Acute Leukemias

PEDIATRIC PAX5-REARRANGED ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) IS A HIGH-RISK MOLECULAR SUBGROUP OF B-ALL WITH A POOR MRD-DEPENDENT PROGNOSTIC PROFILE

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Introduction: PAX5-altered acute lymphoblastic leukemia (PAX5-alt ALL) is a recently defined molecular subtype of BCP-ALL, which displays a specific gene expression and is frequently associated with PAX5 aberrations, including rearrangements (PAX5r). Poor/intermediate outcomes were reported for PAX5-alt ALL. However, evidence on clinical features and prognosis of pediatric PAX5r ALL remains limited.

Methods: Clinical data of all newly diagnosed PAX5r ALL patients (pts) (<18 years) enrolled in the consecutive AIEOP-BFM ALL trials (ALL 2000, NCT0061345; ALL 2009, NCT01117441; ALL 2017, NCT03643276) or observational studies in Italy (AIEOP), Germany and Austria (BFM) between 2001-2024, were retrospectively collected. PAX5 gene fusions were identified either by cytogenetics, FISH, targeted-RNAseq or whole-RNA-seq (WTS).

Results: Overall, 165 pts with a confirmed PAX5r ALL were included in the study. Sixty-five different fusion gene partners were identified, with JAK2 (n=22), NOL4L (N=18), AUTS2 (n=13) and ETV6 (n=12) as the most frequent ones. Median age was 3.4 yrs (0.4-17.8) and 66.1% of the pts were males. Low incidence of CNS involvement (CNS3, 3.8%) and a high rate of hyperleukocytosis (WBC>100x109/L) (22%) was found. According to NCI criteria, 53.3% had high-risk (HR) status. IKZF1plus profile was found in 15.1% of the pts. A tendency to slow treatment response was observed: 13% of pts had prednisone poor response (PPR), 74.7% were PCR-M-RD+ at the end of induction (EOI), with 28.6% showing MRD≥5x10-4, and 31.5% were still PCR-MRD+ at the end of consolidation. Per protocol final risk stratification: 25.8%, 42.9% and 31.3% of the pts were standard-risk (SR), medium-risk (MR) and HR, respectively. Further, we restricted the analyses solely to the consecutive PAX5r pts (n=99) enrolled in the AIEOP-BFM ALL 2017 study and compared their clinical features with all non-PAX5r pts (n=1945) enrolled in the same protocol. ETV6::RUNX1 pts were excluded from the analysis. Lower median age at diagnosis (3.4 vs 4.7 yrs), higher hyperleukocytosis rate (23.2% vs 8%, p<0.001), increased rate of IKZF1plus profile (14.4% vs 7.8%, p=0.02) and NCI HR status (57.6% vs 39.1%, p<0.001) were observed in the PAX5r group. No relevant differences in terms of treatment response and risk-stratification distribution were found between the two groups, except for a higher frequency of PPR (14.4% vs 5.7%, p=0.001) in the PAX5r ALL.

With a median follow-up of 3.6 yrs, 5-yr EFS and OS for the AIEOP-BFM ALL 2009/2017 PAX5r pts (n=116) were 66.8±5.0% and 95.3±2.1%, respectively; 5-yr EFS were 100%, 59.8±9.3% and 43.8±12.7% for standard-risk (SR), medium-risk (MR) and high-risk (HR) groups, respectively, indicating that the poor prognostic impact of PAX5r applies only when EOI MRD is positive (MR/HR).

Conclusions: This multinational retrospective study indicates that PAX5r ALL is frequently associated with HR clinical features and unfavorable outcomes in non-SR pts.