OI-A-3

MENOPAUSAL STATUS AND ESTROGEN RECEPTOR GENOTYPES INFLUENCED THE SEVERITY OF HOT FLASHES AFTER TAMOXIFEN TREATMENT. Y. Jin, MD, T. Skaar, PhD, A. Storniolo, MD, Z. Desta, PhD, A. Nguyen, L. Li, PhD, D. Hayes, MD, D. A. Flockhart, MD, PhD, V. Stearns, MD, Indiana University, University of Michigan, Indianapolis, IN.

BACKGROUND/AIMS: Hot flashes are the most common side effect of tamoxifen treatment. We conducted a prospective observational trial to evaluate factors that influenced hot flash severity after tamoxifen treatment.

METHODS: Hot flashes frequency and severity were recorded in 7-day hot flashes diaries before, and 1, 4, 8, 12 months after tamoxifen treatment in 122 subjects. Hot flashes composit scores were calculated. Demographic information was collected at baseline, and estrogen receptor (ESR1 & 2) genotyping was also performed.

RESULTS: Pre-menopausal women showed the biggest increase in hot flashes severity, from 5.2 ± 10.5 at baseline to 28.5 ± 51.6 at 4 month ($P<0.0001$), whereas there was no significant change in peri- or postmenopausal women. Twenty-two of the 122 women did not develop hot flashes. G allele carriers of the ESR2-02 SNP were 4.2 times more likely to develop hot flashes than homozygotes with AA genotype ($P=0.008$).

CONCLUSION: Pre-menopausal women were most likely to develop hot flashes after tamoxifen treatment. ESR2-02 genotype may also influence the risk of developing hot flashes after tamoxifen treatment.

OI-A-4

GENOME-WIDE APPROACH TO FINDING DETERMINANTS OF SUSCEPTIBILITY TO CHEMOTHERAPEUTIC AGENTS. S. Shukla, MPH, J. Badner, MD, PhD, C. Cheng, PhD, W. Bleibel, BA, M. E. Dolan, PhD, University of Chicago, St. Jude's Children's Research Hopsital, Chicago, IL.

BACKGROUND: Our aim was to identify candidate genes and genetic variants involved in cellular susceptibility to chemotherapeutic agents without *a priori* assumptions about the genes. To date, research has focused on known candidate genes involved in pharmacokinetic and pharmacodynamic pathways for specific chemotherapy.

METHODS: Three-generation CEPH pedigrees were used to evaluate the genetic contribution to cellular growth inhibition by exposing the cells to increasing concentrations of cisplatin for 48 hours or carboplatin for 72 hours.

RESULTS: The heritability of cisplatin- and carboplatin-induced cytotoxicity was found to be between 0.38–0.47 ($p<0.0001$) and 0.36–1.0 ($p<0.02$), respectively. The most significant findings from linkage analysis for cisplatin were on chromosome 1 at 44 cM in variance components analysis and chromosome 12 at 147 cM in nonparametric linkage analysis. Candidate genes within a 1-lod confidence interval surrounding the peaks on chromosome 1 (188 genes) and 12 (106 genes) included *CASP9, SFN, STMN1, UBC, POLE* and *ZNF84*. Using expression array, we compared gene expression differences at baseline and changes over time following treatment with cisplatin. Genes common to linkage analysis and expression array included *ZNF84, RERE, NPPB,* and *SFRS8*.

CONCLUSIONS: These data show the power of using large, extensively genotyped pedigrees with microarray analysis for evaluating the genetic contribution to sensitivity of cell growth inhibition by anticancer agents.

OI-B-1

GRAPEFRUIT JUICE INGESTION REDUCES TALINOLOL SERUM CONCENTRATION. U. I. Schwarz, MD, D. Seemann, R. Oertel, PhD, S. Miehlke, MD, E. Kuhlisch, PhD, M. F. Fromm, MD, R. B. Kim, MD, D. G. Bailey, PhD, W. Kirch, MD, Div. of Clin. Pharmacol., Vanderbilt Univ., Inst. of Clin. Pharmacol., Tech. Univ. Dresden, Med. Depart. I, Tech. Univ. Dresden Hospital, Inst. of Med. Informatics/Biometrics, Tech. Univ. Dresden, Dr. M. Fischer-Bosch-Inst. Stuttgart, Div. of Clin. Pharmacol., Vanderbilt Univ., Dep. of Medicine, Univ. Western Ontario, Inst. of Clin. Pharmacol., Tech. Univ. Dresden, Nashville, TN.

BACKGROUND/AIM: The objective was to evaluate the effect of single and repeated grapefruit juice relative to water on oral pharmacokinetics (PK) of the non-metabolized and P-glycoprotein (Pgp)-transported drug talinolol in humans, and to assess the impact of grapefruit juice on Pgp and intestinal uptake transporters.

METHODS: Oral PK of 50mg talinolol was determined with water, single (300mL), and repeated grapefruit juice intake (6 days, 900mL/day) in 24 healthy Caucasians. *MDR1* mRNA and Pgp levels were measured in duodenal biopsies of 3 subjects before and after juice. All subjects were genotyped for three *MDR1* polymorphisms (1236C>T, 2677G>T/A, 3435C>T).

RESULTS: Single grapefruit juice decreased the talinolol AUC, C_{max}, and urinary excretion values to 56% ($P<.001$), 57% ($P<.001$) and 58% ($P<.001$), respectively, of those with water; repeated grapefruit juice showed a 50 to 65% reduction ($P<.01$). Single or repeated juice intake did not affect CL_R, $t_{1/2}$, and t_{max}. *MDR1* mRNA and Pgp levels in duodenal biopsies did not differ. *MDR1* genotypes were not associated with altered PK of talinolol.

CONCLUSION: Since both single and repeated juice intake lowered, rather than increased talinolol AUC without changing Pgp expression, our findings suggest constituents in grapefruit juice preferentially inhibited intestinal uptake rather than Pgp.

OI-B-2

CYP2A6 GENOTYPE AND TOXICITY OF NICOTINE IN NEVER SMOKERS. D. A. Dempsey, MD, P. Jacob III, PhD, R. F. Tyndale, PhD, E. Hoffmann, MSc, N. L. Benowitz, MD, University of California, San Francisco, University of Toronto, San Francisco, CA.

BACKGROUND/AIMS: To examine genetic factors that influence sensitivity to nicotine (Nic) in never smokers.

METHODS: 20 Caucasian and 20 Asian never smokers received 7 mg nicotine skin patches, with frequent blood levels, subjective and cardiovascular (CV) effect monitoring. CYP2A6, the enzyme primarily responsible for Nic metabolism, was genotyped.

RESULTS: 25 subjects had wild type alleles (*1A and/or *1B) for CYP2A6, while 15 subjects had CYP2A6 variant alleles (*4, *9, *10) which are associated with slower Nic metabolism (Var-2A6). 8 subjects vomited, of whom 75% had Var-2A6 compared to 25% in those who did not ($p<0.02$). Nic levels (AUC 0–90min) were significantly higher in those who vomited. Var-2A6 subjects had more adverse responses to Nic including reduced alertness, concentration and contentedness, and, more lightheadedness and nausea (all $p<0.05$). CV responses did not differ by genotype.

CONCLUSIONS: Variant CYP2A6 (*4, *9, *10) genotype is associated with more toxicity from Nic in never smokers. Genotype could influence responses to the first cigarette in never smokers and responses to Nic medications used to treat Nic addiction. Supported by USDPH-DA02277 and CIHR MOP53248.