Integration of genomics, clinical characteristics and baseline biological profiles to predict the risk of liver injury induced by high-dose methotrexate

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Background:

High-dose methotrexate (HD-MTX) is commonly employed in the treatment of malignant tumors in children and young adults due to its distinctive therapeutic efficacy. Nonetheless, the systemic exposure to MTX often results in liver injury (drug induced liver injury, DILI), thereby imposing limitations on the sustained administration of HD-MTX. Additionally, individual variations including genetic underpinnings attributable to disparities in therapeutic effects and clinical toxicity remain to be elucidated.

Methods:

In this study, 374 patients receiving initial HD-MTX treatment were selected, aiming to establish a predictive model in the form of a nomogram that integrates genetic biomarkers and clinimetric markers for DILI risk assessment. Demographic and clinical characteristics were collected at baseline and post-HD-MTX to explore their correlations with the occurrence of DILI. Besides, genotyping results consisting of 25 single nucleotide polymorphisms from drug transporters and enzymes in the folic acid cycle were obtained through multiple polymerase chain reaction techniques, single-nucleotide extension technology, and Matrix-Assisted Laser Desorption/Ionization-Time of Flight Mass Spectrometry analysis.

Results:

The recessive mutation in ABCB1 rs1128503 and SLCO1B1 rs2306283, female gender, and MTX dosage were identified as independent risk factors for moderate/severe DILI. Patients with GA or AA genotype in ABCB1 rs1128503 showed significant higher 24h MTX concentration than GG, and those with GA or AA genotype in SLCO1B1 rs2306283 exhibited higher AUC0-72h and lower CL. Besides, patient with HD-MTX were more prevalent to suffer DILI than those with HD-MTX plus triple intrathecal injection. The composite predictive model (ROC curve: AUC=0.796), comprising above independent factors, exhibited high accuracy.

Conclusion:

Female patients carrying a recessive mutation in ABCB1 rs1128503 and SLCO1B1 rs2306283, coupled with a range of subsequently elevated MTX concentration, may exhibit increased susceptibility to DILI. The proposed predictive model facilitates early individual risk assessment, enabling the implementation of proactive prevention strategies.

Keywords: methotrexate, drug induced liver injury, therapeutic drug monitoring, pharmacogenomics, nomogram