S13-1 PGx analyses for preventing adverse reactions caused by anti-cancer drugs

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Anti-cancer drugs have relatively low effective rates and high frequencies of adverse reactions, occasionally leading to cessation of treatment. Use of pharmacogenomic (PGx) information could be able to select the patients with high-response and less-adverse reactions, resulting in increase of patients' QOL and proper use of drugs. We have been collaborating with National Cancer Center for PGx analysis of anti-cancer drugs including irinotecan and gemcitabine in Japanese cancer patients. Irinotecan, now used for treatments of many cancers, is metabolically activated to SN-38 and then inactivated to SN-38 glucuronide by UGT1A1. In the *UGT1A1* gene, two representative genetic polymorphisms, **28* and **6*, were detected. When the patients were homozygotes of **28* or **6*, or compound heterozygotes of these polymorphisms, statistically significant decreases were observed in the SN-38 glucuronidation activity and increases in the rate of severe neutropenia, compared to those in the patients without **28* or **6*. Our results and papers were cited in the Japanese labels of irinotecan. Gemcitabine was inactivated by cytidine deaminase (CDA) into 2'-2'-difluorodeoxyuridine. A CDA polymorphism 208G>A (Ala70Thr) was detected at 0.037 frequency and associated with reduced gemcitabine clearance as well as increased frequency of severe neutropenia. In the 4 patients suffered from very severe bone marrow toxicities, 3 patients were homozygous *CDA*3*, suggesting that this polymorphism is exquisite for predicting severe adverse reactions by gemcitabine in Japanese. Several PGx issues on other anti-cancer drugs will be also presented.