

# First-line treatment failure in childhood acute lymphoblastic leukemia

## The polish pediatric leukemia and lymphoma study group experience

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### Abstract

The aim of this study was to evaluate the risk factors of relapse and treatment-related deaths in acute lymphoblastic leukemia (ALL) in children residing in Poland.

A total of 1872 patients with newly diagnosed ALL, treated according to the ALL IC-BFM 2002 protocol in 14 Polish pediatric hematology centers from 2002 to 2012 were included in the study. Three-hundred eighty-four patients experienced treatment failure. The last follow-up was 31 December, 2016.

Univariate analysis identified factors in each risk group that were significantly different between children whose treatment failed and those who remained in the first remission. Multivariate analysis demonstrated that only the age of 10 years or over at primary diagnosis in the high-risk group was an adverse prognostic factor. To facilitate the analysis, patients were divided into three groups: relapsed children who survived; relapsed children who died; children without relapse who died due to toxicity.

Our analysis showed that age older than 10 years is a particular risk factor for the failure of first-line of treatment, both in terms of relapse and treatment-related mortality.

**Abbreviations:** ALL = acute lymphoblastic leukemia, ALL IC-BFM 2002 protocol = acute lymphoblastic leukemia intercontinental Berlin-Frankfurt-Münster protocol, BCP-ALL = B-cell precursor acute lymphoblastic leukemia, CNS = central nervous system, CR = complete remission (CR), CSF = cerebro-spinal fluid, HR = hazard ratio, HR = high-risk group, ID = induction death, SCT = stem cell transplantation, TRD = treatment-related death, WBC = white blood cell count.

**Keywords:** acute lymphoblastic leukemia, children, therapy failure

### 1. Introduction

Therapy of childhood acute lymphoblastic leukemia (ALL) has been successful during the last decades due to improvements in intensive combination chemotherapy and supportive measures.

Currently, treatment can cure approximately 75% to 80% of children with the disease.<sup>[1,2]</sup>

The vast majority of children are cured but some still experience first-line treatment failure. The most important reason for therapy failure is relapse. This occurs in approximately 15%

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to 20% of children with ALL, resulting in a relapse frequency of approximately 0.7 of 100 000 patients per year in Europe.<sup>[3]</sup> The overall survival from recurrent ALL is around 40% for patients undergoing intensive therapy, which may include stem cell transplantation (SCT).<sup>[3,4]</sup>

Another cause of first-line therapy failure are complications of chemotherapy.

The incidence of treatment-related deaths (TRDs) ranges from 2% to 3%.<sup>[5]</sup> Infections are the most common cause of death, but every organ can be affected by acute side effects of anti-leukemic chemotherapy.<sup>[1,5]</sup>

Here, we report on a large retrospective study regarding first-line treatment failures of patients with ALL in the Polish population. The present study may be useful for clinicians, because it involved a homogeneous group of children with ALL treated with the same protocol and in similar epidemiological conditions.

Part of the data on clinical outcomes of patients treated with this retrospective protocol have been reported elsewhere, but not in the context of a first-line therapy failure analysis. Therefore, we aimed to evaluate the risk factors of relapse and treatment-related deaths in children undergoing treatment with the ALL IC 2002 protocol in Poland.<sup>[5]</sup>

## 2. Materials and methods

A total of 1872 patients with newly diagnosed ALL, treated according to the ALL IC-BFM 2002 (Acute Lymphoblastic Leukemia Intercontinental Berlin-Frankfurt-Münster) protocol in 14 pediatric hematology centers from October 2002 to December 2012 in Poland were included in this retrospective study. Children were aged 1 to 18 years at the time of diagnosis. Children with Down's syndrome were excluded from the analysis. A total of 384 (20.5%) patients who experienced treatment failure were reported. The date of the last follow-up was 31 December, 2016. The demographic details are presented in the Results section in Table 2.

