p53 genotypes at the three polymorphic sites (intron 3,exon 4 codon 72, intron 6) and XRCC1-Arg399Gln exon 10 polymorphism was determined by a PCR-RFLP. Mutant p53 protein expression was detected in tumor of lung cancer by using immunohistochemical staining.

Results: We found that aberrant p53 protein expression is positively correlated (p=0,03,CI95%=1,37-5,83) with null-genotypes of GSTM1 and GSTT1 genes in lung cancer patients. Also, we found that functionally inactive genotypes of GST M1(p=0,023, CI95% =1,11-4,42) and GSTT1(p=0,077, CI95% =0,94-3,6) genes are associated with lymph node involved lung cancer patients.

In parallel, we observed that lung cancer risk was significantly increased at the presence of Gln/Gln genotype (homozygous on minor-variant allele) of XRCC1 gene (p=0,03, CI95%= 1.00-3.49) and decreased for individuals bearing Arg/Gln genotype (p=0,01, CI95%= 0.34-0.94). To further explore the role of XRCC1 and p53 genes polymorphism in lung cancer risk we found high frequency of the combination XRCC1/p53(in3/ex4/in6) [M/M]/[W/W-W/W-W/W] from lung cancer patients against control subject (12% and 4%, respectively, p=0,05,CI95%=1,00-10,32).

Discussion: Our results suggest the role of null-GST genes in lung cancer progression. We found that Gln/Gln genotype of XRCC1 gene at the presence of combination wild -type genotypes of p53 gene may be considered as important genetic event in the development of lung cancer, because the XRCC1-399Gln allele is associated with lower efficiency of DNA repair and play critical role in the successful DNA repair.

Conclusion: Data obtained suggest that the polymorphism in metabolic enzymes (GSTT1 and GSTM1) and DNA repair (XRCC1) genes may affect risk and progression of lung cancer due to their influence on p53 function.

P2-009 **BSTB: Cancer Genetics Posters, Tue, Sept 4**

Influence of the organic anion transporting polypeptide 1B1 (OATP1B1) polymorphisms on irinotecan-pharmacokinetics and clinical outcome of patients with advanced non-small cell lung cancer

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Background: The organic anion transporting polypeptide (OATP) 1B1 is a drug uptake transporter located at the basolateral membrane of hepatocyte. Here we investigated the association of single nucleotide polymorphisms (SNP) in the SLCO1B1 gene encoding for OATP1B1 with irinotecan-pharmacokinetics, toxicity and survival of patients with advanced non-small cell lung cancer (NSCLC).

Methods: Peripheral blood samples from 81 NSCLC patients prospectively enrolled in a phase II study of irinotecan and cisplatin chemotherapy were used for genotyping SLCO1B1 -11187G>A, 388A>G, and 521T>C.

Results: Patients with the 521C allele showed a trend for higher SN-38 AUC (p=0.054) compared to those without this allele. When haplotypes were assigned, patients with at least one *15 haplotype (containing 388A>G and 521T>C variants) showed significantly higher SN-38 AUC than noncarriers (p=0.009). The most common severe toxicity was NCI-CTC grade 4 neutropenia (G4N), which occurred in 22 (27%) patients. Patients with 521C allele showed higher incidence of G4N and lower delivered dose of irinotecan (p=0.047) than those without this allele. Patients with the -11187A allele also showed a trend for higher G4N (p=0.057) and lower delivered dose of irinotecan (p=0.029). Grade 3 diarrhea was developed in 8 (10%) patients those with the 388GG genotype (p=0.046). In survival analysis, patients with *1b/*1b diplotype showed worse overall survival than others (p=0.004), which was retained in multivariate analysis.

Conclusions: These findings suggest that OATP1B1 variants are involved in transporting SN-38 and highly predictive for toxicity and prognosis of NSCLC patients treated with irinotecan-based chemotherapy.

P2-010 **BSTB: Cancer Genetics Posters, Tue, Sept 4**

Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer

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Background: To investigate whether ABCB1, ABCC2, and ABCG2 genetic polymorphisms affect pharmacokinetics (PK) of irinotecan and treatment outcome of patients with advanced non-small cell lung cancer (NSCLC).

Methods: Blood samples from 107 NSCLC patients treated with irinotecan and cisplatin chemotherapy were used for genotyping ABCB1 (1236C>T, 2677G>T/A, 3435C>T), ABCC2 (-24C>T, 1249G>A, 3972C>T), and ABCG2 (34G>A, 421C>A) polymorphisms. Genotypes were correlated with irinotecan PK, toxicity, tumor response, and survival.

Results: Among 8 polymorphisms, 3435TT and 2677TT were associated with SN-38G AUC and SN-38G clearance. When haplotypes are assigned, 2677TT/3435TT carriers showed significantly lower SN-38G AUC (P=0.006), whereas, 2677GG/3435CC carriers showed significantly higher SN-38 AUC (P =0.039). These findings suggest that 2677TT and 3435TT variants are associated with higher efflux activity. In toxicity, the 2677G/T or A was associated with grade 4 neutropenia. The 2677GG carriers showed significantly lower absolute neutrophil count during the 1st cycle (p=0.012) as well as entire course of chemotherapy (p=0.042). The 3435TT was associated with higher frequency of grade 3 diarrhea (p=0.047). In tumor response, ABCC2 -24TT and 3972TT genotypes were associated with higher response rates (p=0.031 and 0.046, respectively) and longer progression-free survival (p=0.035 and 0.038, respectively), which was sustained in haplotype analysis.

Conclusions: Specific polymorphisms of ABCB1 and ABCC2 can influence the disposition and tumor response to irinotecan by regulating transporter activity. These findings may help to individualize irinotecan-based chemotherapy in patients with advanced NSCLC.