PHARMACOGENETIC PATHWAY ANALYSIS OF IRINOTECAN

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Irinotecan is a chemotherapeutic agent in clinical use to treat various solid tumors. It is a prodrug requiring activation to SN-38, an inhibitor of topoisomerase I. Given irinotecan's complex pharmacokinetics, there are multiple potential genetic sources of variability. One such source, a common polymorphism in the promoter of UGT1A1, has already been identified as being a risk factor for irinotecan-induced myelosuppression. In this study, we sought to extend our primary work, exploring the use of principal component analysis (PCA) as a means of generating hypotheses about the relationships between pharmacokinetic parameters and polymorphisms in genes associated with irinotecan's metabolism and transport.

We analyzed data from 86 patients who received single-agent irinotecan (either 300 mg/m^2 or 350 mg/m^2) in the context of a prospective study evaluating the relationship between UGT1A1 genotype and irinotecan toxicity. We had measured concentrations of irinotecan and three of its metabolites [SN-38, SN-38 glucuronide (SN-38G) and APC] over time. We fit a compartmental model to characterize the pharmacokinetics of irinotecan and metabolites. The compartmental model included enterohepatic recirculation of SN-38. We applied PCA to the matrix of centered and standardized log-transformed, patient-specific pharmacokinetic model parameters. We applied varimax rotation to the final set of principal components to improve interpretability and, hopefully, lead to linear combinations of the parameters that we could interpret in terms of irinotecan's metabolic pathways. We then analyzed the associations between several candidate polymorphisms and the rotated principal components to identify polymorphisms affecting the pharmacokinetic variability of irinotecan disposition. We assessed the strength of evidence for associations using Bayes factors based on Zellner's G-priors.

We found 9 principal components with pathway-specific interpretation. Principal component #1 corresponded to the pathway from irinotecan to SN-38 with SN-38 recirculation. We found strong associations between this principal component and variants in the UGT1 and ABCC1 genes. Principal component#2 was related to the irinotecan compartments and was associated with HNF1α, ABCC1, and ABCC2 polymorphisms. Principal component #3 concerned the conversion of SN-38 to SN-38G and the elimination of SN-38G. We found strong evidence of associations with polymorphisms in the UGT gene.

PCA is a useful way to reduce the dimension of multiple pharmacokinetics parameters and to produce pathway-specific and interpretable measures relating to pharmacokinetics. Our results are consistent with genes associated with irinotecan and its metabolites in cases where the associations are known. In addition, the use of PCA in pharmacogenetics analysis may allow identification of potential functional polymorphisms not yet characterized.