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GENETIC POLYMORPHISMS FOR TNF, LT-ALPHA, AND MTHFR - DO THEY PLAY A ROLE REGARDING PROGNOSIS AND THERAPY-RELATED TOXICITY IN PEDIATRIC NON-HODGKIN'S LYMPHOMA? RESULTS FROM 496 UNSELECTED PATIENTS

K. Seidemann[1], M. Book[1], M. Stanulla[1], M. Zimmermann[1], A. Reiter[2],
For The NHL-BFM Study Group
[1]*University Children's Hospials, Hannover* [2]*GIEBEN,Germany*
Kseidemann@web.de

Background: Polymorphisms for TNF (G308A, alleles TNF 1/2) and LT-alpha (A252G, alleles LT-alpha 5.5kb/10.5kb) are associated with prognosis in systemic inflammatory disease. Poly-morphisms in the MTHFR gene (C677T) alter folate metabolism and may effect antifolate ther-apy with Methotrexate. These genetic polymorphisms might influence outcome in pediatric NHL. Patients, Methods: Genomic DNA was isolated from bone marrow aspirates of 496 unselected pediatric patients enrolled in multicenter therapy trial NHL-BFM 95. Genotyping was performed by conventional PCR. Clinical data of patients were examined regarding their association with genotypes for MTHFR, TNF, LT-alpha. Therapy-associated toxicity was recorded according to NCI-/CBC-criteria. Results: Genotypes for TNF, LT-alpha, MTHFR were neither associated with NHL-entities nor with therapy-related toxicity. Polymorphisms for TNF and LT-alpha were not associated with outcome in patients with lymphoblastic lymphoma, anaplastic large cell lymphoma, diffuse large B-cell lymphoma. In Burkitt's lymphoma (BL) and B-ALL (n=222), patients with at least two mutated alleles for either TNF (2 (and/or LT-alpha (5.5kb) had a significantly worse prognosis: Event-free survival at 5 years was 91% (SE 2%) for 'favorable' haplotypes versus 79% (SE 5%) for patients with at least two mutated alleles ('unfavorable' haplotypes); p=0.025. In BL/B-ALL and high tumor burden (LDH >500 U/l), the difference was even more pronounced (86%, SE4% versus 66%, SE 9%; p=0.035). Conclusions: Polymorphisms for TNF, LT-alpha, and MTHFR do not appear to play a role in the pathogenesis or therapy-related toxicity of pediatric NHL. Patients with BL/B-ALL carrying at least two mutated alleles for TNF and/or LT-alpha have a worse prognosis.