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603.LYMPHOID ONCOGENESIS: BASIC

A New t(7;9)(p12;q34) Involving *NOTCH1* and *IKZF1* in Pediatric T-Cell Lymphoblastic Lymphoma

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Background

Notch1 pathway activation is demonstrated in approximately 50% of T-cell acute lymphoblastic leukemias/lymphomas (T-ALL/LL) mainly by the presence of activating somatic mutations of *NOTCH1* involving homodimerization and/or PEST (proline, glutamic acid, serine, threonine) domains. The oncogenic role of *NOTCH1* was however primarily described with the characterization of the recurrent although rare t(7;9)(q34;q34). By positioning the coding region of the intracellular part of Notch1 (ICN1) under the control of the *TCR* beta-gene promoter, this translocation generates a truncated Notch1 receptor resulting in constitutive activation of the Notch1 pathway, independent of ligand binding. In murine models ICN1 is much more pro-oncogenic than *NOTCH1* activating mutations. While several retrospective studies identified *NOTCH1* activating mutations as an independent good-prognostic factor in human T-ALL/LL, search for truncated ICN1 in *NOTCH1* wild-type patients was usually not performed/considered.

Aim

To describe and characterize a new translocation in a pediatric patient with T-LL.

Method

Somatic cytogenetics of blastic T-cells from diagnosis was explored by conventional karyotype. A specific fluorescence *in situ* hybridization (FISH) Breakapart probe was designed to explore the *NOTCH1* locus on chromosome 9q34. Targeted locus amplification based sequencing (TLA) using genomic DNA was used to confirm/determine the partners involved in the new fusion found. Targeted RNA-sequencing using the Illumina TruSight RNA Fusion Panel was used to determine the putative transcript produced by the fusion.

Results

The patient, a 14-year-old young female, was diagnosed with stage 3 T-LL characterized by a large mediastinal mass with massive pleural effusion. Flow cytometry demonstrated a CD7+, CD1a+, CD4+/CD8+ double positive phenotype corresponding to EGIL type III T-LL. Conventional karyotype on T-lymphoblastic cells showed two clonal abnormalities, a deletion del(6)(q13q22) and a translocation t(7;9)(p12;q34) in 10 metaphases analyzed. Involvement of *NOTCH1* in this new t(7;9)(p12;q34) was confirmed by molecular cytogenetics using a FISH Breakapart probe targeting the *NOTCH1* locus. Targeted locus amplification based sequencing (TLA) revealed *IKZF1* as the fusion partner involved in this new fusion. DNA sequencing revealed a predictive fusion between the intracellular domain of *NOTCH1* (ICN1; breakpoint in intron 26 (NM_017617.5)) and *IKF1* (breakpoint in intron 5 (NM_006060)). The targeted RNA-sequencing performed on the pleural effusion confirmed an in frame *NOTCH1-IKZF1* fusion transcript. Sequencing of exons 26-27 and 34 of *NOTCH1* showed wild-type alleles. After a swift response to the induction phase, the patient is in complete remission one year after completing her treatment according to the EuroLB-02 protocol.

Summary/perspectives

This new t(7;9)(p12;q34) involving ICN1 illustrates the importance to look for ICN1 more extensively in parallel to *NOTCH1/FBXW7* mutations in the screening of Notch1 activation pathway in T-ALL/LL specially in the event of a stratification on Notch1 status for treatment. As both *NOTCH1* and *IKZF1* are major actors of normal T-cell differentiation/proliferation, the oncogenic role of the fusion *NOTCH1::IKZF1* in T-ALL/LL deserves a better understanding in a larger population and will be further explored.

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