear model (Limma) to identify genes that were associated with a successful clinical response to either treatment regimen. P-values were adjusted using false discovery rate for multiple testing.
Results: A small number of genes were identified with significant predictive value for reduction in tumor volume (as assessed by ultrasound) in response to both Docetaxel (3 genes) and FEC100 (7 genes) treatment. Pre-treatment PET "standardized uptake volume" (SUV) inversely correlates with the likelihood of complete pathologic response. Gene array was able to identify of a group of 12 genes for which the expression profiles correlated with the pre-treatment PET SUV values. The next step in this work will be to validate the genes identified using quantitative PCR, and evaluate their predictive value in a prospective study.
Conclusion: We have identified a number of genes that may be useful markers to predict response to NCT in breast cancer. Validation studies are ongoing.