### 2.1. Definitions of first-line treatment failure

The definition of induction failure was the persistence of leukemic blasts in the bone marrow (M2 marrow defined as bone marrow with 5% to 24% blasts or M3 marrow with  $\geq 25\%$  blasts compared to M1 marrow with  $< 5\%$  blasts) on the 33rd day of induction phase of therapy. The definition of relapse, which occurred after the first complete remission was  $> 5\%$  blasts in the bone marrow, or leukemic infiltration elsewhere. Treatment-related deaths were defined as deaths due to chemotherapy complications or allogeneic stem cell transplantation (SCT).<sup>[2,5]</sup>

Criteria for the central nervous system (CNS) involvement at presentation of disease and relapse were as follows: absence of CNS involvement was defined as status 1; pleocytosis  $\leq 5/\mu\text{l}$  with clearly identified blasts on cytopsin of cerebro-spinal fluid (CSF) contaminated with blood was named status 2; non traumatic lumbar puncture with pleocytosis  $> 5/\mu\text{l}$  or damage to the brain/meninges seen in imaging studies or the presence of neurological symptoms were determined as status 3.<sup>[2,5]</sup>

### 2.2. The treatment protocol

Patients were treated according to the ALL IC-BFM 2002 protocol and stratified into risk groups (standard, intermediate,

high) depending on age, immunophenotype, genetics (fusion genes *BCR/ABL1*, *KMT2A/AFF1*), white blood cell count (WBC) at diagnosis, response to steroids and results of bone marrow on the 15th or 33rd day of therapy. The evaluation of minimal residual disease was not a standard in this protocol. Details of therapy and the stratification criteria in the risk groups were published by Sary et al.<sup>[5]</sup>

### 2.3. Supportive care

Supportive care procedures were defined in the treatment protocols. Those included prophylaxis with cotrimoxazole, preventing pneumonia caused by *Pneumocystis carinii*, broad-spectrum antibiotics and antifungal agents in patients with prolonged neutropenia and fever, recommendations for transfusion and guidelines for the prevention of tumor lysis syndrome.<sup>[5]</sup>

### 2.4. Statistical analysis

The statistical analysis was performed using the STATISTICA 12.0 software. Non-parametric tests such as Mann-Whitney U for comparing two groups and Kruskal-Wallis for comparing three groups, were used to perform a univariate analysis. Cox's proportional hazards regression model was used for a multivariate analysis of prognostic factors, estimating hazard ratio (HR) with 95% confidence intervals. A *P value*  $< .05$  was considered as statistically significant.

The study was approved by the ethics committee of the Medical University of Lublin, Poland.

The committee's reference number is: KE-0254/178/2002.

## 3. Results

Males were significantly more prevalent than females in the group of patients with treatment failure compared to children who were alive in the first complete remission (CR1) of the disease. The median age of children who experienced therapy failure was significantly higher than that of patients in CR1 (Table 1).

Univariate analysis identified factors in each risk group that were significantly different between children whose treatment failed and those who remained in the first remission: in the standard risk group, only the bone marrow blast count on the 15th day of the induction phase was significant, which is due to the stratification criteria; in the intermediate risk group, we found four prognostic factors: age, gender, CNS involvement and the bone marrow blasts count on the 15th day of therapy; in the high-risk group (HRG), we identified two factors, age and marrow blasts count on the 15th day of therapy. In our analysis, *KMT2A/AFF1* and *BCR/ABL1* rearrangement were not risk factors for first line therapy failure in the univariate analysis (Table 2).

**Table 1**  
Patient data with and without therapy failure.

Factor	Patients with therapy failure	Patients without therapy failure
Median age (years)	8.57 (quartile 3.7–13.2)	4.9 (quartile 3.08–8.96)
Sex		
Female	143 (37.2%)	670 (45%)
Male	241 (62.8%)	818 (55%)

**Table 2**

The univariate analysis of factors that were significantly different in ALL children whose first line treatment failed, as compared to those who remained in the first remission depending on risk groups.

