Association of MTHFR C677T and A1298C polymorphism and methotrexate induced toxicities in children with acute lymphoblastic leukemia

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Introduction: Improvement in the treatment of childhood acute lymphoblastic leukemia has increased five years event free survival to approximately 85%. Because high toxic drugs are used in the treatment of ALL, main focus of current studies is reduction of treatment related toxicities. The two commonest polymorphisms in MTHFR gene, C677T and A1298C have been reported to be associated with methotrexate toxicities with still controversial results. The objective of our study was evaluation of the correlation of MTHFR C677T and A1298C polymorphism with the occurrence of toxic effects during therapy with high doses of methotrexate.

Materials and Methods: Our study included 65 children with ALL treated with high doses of methotrexate (5g/m^2) during protocol M, part of the ALL BFM 2000 protocol. Genotyping for C677T and A1298C polymorphisms of MTHFR gene was performed using the PCR-based restriction fragment length polymorphism assay. Toxic effects were analyzed according to the criteria for toxicity from the protocol ALL BFM 2000 (absence or presence of toxic effects) in correlation with the type of present polymorphism.

Results: Subjects with MTHFR 1298 AC polymorphism manifested less hepatotoxicity then subjects with AA and CC polymorphism, (p=0,023). Other toxic effects, which were manifested in less than 5% of the patients (cardiotoxicity, skin toxicity, central and peripheral neurotoxicity) were more common in subjects with MTHFR 1298CC polymorphism (p=0,005) Infections were more common in subjects with MTHFR 677CT and TT polymorphism without statistical significance. No other toxic effects in correlation with this polymorphisms were registered.

Conclusions: The present study suggests that MTHFR A1298C and C677T polymorphisms can be considered as markers for predicting toxicities during therapy with high doses MTX in childhood ALL. Further multicenter studies with larger data should be performed for future individualization of treatment in childhood ALL in correlation with this pharmacogenetic markers.