Detection of Deletion in the IKZF1 Gene and the NOTCH1 Signaling Pathway in Patients with T-cell Acute Lymphoblastic Leukemia: Data of the RALL Study Group

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Background

In 2017, two new groups from lymphoid precursors were identified in the WHO classification of tumors: early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) and BCR-ABL1-like acute lymphoblastic leukemia (ALL). ETP-ALL is characterized by a unique immunophenotype, unfavorable molecular anomalies and low survival.

Mutation in the *NOTCH1* is the most frequent event in patients with T-acute lymphoblastic leukemia (ALL). This mutation is associated with a favorable prognosis. Deletion of the *IKZF1* gene, occurring in patients with T-ALL in about 10% of cases, is a prognostically unfavorable anomaly.

Objective

To evaluate the survival of patients with T-ALL depending on the immunophenotype, as well as to analyze the frequency of occurrence of anomalies in the *NOTCH1* and *IKZF1* genes.

Materials & Methods

The analysis included 91 patients with T-ALL/LBL receiving therapy according to the ALL-2016 protocol. The immunophenotype was determined by flow cytofluorimetry.

Anomalies in the *NOTCH1* and *IKZF1* were investigated by fragment analysis according to Caye A, et al and Campregher PV, et al in 25 and 29 patients, respectively.

Results

From December 2016 to June 2021, 91 patients with T-ALL were included in the ALL-2016 protocol (64 men and 27 women (median 32 years)): 6 – TIV, 11 - ETP-ALL, 32 – TI/II, 42 – TIII.

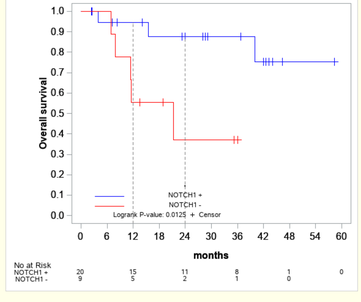
3-year overall survival in the ETP group was 28%, TI/II – 50%, TIII – 73%, TIV – 83%. Molecular anomalies in the NOTCH1 were analyzed by fragment analysis in 29 patients (1 – undifferentiated variant, 8 - ETP-ALL, 9 - TIII, 10 - TIII, 1 - TIV), in *IKZF1* genes in 25 patients (1 – undifferentiated variant, 5 - ETP-ALL, 8 - TIII, 10 - TIII, 1 - TIV). None of the patients had deletions in the *IKZF1*. Anomalies in the *NOTCH1* were detected in 20 (69%) patients (4 – ETP-ALL, 7 – TII, 8 – TIII, 1 – TIV).

At the same time, 16 of them (55%) had *NOTCH1* deletions, 4 (14%) had insertions.

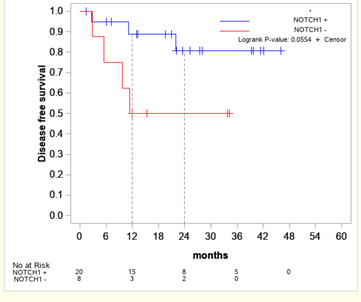
5 patients without abnormalities in the *NOTCH1* (55%) died as a result of a resistant or relapse, 4 patients are alive in remission. In the group of patients with an anomaly in the *NOTCH1*, 3 patients (15%) died, the remaining 17 patients (85%) are alive in remission.

Overall survival was 85% in the group with anomalies versus 44% in the group without anomalies (p=0.0125).

Disease free survival was 85% in the group with anomalies versus 50% in the group without anomalies (p=0.05). One patient in the group without the anomaly was unable to achieve remission.



Overall survival in the groups with anomalies in *NOTCH1* and without anomalies in *NOTCH1*



Disease free survival in the groups with anomalies in *NOTCH1* and without anomalies in *NOTCH1*

Conclusion

The identification of genetic markers of an unfavorable prognosis is of fundamental importance for the choice of tactics for the treatment of acute lymphoblastic leukemia.

ETP-ALL is an unfavorable immunophenotype of T-ALL and requires intensification of therapy with the inclusion of allogeneic bone marrow transplantation in the first remission.

Anomalies in the NOTCH1 signaling pathway are the most common in patients with T-ALL. This mutation is associated with a more favorable course of the disease.