Factor	SRG			IRG			HRG		
	Patients with therapy failure n=66	Patients without therapy failure n=545	P	Patients with therapy failure n=181	Patients without therapy failure n=717	P	Patients with therapy failure n=137	Patients without therapy failure n=226	P
Median age (years)	3.4	3.5	.7	9.4	7.7	.008	11.3	6.6	< .001
Sex			.02			.04			.07
Female	30 (45.59%)	251 (46.1%)		65 (35.9%)	318 (44.4%)		48 (35%)	101 (44.7%)	
Male	36 (54.5%)	294 (53.9%)		116 (64.1%)	399 (56.6%)		89 (65%)	125 (55.3%)	
WBC			–			.09			.3
< 20,000/ $\mu$ l	66 (100%)	545 (100%)		83 (45.9%)	371 (51.7%)		53 (38.7%)	95 (42%)	
$\geq$ 20,000/ $\mu$ l < 100,000/ $\mu$ l	–	–		73 (40.3%)	276 (38.5%)		43 (31.4%)	79 (35%)	
$\geq$ 100,000/ $\mu$ l	–	–		25 (13.8%)	70 (9.8%)		41 (29.9%)	52 (23%)	
CNS status			.3			.02			.5
1	60 (91%)	506 (92.8%)		149 (82.3%)	639 (89.1%)		115 (83.9%)	194 (85.8%)	
2	3 (4.5%)	25 (4.6%)		16 (8.8%)	40 (5.6%)		9 (6.6%)	15 (6.6%)	
3	3 (4.5%)	14 (2.6%)		16 (8.8%)	38 (5.3%)		13 (9.5%)	17 (7.5%)	
KMT2A/AFF1 status			–			–			.8
Positive	–	–		–	–		9 (6.7%)	12 (5.3%)	
Negative	–	–		–	–		98 (71.53%)	160 (70.8%)	
No data	–	–		–	–		30 (21.9%)	54 (23.9%)	
BCR/ABL1 status			–			–			.3
Positive	–	–		–	–		27 (19.7%)	39 (17.3%)	
Negative	–	–		–	–		100 (73%)	175 (77.4%)	
No data	–	–		–	–		10 (7.3%)	12 (5.3%)	
Immunophenotype			.4			.3			.8
PreB common positive	57 (86.4%)	449 (82.4%)		125 (69.1%)	518 (72.2%)		85 (62%)	136 (60.1%)	
PreB common negative	8 (11.1%)	88 (16.1%)		30 (16.6%)	116 (16.2%)		16 (11.7%)	30 (13.3%)	
T-ALL	1 (1.5%)	8 (1.5%)		24 (13.3%)	82 (11.4%)		35 (25.5%)	60 (26.5%)	
AHL	–	–		2 (1.1%)	1 (0.1%)		1 (0.7%)	0 (0%)	
Prednisone response			–			–			.07
Good	–	–		–	–		62 (45.3%)	81 (35.8%)	
Poor	–	–		–	–		75 (84.7%)	145 (64.1%)	
BM 15 day			.04			.001			.003
M1	48 (72.7%)	451 (82.8%)		126 (69.6%)	579 (80.8%)		32 (23.4%)	83 (36.7%)	
M2	18 (27.3%)	94 (17.3%)		49 (27.1%)	123 (17.2%)		31 (22.6%)	53 (23.5%)	
M3	–	–		6 (3.3%)	15 (2.1%)		74 (54%)	90 (39.8%)	
BM 33 day			–			–			.5
M1	–	–		–	–		116 (84.7%)	196 (86.7%)	
M2	–	–		–	–		12 (8.8%)	26 (11.5%)	
M3	–	–		–	–		9 (6.6%)	4 (1.8%)	

“–” not analyzed due to these factors were stratification criteria for IRG (KMT2A/AFF1 & BCR/ABL1 negative status; good prednisone response; BM 33 day). AHL = acute hybrid (biphenotypic) leukemia, BM = bone marrow, CNS = central nervous system, HRG = high-risk group, IRG = intermediate-risk group, M1 = blasts < 5%, M2 = blasts  $\geq$  5 < 25%, M3 = blasts  $\geq$  25%, SRG = standard risk group, WBC = white blood cells.

The multivariate analysis demonstrated that only the age of 10 years or over at primary diagnosis in the HRG was an adverse prognostic factor (Table 3).

In our study, 253 out of 1872 children relapsed (13.5% relapse rate), a rate similar to that of many countries. CNS-positive status at relapse occurred in 4 out of 253 (1.6%) patients. Out of 4 children, 3 died. A total of 131 patients, who did not show ALL recurrence, died because of treatment toxicity. The studied patients were divided into three groups and clinical details of these groups are presented in Table 4. We found statistically significant differences in terms of clinical features among these groups. The children who died due to relapse or toxicity were older, had higher WBC, more often experienced T-cell ALL (T-ALL) or acute hybrid/biphenotypic leukemia (AHL) and were more frequently included in the HRG compared to relapsed patients who remained alive. Moreover, the patients who died

**Table 3**

The multivariate analysis of factors that was significantly different in children with ALL whose first line treatment failed, as compared to those who remained in the first remission depending on risk groups.

