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GERMLINE VARIATIONS OF ETV6 MUTATION IN PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIAS: A STUDY OF FAMILIES WITH VERIFIED GERMLINE ETV6 MUTATION IN POLAND

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INTRODUCTION

ETV6 gene encodes a transcription factor connected to type 5 thrombocytopenia and acute lymphoblastic leukemia.

Its involvement in other regulatory pathways and recent case reports indicate, that it may influence the toxicity of treatment of acute lymphoblastic leukemia and incidence of adverse events.

In this study, we report on patients diagnosed with acute lymphoblastic leukemia and germline ETV6 mutation, with focus on how the mutation influenced the course and outcome of treatment

AIM

To establish incidence of germline *ETV6* mutation is population of polish pediatric patients with acute lymphoblastic leukemia and effect it may have on treatment

METHOD

Between October 2018 and January 2024 consecutive pediatric patients with were screened for germline ETV6 mutations.

On confirmation, additional blood and bone marrow samples were taken from subjects and their families for further genetic diagnostics, blood and bone marrow cells subpopulations composition and immunoglobulin levels analysis.

The treatment of patients was monitored through reports to investigators, medical history and medical follow-up.

CONCLUSIONS

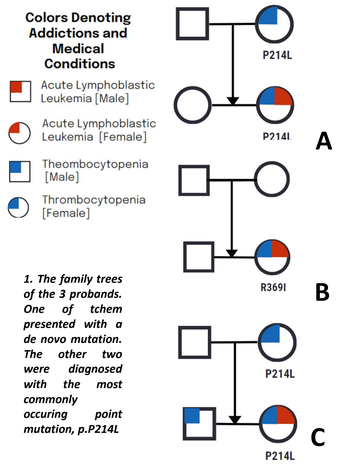
Patients with diagnosed germline *ETV6* experienced adverse events during treatment, that resulted in delays in protocol and intermissions, mainly due to severe thrombocytopenia.

Obtained results show, that thrombocytopenia induced by germline *ETV6* mutations may influence the treatment and prolong it. Routine diagnosis of patients with ALL for germline *ETV6* mutatiions may help prevent adverse events during treatment.

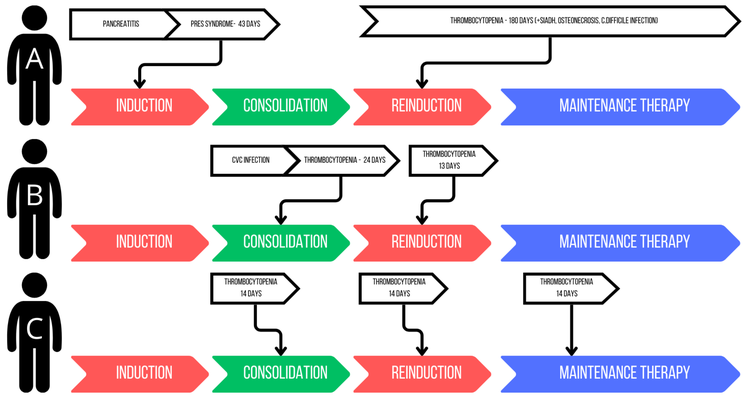
Further study on a bigger group is necessary in order to establish the link between germline *ETV6* mutations and adverse events.

RESULTS

Out of 1276 persons diagnosed with acute lymphoblastic leukemia between years 2018 and 2024 in Poland, 3 were diagnosed with germline *ETV6* mutations. The results of their genetic testing, family history and medical history are presented below. All were treated according to AIEOP BFM 2017 protocol:



1. The family trees of the 3 probands. One of tchem presented with a de novo mutation. The other two were diagnosed with the most commonly occuring point mutation, p.P214L



2. Timelines representing intermissions during treatment in all 3 probands, their lenghth and when did they occur. All patients experienced thrombocytopenia severe enough, that the treatment protocol needed to be modified based on the platelet count, not leukocyte count. The intermissions occured mostly in consolidation phase and later.

	Proband A	Proband B	Proband C
CBC upon admission (white-blood cell count, hemoglobin, platelet count,neutrophile count, erythrocyte volume]	WBC – 4.30 [thd/ul] Hgb – 8.9 [g/dL] PLT – 30 [thd/ul] ANC – 3.23 [thd/ul] MCV – 90 [fl]	WBC – 2.6 [thd/ul] Hgb – 6.5 [g/dL] PLT – 107[thd/ul] ANC – 0.88 [thd/ul] MCV – 103 [fl]	WBC – 2.33 [thd/ul] Hgb – 10.9 [g/dL] PLT – 2 [thd/ul] ANC – 0.28 [thd/ul] MCV – 92 [fl]
***ETV6* mutation DNA and protein annotation, inheritance**	c.641C>T p.Pro214Leu Maternal inheritance	c.1157G>T (pArg386Ile) De novo mutation	c.641C>T p.Pro214Leu Maternal inheritance
Leukemia subtype, organ involvement, risk group	preB-ALL CNS 1 no organ involvement High Risk	preB-ALL CNS 2a splenomegaly Standard Risk	preB-ALL CNS 1 no organ involvement Standard Risk
Leukemia molecular characteristics (gene fusions, karyotype, somatic mutations)	*IKZF* and *PAX5* deletion – *IKZF plus* deletion profile	Hiperdiploidy	Hiperdiploidy
Treatment course, response to therapy, prednisone response, Minimal Residual Disease	Prednisone Good Response 15th day MRD – 3.99% TP1 MRD– positive ($3*10^3$/ml) TP2 MRD - negative No HRCT indications	Prednisone Good Response 15th day MRD – <0.1% TP1 MRD –negative TP2 MRD - negative No HRCT indications	Prednisone Good Response 15th day MRD – 0.03% TP1 MRD –negative TP2 MRD - negative No HRCT indications
Time of follow-up, disease status, last platelet count, therapy stage	10 months after end of treatment In remission PLT – 44 [thd/ul]	Undergoing maintenance therapy In remission PLT – [111 thd/ul]	3 years after end of treatment In remission PLT – [24 thd/ul]

3. Leukemia characteristics of all 3 probands. All of them were diagnosed with B-cel ALL. All achieved remission. Proband B is still undergoing maintenance therapy

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