Jing Li et al., Metabolomics 2016, 6:3(Suppl)
http://dx.doi.org/10.4172/2153-0769.C1.034

Pharmacometabolomics reveals mechanisms of action underlying the antitumor activity and toxicity of Irinotecan

Jing Li[1], Jianmei Wu[1], Xun Bao[1], Seongho Kim[1] and Patricia LoRusso[2]
[1]Wayne State University, USA
[2]Yale School of Medicine, USA

Irinotecan, a topoisomerase-I inhibitor inhibits DNA replication and transcription. Irinotecan is widely used for treating various solid tumors. Its major toxicities include neutropenia, diarrhea, and steatohepatitis. This study investigated the metabolic changes induced by irinotecan in cancer patient and cell lines, which may provide mechanistic insights into the antitumor activity and toxicity of irinotecan. Plasma samples were collected at pretreatment, 1.5, 5.5, 28, and 48 h following 1.5-h irinotecan infusion (100 mg/m^2) in 11 cancer patients. ~250 metabolites were quantitatively determined in patient plasma using a LC-MS/MS based targeted metabolomics platform. Additionally, metabolomic profiling was performed for human primary liver cells and two breast cancer cell lines (MDA-MB-231 and T47D) treated with SN-38 (an active metabolite of irinotecan) at 50 and 500 nM for 1, 6 and 24 h. Irinotecan caused time-dependent changes of metabolites including nucleosides, nucleobases, amino acids, acylcarnitines and aminoadipic acid in patient plasma. SN-38 induced time- and concentration-dependent increases of nucleosides and nucleobases in culture medium of both human liver cells and cancer cells, while aminoadipic acid (an oxidative stress marker) was elevated in liver cell medium only. SN-38 induced formation of reactive oxygen species in liver cells but not in cancer cells. In conclusion, elevated circulating levels of nucleosides and nucleobases seem associated with irinotecan-induced inhibition of DNA replication. Oxidative stress appears to be implicated in irinotecan toxicities especially steatohepatitis. Further studies are needed to investigate whether these circulating metabolite changes could serve as mechanistic biomarkers for predicting irinotecan efficacy and toxicity.

Biography

Jing Li has completed her PhD at National University of Singapore and Post-doctoral training at John Hopkins University. She is currently an Associate Professor at Wayne State University School of Medicine and Director of Pharmacology Core at Karmanos Cancer Institute. Her research focuses on the clinical pharmacology of anticancer drugs with emphasis on pharmacokinetics and pharmacometabolomics. She has published over 50 papers in reputed journals and has been serving as an Editorial Board Member and Reviewer for a number of journals.

lijin@karmanos.org

Notes: