Oral

[O26-3] O26-3: Pharmacogenomics (1)

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[O26-3-3] DPYD polymorphisms and fluoropyrimidine toxicity —a single institution case control study

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Background

Fluoropyrimidines (FP) are frequently used in oncology. Dihydropyrimidine-dehydrogenase (DPD) is the rate-limiting enzyme of FP metabolism, degrading 80% of FP. Patients with partial or complete enzyme-deficiency have increased toxicity risk, possibly detectable by genotyping. Here we present preliminary results of a single-institution case-control cohort genotyped for *DPYD*-polymorphisms and monitored for toxicity during FP therapy.

Methods

Fluoropyrimidine-treated patients (N=305) were genotyped for five *DPYD*-polymorphisms (**2A, *13, c.2846A>T, c.1236G>A* and *c.496A>G*). Those receiving irinotecan were also genotyped for *UGT1A1*28*. Side-effects were followed-up for three months. The observed patient group included grade III and IV toxicity (N=138), whereas controls comprised grade I and II (N=167). DNA was isolated from whole blood (3ml) and genotyped according to manufacturer’ s propositions using Real-time PCR (TaqMan® for *DPYD*, LightCycler® for *UGT1A1*). Polymorphism frequency distribution was analyzed by non-parametric tests and binary logistic regression.

Results

During the study, we recorded a total of 705 adverse events (273 of high- and 432 low grade). Subjects in the observed group developed adverse effects more rapidly (2^{nd} vs. 3^{rd} cycle of chemotherapy) and accumulated greater total number of events *per capita* (3 vs 1.7). Aggregated *DPYD* polymorphisms (N=93; 30.5%) were distributed unevenly with higher frequency of carriers in the observed group (49.3% vs. 15%), thus creating a statistically significant increase of risk for severe toxicity among carriers of mutated *DPYD* variant (OR=4.91; P<0.001). All *DPYD*2A* carriers (N=11; 3.6%) developed high-grade toxicity with one lethal event in a homozygote. *c.496A>G* carriers (N=69; 22.6%) had increased risk for toxicity (OR=4.64; P<0.001) with three of them being compound heterozygotes for *DPYD*2A*. Detected frequencies of *c.2846A>T* and *c.1236G>A* were too low to draw any statistically significant conclusion on their particular impact. We did not detect any *DPYD*13* polymorphism. *UGT1A1*28* variant had stronger influence on toxicity risk than *DPYD* polymorphisms when irinotecan was given in combination with FP (OR=8.1; P<0.001), as expected.

Conclusions

Significant association and predictive value of *DPYD*-mutation status considering FP-toxicity is shown, while *UGT1A1*28* remained important for irinotecan toxicity. The detected frequencies of polymorphisms were slightly inconsistent with published data, thus emphasizing the importance of genetic background for

selection of variants to be genotyped in particular ethnic groups.