NOTCH1 gene fusions in pediatric T-cell precursor lymphoblastic lymphoma

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T-cell lymphoblastic lymphoma (T-LBL) is a common pediatric malignancy accounting for approximately 20% of the non-Hodgkin lymphomas during childhood. Survival rates of T-LBL are ~80%, but outcome after relapse is dismal, with salvage rates reaching only ~15%. Currently, we can identify a genetically low-risk subgroup in pediatric T-LBL, yet these high-risk patients who need intensified or alternative treatment options remain undetected. Therefore, there is an urgent need to recognize these high-risk T-LBL patients through identification of molecular characteristics and biomarkers. RNA sequencing (RNAseq) has been developed into an important diagnostic tool for the identification of gene fusions and gene expression profiles in many types of diseases including acute lymphoblastic leukemia and lymphomas. Using this technique on 29/49 T-LBL patients diagnosed in the Princess Maxima Center for Pediatric Oncology between 2018-2023, we discovered a previously unknown high-risk biological subgroup of children with T-LBL. This subgroup is characterized by *NOTCH1* gene fusions, found in 21% of our T-LBL cohort (6/29). All patients presented with a large mediastinal mass, pleural/pericardial effusions, and absence of blasts in the bone marrow, blood, and central nervous system. Blood CCL17 (C-C Motif Chemokine Ligand 17, also known as TARC) levels were measured at diagnosis in 26/29 patients, and all six patients with *NOTCH1* gene fusions patients exclusively expressed highly elevated blood CCL17 levels, defining a novel and previously not known clinically relevant blood biomarker for T-cell lymphoblastic lymphoma. Four out of these six patients relapsed during therapy, a fifth developed a therapy-related acute myeloid leukemia during maintenance therapy. These data indicate that T-LBL patients with a *NOTCH1* fusion have a high risk of relapse which can be easily identified using a blood CCL17 screening at diagnosis. *CCL17* transcript levels were increased in T-LBLs that carried a *NOTCH1* gene fusion, suggesting that the high CCL17 blood levels were expressed by the tumor. Furthermore, T-LBL tumors with a *NOTCH1* gene fusion exhibited highly elevated expression levels of CD1a compared all other T-LBL samples. CD1a is currently explored as a potential target for CAR T-cell therapy for which these high-risk patients might benefit as well. In conclusion, we have identified a high-risk group of patients, that can be identified by RNAseq and a blood biomarker, with a possible target for therapy.