soho2023
ELEVENTH ANNUAL MEETING

CLINICAL AND MOLECULAR FEATURES OF PEDIATRIC BCP-ALL WITH TSLP RECEPTOR (CRLF2) EXPRESSION

J. KOŁODRUBIEC[1], K. MIARKA-WALCZYK[1], Z. URBAŃSKA[1], L. SĘDEK[2], M. LEJMAN[3], J. TRELIŃSKA[1], S. JANCZAR[1], W. MŁYNARSKI[1]

1. Department of Pediatrics, Oncology, and Hematology, Medical University of Lodz, Lodz, Poland
2. Department of Pediatric Hematology and Oncology, Zabrze, Medical University of Silesia, Katowice, Poland
3. Laboratory of Genetic Diagnostics, Medical University of Lublin, Lublin, Poland

MEDICAL UNIVERSITY OF LODZ

INTRODUCTION

B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is a heterogeneous disease with multiple molecular subtypes associated with different prognostic significance. High expression of TSLP receptor (CRLF2) protein on the leukemic surface has been correlated with poor outcomes and reduced survival.

AIM

The aim of this study was to determine whether high expression of CRLF2 as a single factor or coexistence of other molecular rearrangements and activation of the JAK/STAT signaling pathway is responsible for poor prognosis in BCP-ALL patients.

Since June 2021, all newly diagnosed patients with ALL, from 16 Pediatric Oncology Centers in Poland, treated according to the clinical AIEOP BFM 2017 Poland clinical trial were enrolled in the study.

METHOD

426 pediatric patients enrolled in the study and examined for TSLPR surface expression on leukemic cells

Flow Cytometry

21 patients positive for TSLPR surface expression tested for point mutations and gene fusions

FISH, RNA-seq

RESULTS

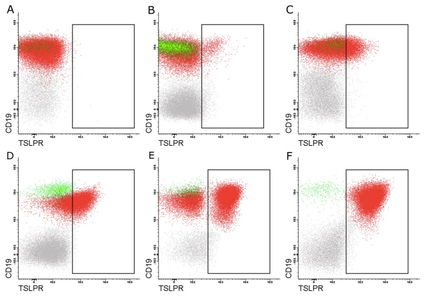


*Figure 1. Flow cytometry profiles showing different TSLPR expression patterns on leukemic cells. Representative FACS plots showing surface TSLPR staining in (**A**) negative control sample and TSLPRpos patients with (**B**) bimodal dim pattern (low expression on the blast subclone) (**C**) heterogeneous low expression (negative to dim) in some blasts; (**D**) homogeneous dim expression on all blasts; (**E**) bimodal strong pattern (high expression on the blast subclone); and (**F**) homogeneous strong expression on all blasts.*
Note: The rectangles represent blasts positive for TSLPR; red- leukemic blasts; green- mature B-cells (TSLPR negative), gray - other cells (TSLPR negative)

Nr	Age	Sex	WBC initial 1/µl	Risk Group	TSLPR	IKZF1	JAK/STAT	Gene fusions	Other fusion	Point mutations
1	2	F	2360	SR	99,0	negative	positive	CRLF2::P2RY8		JAK2
2	3	M	4280	MR	11,0	negative	negative	PAX5::CBFA2T3		KRAS
3	4	F	18840	SR	99,0	positive	positive	CRLF2::P2RY8		JAK2
4	**17**	**F**	**549280**	**HR**	**100,0**	**negative**	**positive**	**CRLF2::IGH**		**CRLF2**
5	2	M	110180	SR	91,0	ND	positive	CRLF2::P2RY8	KMT2A::ZC3H7B	NRAS
6	10	M	82840	HR	100,0	positive	positive	CRLF2::P2RY8		JAK2
7	2	F	3090	MR	15,0	negative	positive	NUP214::ABL1	TFG::GPR128	-
8	3	M	1440	SR	10,0	negative	negative	TFG::GPR128		-
9	2	M	3260	MR	100,0	negative	positive	CRLF2::P2RY8		JAK2
10	3	M	6040	SR	98,0	negative	positive	CRLF2::P2RY8		CRLF2
11	**15**	**M**	**107570**	**HR**	**97,0**	**positive**	**positive**	**CRLF2::IGH**		**JAK2**
12	5	M	15310	MR	100,0	negative	positive	CRLF2::P2RY8		
13	**5**	**F**	**13470**	**MR**	**100,0**	**negative**	**positive**	**CRLF2::P2RY8**		**NRAS**
14	11	F	117	HR	24,0	ND	negative	KMT2A::MLLT3		-
15	2	M	14360	MR	100,0	negative	positive	CRLF2::P2RY8		JAK2
16	2	F	6660	SR	98,0	negative	positive	CRLF2::P2RY8		CRLF2
17	10	F	3460	MR	99,0	negtive	positive	CRLF2::P2RY8		NRAS
18	4	M	40000	MR	99,0	negative	positive	CRLF2::IGH		JAK2
19	**14**	**M**	**120860**	**HR**	**96,0**	**positive**	**positive**	**CRLF2::IGH**		**KRAS**
20	3	F	84000	SR	97,0	negative	positive	CRLF2::P2RY8		JAK2
21	**3**	**F**	**24820**	**HR**	**99,0**	**negative**	**positive**	**CRLF2::P2RY8**		**-**

