Identification and validation of ADME polymorphic variants correlated to taxane neurotoxicity and survival in breast cancer patients by DMET microarray platform

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Purpose

Peripheral neuropathy is a common, potentially disabling and dose-related adverse event (AE) of taxane-based chemotherapy. Inter-individual variability underlying genetic polymorphisms in drug transporters and drug-metabolizing enzymes (ADME) may account for the occurrence of taxane-associated neuropathy (TAN). We investigated correlation between single nucleotide polymorphisms (SNPs) in ADME genes and grade≥2-3 TAN (G≥2-3 TAN) by the novel drug-metabolizing enzyme and transporter (DMET) microarray genotyping platform in a discovery set of breast cancer patients and than validated in an independent set of breast cancer patients.

Patients and Methods

Seventy nine patients with breast cancer, who received a taxane-based chemotherapy (docetaxel or paclitaxel), were enrolled in the discovery set as a retrospective case-control study; 27 experienced TAN (≥ grade2-3 according to NCI criteria) and were indicated as case group, while 52, who never developed TAN, were selected as matched controls. DNA extracted from peripheral blood cells was genotyped by DMET Plus chip on Affymetrix array system. Primary study end-point was the association between SNPs and TAN; the association between TAN related SNPs and Overall Survival (OS) was a secondary endpoint. Genotype association was statistically evaluated by Fisher exact test (two tailed). We validated the identified SNP biomarkers in an independent series (54) of breast cancer patients (validation set) by DNA direct sequencing. Data were statistically analyzed by the receiver operating characteristics (ROC) curves. Validated SNPs were subsequently analyzed, in combined discovery plus validation sets, through Kaplan-Maier survival curves and Log-Rank test, for their correlation with OS.

Results

We identified an association between 21 SNPs and TAN. After Bonferroni's correction for multiple testing, 5 SNPs, mapping on two genes, NR1I3 (rs11584174) and UGT2B7 (rs7438284, rs7662029, rs7439366 and rs7668258), were significantly associated with G≥2-3 TAN (p≤0.002). The homozygous GG genotype was correlated to G≥2-3 TAN protection, occurring in 46/52 control patients vs. 15/27 cases (p=0.001, OR= 4.600, 95% C.I.= 1.5815 - 13.3797) while the AG genotype, found in 12/27 cases vs. 6/52 control patients, was associated to G≥2-3 TAN (p=0.001, OR= 6.133, 95% C.I.= 1.9612 - 19.1810). In the UGT2B7 gene four polymorphic variants, in pairwise linkage disequilibrium, were associated to protection from G≥2-3 TAN: the homozygous variant allelic genotypes (AA) of rs7662029 and (TT) of rs7668258 (p=0.002, O.R.= 6.344, 95% C.I.= 1.6964 -

23.7306) were correlated to a protective effect, while the protective effect of the homozygous ancestral allele genotype (AA) of rs7438284 and (TT) of rs7439366 (p=0.002, OR= 6.344, 95% C.I.= 1.6964 - 23.7306) was demonstrated. Internal cross-validation of the discovery set confirmed the predictive value of toxicity-related SNPs. G≥2-3 TAN SNPs identified were validated in independent set of breast cancer patients (validation set) based on predictive value of Discriminant Analyses (DA) by ROC curve. Furthermore, in a full evaluation of both patient sets, we found that protective G≥2-3 TAN homozygous genotypes of the four UGT2B7 polymorphic variants were associated to worst overall survival by Pearson Chi Square test and this effect occurred according to different immune phenotypes of breast cancer.

Conclusions

Five polymorphic variants in NR1I3 and UGT2B7*2c genes predicted for G≥2-3 TAN protection. UGT2B7*2c was also correlated to worst long term survival. These biomarkers may be important for personalized treatment of metastatic breast cancer. These findings confirm DMET platform as a robust tool for genetic biomarkers discovery.