UGT1A1/ABCC2 AND PHARMACOKINETICS OF IRINOTECAN HYDROCHLORIDE

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Irinotecan hydrochloride (irinotecan) is active against various solid tumors including colorectal cancer. UGT1A1 catalyzes the detoxification of the active SN-38 to a polar inactive SN-38 glucuronide that is excreted into the bile via transporters such as ABCC2.

Severe, occasionally life-threatening toxicity occurs sporadically, even relatively low-risk patients were treated with irinotecan. Interindividual variability in the pharmacokinetics (PK) of SN-38 resulting from glucuronide formation is at least one of the major causes of irinotecan-induced severe toxicity. Various retrospective and prospective studies have revealed that patients homozygous for UGT1A1*28 had higher risk of grade 4 neutropenia than patients heterozygous for UGT1A1*28 or wild-type patients. In response to these findings, genetic test of UGT1A1*28 has been approved by United States Food and Drug Administration to find the homozygote of UGT1A1*28 to reduce the initial dose of irinotecan at least one level, although the effectiveness of the test has not been prospectively examined yet.

On the other hand, UGT1A1*6, observed in Japanese but not in whites, has been increasingly elucidated to be association with irinotecan PK. In the Japanese population, the metabolic ratio of the area under the curve (AUC) for SN-38/AUC for SN-38 glucuronide was statistically significantly higher in patients who were homozygous for UGT1A1*6 or heterozygous for both UGT1A1*28 and *6 than in those with other genotypes (P = 0.004). These genotypes have also been reported to be associated with severe irinotecan-related neutropenia. Therefore, Ministry of Health, Labour and Welfare in Japan has approved genetic test of UGT1A1*28 and *6. However, according to our prospective study, only 2 out of 300 patients were UGT1A1*28 homozygote (0.7%). Considering the frequencies of UGT1A1*28 and UGT1A1*6 seen in Japanese population, the genetic test of UGT1A1 might not be essential to find patients homozygous for UGT1A1*28, but meaningful to identify those homozygous for UGT1A1*6 as well as those both heterozygous for UGT1A1*6 and *28 to avoid irinotecan-induced severe toxicity in Japanese population. In a meta-analysis assessed the association of irinotecan dose with the risk of irinotecan-related severe hematologic toxicities in patients homozygous for UGT1A1*28, the risk appears to be a function of the dose of irinotecan administered. Supporting the meta-analysis, gradual increases of the metabolic ratio in respective patients homozygous for UGT1A1*28, UGT1A1*6 or heterozygous for both UGT1A1*28 and *6 were observed, when the dose of irinotecan was escalated from 25 to 150 mg/m². The dose matter of irinotecan should also be considered for the genetic test of UGT1A1.

Effects of the ABCC2 genotype on the PK of irinotecan were examined on Japanese patients with metastatic colorectal cancer receiving irinotecan plus infusional 5-fluorouracil/leucovorin (FOLFIRI). Lower AUC of irinotecan was seen in patients with A/A or G/A genotypes at 1249 of the ABCC2 gene than others (P = 0.011). AUC of SN-38 seen in patients with A/A or G/A genotypes at -1023 was significantly lower than that seen in others (P = 0.018). Thus, ABCC2 genotype is one of the predictors of the variability of irinotecan PK in Japanese patients with colorectal cancer treated with FOLFIRI.

References: