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618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Genetic and Cytometric Characteristics of Pediatric B-Other Acute Lymphoblastic Leukemia Cohort

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Background:
According to WHO-HAEM5, the majority of precursor B-cell acute lymphoblastic leukemia (B-ALL) cases are classified based on cytogenetic testing according to ploidy changes or well-known chromosomal rearrangements. Approximately 30% of patients with B-ALL, however, display none of the major chromosomal abnormalities. This population is classified together as B-other-ALL, a highly diverse subgroup with heterogenous genetic profiles, clinical characteristics, and outcomes.
Recent advances in gene expression profiling and sequencing allowed to identify multiple genetic drivers that confer distinct clinical and prognostic features in B-other ALL resulting in better understanding of this subgroup. Among them, B-ALL with specific gene expression signatures (i.e. BCR-ABL1-like and ETV6-RUNX1-like) have been described and included in the classification. However, due to the complex mechanisms underlying the phenotype, standard molecular and cytogenetic workup is not sufficient to make a diagnosis and there is still no universally accepted definition or diagnostic algorithm. Therefore, there is a need to improve our understanding of genetic aberrations driving B-other ALL, screen for unknown lesions, and associate these findings with clinical picture.
Aims:
Genetic and cytometric characteristics of pediatric B-other ALL cohort treated in a single center in Poland to evaluate population frequencies of known ALL subtypes, genetic aberrations, immunophenotypes, and evaluate their associations with outcome and clinical and demographic parameters.
Methods
The study included 54 consecutive children (aged 1-18 years) diagnosed in 2014-2022 with B-other ALL, i.e. excluding hyperdiploidy, hypodiploidy, ETV6-RUNX1, BCR-ABL1, TCF3-PBX1, and KMT2A-fusions. In all samples, targeted RNA sequencing using FusionPlex Acute Lymphoblastic Leukemia library preparation kit (ArcherDx) and digital MLPA using SALSA digital MLPA assay were performed. The samples were sequenced on Illumina MiSeq platform. RNAseq data were analyzed using Archer Analysis software v7.0 and aimed to identify fusions, point mutations and expression levels in 81 genes, including fusion transcripts with unknown partners. MLPA data were analyzed using Coffalyser digitalMLPA software. All novel in-frame fusion transcripts were confirmed with Sanger sequencing. Cytometric evaluation included both standard and extended panel of immunophenotypic markers, i.e. CD45, CD3, CD19, CD34, HLA-DR, phospho-TYR, phospho-STAT3, phospho-STAT5, phospho-CRKL, CRLF2 CD127, CD115, CD25, SOCS1, BLNK, CD97, CD99, CD140A, CD140B, and viability stains (FVS780 and/or 7AAD). Clinical data was obtained retrospectively from medical records.
Results:
The cohort included 35% of BCR-ABL1-like cases, 2% ETV6-RUNX-like, and 5,5% PAX5 rearranged (1 fusion, 2 mutations). Mutations activating RAS/RAF-MAPK signaling were observed in 64% of cases and spread across all subtypes. JAK-STAT class aberrations were observed in 37% cases whereas ABL-class aberrations - in 7,2%.
Three novel in-frame fusion transcripts were detected, including two lesions affecting cytokine/kinase signaling related to BCR-ABL1-like phenotype (TCOF3/PDGFRB and CD74/PDGFRB) and one affecting DNA repair mechanisms (SSBP2/CHD1).

Novel aberrations were associated with poor prognosis. In addition, HOOK3/FGFR1 fusion transcript previously described for other hematological malignancies, but not in ALL, was detected in a single subject. Except for CRLF2, none of the single markers alone allowed to distinguish new subtypes of ALL. However, multiparameter statistical analysis of the data allowed to build a Ph-like ALL predictor for the identification of Ph-like ALL cases

Conclusion:

Our study shows population-based frequencies of novel ALL subtypes, including both recurrent and novel genetic aberrations. This data widens our knowledge on the interplay between molecular aberrations and clinical course of the disease and provides clues for diagnostics optimization.

Disclosures No relevant conflicts of interest to declare.

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