

IRINOTECAN PHARMACOGENETIC STUDIES IN PEDIATRIC CANCER PATIENTS

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Irinotecan is an anti-cancer agent with efficacy against numerous pediatric tumors, yet its use is complicated by its significant gastrointestinal toxicity. Irinotecan is a prodrug metabolized *in vivo* to the active metabolite, SN-38, which is glucuronidated via the UGT1A1 enzyme to SN-38 glucuronide. It is speculated that variable interindividual UGT1A1 activity causes disparity in SN-38 glucuronidation, which may produce toxicity in pediatric cancer patients. Single nucleotide polymorphisms (SNPs) within the ABCG2 gene may also increase the bioavailability and efficacy of irinotecan, since these SNPs have been associated with prolonged SN-38 exposure in tumor cells. This research examined the effect of UGT1A1 and ABCG2 genotypes (n= 60 and 21, respectively) on single-agent oral irinotecan pharmacokinetics in patients. Patient DNA samples were analyzed following PCR amplification and DNA sequencing. Statistically significant differences were discovered in irinotecan clearance, irinotecan AUC, and total and lactone SN-38 glucuronide:SN-38 AUC ratio values between wild-type patients and patients with a polymorphism within the UGT1A1 gene. Discernable, yet non-significant, trends were discovered involving ABCG2 SNPs and irinotecan bioavailability. Throughout the course of this research, significant associations were discovered between UGT1A1 genotype and the irinotecan metabolic pathway. Our results suggested that including a larger sample size in future studies may reveal a stronger association between ABCG2 and irinotecan oral bioavailability. Ultimately, pre-treatment UGT1A1 and ABCG2 genotyping may be utilized to maximize the efficacy of irinotecan-based chemotherapeutic therapies.

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