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PB1750 REARRANGEMENTS OF T-CELL RECEPTOR (TCR) LOCI IN CHILDREN WITH T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

Topic: 01. Acute lymphoblastic leukemia - Biology & Translational Research

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Background:

T-cell acute lymphoblastic leukemia (T-ALL) is a clinically and genetically heterogeneous disease that constitutes 10%–15% of newly diagnosed pediatric ALL cases and is caused by the accumulation of genetic abnormalities that alter the mechanisms controlling normal T-cell development. The most common structural aberrations involve rearrangements of the T-cell receptor (TCR) loci – *TRA/TRD* (14q11) and *TRB* (7q34), which are found in ~25% of patients. These aberrations are the main factors initiating the events in T-ALL carcinogenesis and juxtapose TCR genes and protooncogenes that encode pivotal transcription factors, leading to their aberrant expression. The outcomes of children with T-ALL significantly improved on intensified protocols, however, ~20% of patients relapse and die owing to acquired therapy resistance. Moreover, survivors also endure the acute and long-term effects of intensive toxic chemotherapy.

Aims: To analyze *TCR* loci rearrangements and associated genetic abnormalities in children with T-ALL treated according to BFM-based protocols, and to correlate our findings with the clinical features and the treatment responses.

Methods: The bone marrow samples of 66 children diagnosed between 1996-2017 (46 boys, 20 girls, age median 7.9 years, follow-up median 86.4 months) were analyzed with cytogenomic methods. For the detection of *TCR* loci rearrangements and other recurrent aberrations of the genes *TLX3*, *CDKN2A/CDKN2B* and *ABL1* interphase FISH (DAKO, Abbott Molecular) was used. MLPA analysis with ALL-IKZF1 probemix (MRC-Holland) was performed to detect deletions/amplifications of additional genes. Complex karyotypes were analyzed with multicolor FISH (MetaSystems) or array CGH/SNP (Agilent). Differences in OS and EFS were assessed using Kaplan-Meier method and the Mantel-Cox test.

Results: Rearrangements of *TCR* loci were detected in 18/66 (27%) patients. Translocations involving the *TRA/TRD* locus were demonstrated in nine children, the *TRB* locus in five and the simultaneous occurrence of these aberrations in two cases, respectively. In 10/18 patients, known recurrent chromosomal translocations affecting the oncogenes *TAL1* (3x), *LMO2* (3x), *TLX1* (2x), *TAL2* (1x) and *MYC* (1x) were identified. In the remaining cases, *TCR* rearrangements were cryptic or were a part of complex karyotype. Additional chromosomal aberrations were detected in all but one patient with the deletion of *CDKN2A* gene being the most frequent one. Immunophenotypic data classified the patients into cortical-T (12x) and mature-T (5x) groups (1x no data). Children with aberrations of *TCR* loci had a significantly better prognosis - EFS (p=0.011) and OS (p=0.0074), all patients are living in the first complete remission.

Summary/Conclusion:

Aberrations of T-cell receptors form a genetically heterogeneous group of rearrangements, leading to aberrant

expression of oncogenes involved in T-cell maturation and proliferation. They mostly occur with abnormalities of genes involved in the regulation of the cell cycle and/or signaling pathways, confirming the multistep process of T-ALL pathogenesis. In our cohort, patients with *TCR* rearrangements had an excellent prognosis regardless of the presence of other aberrations. Although data on larger series are clearly required, we suppose, that these children could benefit from less-intensive therapy because they may experience fewer therapeutic consequences of toxic treatment.

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