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J Clin Toxicol 2017, 7:3(Suppl)
DOI: 10.4172/2161-0495-C1-025

9th Euro-Global Summit on

Toxicology and Applied Pharmacology

June 22-24, 2017 Paris, France

Genetic determinants of methotrexate toxicity in Tunisian patients with rheumatoid arthritis: A study of polymorphisms in key methotrexate pathway genes

Abdellatif Maalej[1] , Souhir Chaabane[1], Sameh Marzouk[2], Rim Akrout[2], Mariem Ben Hamad[1], Yosser Achour[1], Ahmed Rebai[3], Leila Keskes[1], Hela Fourati[2] and **Zouhir Bahloul[2]**

[1]Laboratory of Human Molecular Genetics, Faculty of Medicine, Sfax, Tunisia

[2]University Hospital Hedi Chaker, Sfax, Tunisia

[3]Department of Bioinformatics, Center of Biotechnology, Sfax, Tunisia

Introduction: Methotrexate (MTX) is a disease-modifying anti-rheumatic drug used in the treatment of rheumatoid arthritis (RA). It is the first line drug in the treatment of this disease. However, MTX-related adverse drug reactions (ADRs) are present in 40% of the patients.

Aim: The purpose of this study was to investigate the influence of genetic polymorphisms in genes involved in the folate metabolic pathway (MTHFR, DHFR), methionine pathway (MTR, MTRR), pyrimidine synthesis (TYMS) and the MTX transport pathway (RFC1, ABCB1, ABCC2) on the occurrence of MTX-related toxicity (overall and gastrointestinal) and to identify pharmacogenetic markers of MTX toxicity in a group of Tunisian RA patients.

Methods: A total of 182 patients with rheumatoid arthritis, under MTX treatment were investigated in this study. Clinicopathological data were collected and ADRs were recorded. A genotyping approach was performed using PCR, PCR-RFLP and TaqMan allelic discrimination method to determine the studied polymorphisms. Association analyses with regard to MTX-related toxicity were evaluated using χ^2 test, genotype relative risk (GRR) and the toxicogenetic risk index (TRI).

Results: Statistical analysis revealed that RFC1 80G/G genotype had increased risk of gastrointestinal toxicity (p=0.032), as well as the T/T genotype of MTHFR C677T polymorphism was associated with both overall and gastrointestinal toxicity (p=0.0007), while TYMS 2R→3R polymorphism had a protective effect against overall MTX toxicity (p=0.031). However, we did not find any association of the MTHFR A1298C, DHFR 19–base pair deletion allele, MTR A2756G, MTRR A66G, ABCB1 C3435T and ABCC2 G1249A polymorphisms with MTX toxicity.

Conclusion: This study demonstrated that genotyping of MTHFR C677T and RFC1 G80A may be a possible predictor to identify patients with increased risk for developing overall and gastrointestinal toxicity related to MTX treatment in Tunisian patients.

abdellatifmaalej@yahoo.fr

Genotoxicity of gemcitabine low dose in white rat bone marrow cells

Abdul Rahman A I Alyahya

Shaqra University, Saudi Arabia

Gemcitabine is a modern chemical drug used widely against many serious diseases including advanced cancers such as lung cancer, bladder and ovarian cancers a several blood cancers. Gemcitabine is one of the preferred choices in the treatment of pancreatic cancer. A short-term test was conducted and the drug showed rapid and strong ability to detect toxicity or distorting the material studied in the neighborhood cells. Results showed that there are some changes in cell parameters which can be determined by cellular examination accurately. Exposing male inbred line SWR/J of laboratory mice to low dose of the drug (125 mg/kg) Gemcitabine individually and in combination affected significantly in different times intervals mitotic divisions and chromosomal aberrations and abnormalities. The severity of abnormalities was increased with the passage of treated time.

alya7ya@su.edu.sa