Table 1. The study group consisted of patients with BCP-ALL in which expression of CRLF2 was found. 17 patients had strong, and 4 had a dim expression of CRLF2. In 18 patients gene fusions as CRLF::P2RY8; CRLF2::GH, and NUP214::ABL1 were detected. Point mutations In CRLF2 and JAK2 were identified in 3 and 6 patients, respectively. In 10 patients, more than one rearrangement was noticed, and in 4 patients neither gene fusion nor point mutations responsible for the positive expression of CRLF2 were found. 4 patients harbored IKZF1 deletion. Patients were stratified into standard (n=7; 33,3%), medium (n=8; 38,1%), and high (n=6; 28,6%) risk groups. Median age of the study group was 3.0 years.
Note: bolded- 5 patients who received targeted therapy (ruxolitinib).

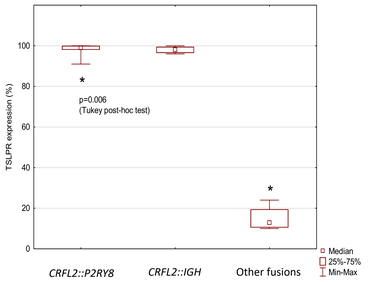


Figure 2. Level of TSLPR expression on presence of CRLF2::P2RY8/ CRLF::IGH/other fusion
p=0.0065 in global test Kruskall-Wallis test.
Note: Expression of TSLPR in the whole group median (range) 99% (96 – 100%)
CRLF2::P2RY8 99% (98 – 100%)
CRLF2::IGH 98% (96.5 – 99.5-%)
Other fusion 13% (10.5 – 19.5-%)

CONCLUSIONS

Patients with TSLPR expression are subjected to advanced molecular diagnostics as they consist a very heterogeneous molecular subgroup.

Patients with CRLF2::IGH fusion were stratified more often into the high-risk group (75%) and the median age of this group was 14.5 years.

The most frequent point mutations in TSLPR-positive patients were as follows *CRLF2, JAK2, NRAS,* and *KRAS.*

In patients with poor response to the standard treatment and kinase-activating aberrations, targeted therapy with JAK/STAT inhibitors (ruxolitinib) may be considered.

REFERENCES

Wang J et al. The prognostic significance of CRLF2 expression at diagnosis in adult Ph-negative B-cell precursor acute lymphoblastic leukemia.
Leuk Lymphoma. 2023 Mar;64(3):698-706

Harvey R-C et al. Clinical diagnostics and treatment strategies for Philadelphia chromosome–like acute lymphoblastic leukemia.
Blood Adv 2020; 4 (1): 218–228

Pastorczak A et al. Surface expression of Cytokine Receptor-Like Factor 2 increases risk of relapse in pediatric acute lymphoblastic leukemia patients harboring IKZF1 deletions.
Oncotarget. 2018 May 25;9(40):25971-25982

Jain N et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults.
Blood. 2017 Feb 2;129(5):572-581

ACKNOWLEDGEMENTS

The study was supported by Childhood ALL in Poland (CALLPOL) project: a national harmonization of diagnostics and treatment of acute lymphoblastic leukemia in children (2019/ABM/01/00069-00), and the Polish Medical Research Agency.

CONTACT INFORMATION

Julia Kołodrubiec, M.D., Ph.D. Candidate
Department of Pediatrics, Oncology, and Hematology
Medical University of Lodz
Sporna Street 36/50, 91-738 Lodz
julia.kolodrubiec@stud.umed.lodz.pl