Factor	Hazard ratio (range)	P
Age, years 10–18 vs 1 - < 10	1.99 (1.62–2.45)	< .001
WBC $\geq$ 100,000/ $\mu$ l vs < 100,000/ $\mu$ l	1.17 (1.01–1.36)	.03
CNS status 3 vs 1,2	1.25 (1.04–1.5)	.02
Risk group, HR vs SR or IR	1.49 (1.28–1.75)	< .001
Prednisone response, PGR vs PPR	0.67 (0.47–0.95)	.02
BM 15 day M3 vs M1, M2	1.62 (1.29–2.05)	< .001

BM = bone marrow, CNS = central nervous system, HRG = high-risk group, IRG = intermediate-risk group, M1 = blasts < 5%, M2 = blasts  $\geq$  5 < 25%, M3 = blasts  $\geq$  25%, PGR = prednisone good response, PPR = prednisone poor response, SRG = standard risk group, WBC = white blood cells.

**Table 4**

**Clinical details of children with ALL who underwent the first line treatment failure divided into three groups of those patients: relapsed children who survived (group 1), relapsed ones who died (group 2), children without relapse, who died due to toxicity (group 3).**

Clinical features	Group 1 n=116	Group 2 n=137	Group 3 n=131	P
Median age (years)	5.5	9.6	10.1	.001
Median time of follow up, range	8.6 (4.1–13.8)	2.4 (0.4–8.6)	0.6 (0.003–9.1)	.001
Sex				.54
Male	77 (66.4%)	86 (62.8%)	78 (59.5%)	
Female	39 (33.6%)	51 (37.2%)	54 (41.2%)	
WBC				.001
< 20,000/ $\mu$ l	73 (62.9%)	62 (45.3%)	66 (50.4%)	
$\geq$ 20,000/ $\mu$ l < 100,000/ $\mu$ l	32 (27.6%)	50 (36.5%)	35 (26.7%)	
$\geq$ 100,000/ $\mu$ l	11 (9.5%)	25 (18.2%)	30 (22.9%)	
CNS status				.25
1	103 (88.8%)	113 (82.5%)	108 (82.4%)	
2	8 (6.9%)	9 (6.6%)	11 (8.4%)	
3	5 (4.3%)	15 (10.9%)	12 (9.2%)	
<i>KMT2A/AFF1</i> status				.11
Positive	2 (1.7%)	3 (2.2%)	4 (3.1%)	
Negative	85 (73.3%)	102 (74.5%)	94 (71.8%)	
No data	29 (25.0%)	32 (23.4%)	33 (25.2%)	
<i>BCR/ABL1</i> status				.83
Positive	4 (3.4%)	9 (6.6%)	14 (10.7%)	
Negative	106 (91.4%)	117 (85.4%)	105 (80.2%)	
No data	6 (5.2%)	11 (8.0%)	12 (9.2%)	
Immunophenotype				<.001
PreB common positive	99 (85.3%)	83 (60.6%)	85 (64.9%)	
PreB common negative	7 (6.0%)	27 (19.7%)	20 (15.3%)	
T-ALL	10 (8.6%)	27 (19.7%)	24 (18.3%)	
AHL	0 (0%)	0 (0.0%)	2 (1.5%)	
Risk group				<.001
SR	37 (31.9%)	12 (8.8%)	17 (13.0%)	
IR	61 (52.6%)	74 (54.0%)	46 (35.1%)	
HR	18 (15.5%)	51 (37.2%)	68 (51.9%)	
Prednisone response (8th day of therapy)				.001
Good	107 (92.2%)	106 (77.4%)	96 (73.3%)	
Poor	9 (7.8%)	31 (22.6%)	35 (26.7%)	
BM 15 day				.003
M1	76 (65.5%)	66 (48.2%)	64 (48.9%)	
M2	28 (24.1%)	39 (28.5%)	31 (23.7%)	
M3	12 (10.3%)	32 (23.4%)	36 (27.5%)	
BM 33 day				.03
M1	114 (98.3%)	128 (93.4%)	121 (92.4%)	
M2	2 (1.7%)	5 (3.6%)	5 (3.8%)	
M3	0 (0.0%)	4 (2.9%)	5 (3.8%)	

AHL = acute hybrid (biphenotypic) leukemia, BM = bone marrow, CNS = central nervous system, HR = high-risk, IR = intermediate-risk, M1 = blasts < 5%, M2 = blasts  $\geq$  5 < 25%, M3 = blasts  $\geq$  25%, SR = standard-risk, WBC = white blood cells.

demonstrated a poor response to the induction phase of chemotherapy (on the 8th, 15<sup>th</sup>, or 33rd day of therapy), in contrast to children with ALL recurrence who survived ( $P < .05$ ). In the group of non-relapsed patients who died due to toxicity, the presence of the Philadelphia chromosome was more frequent (10.7%) than in the other groups; however, the difference was not statistically significant ( $P > .05$ ).

We did not find differences between the groups of patients who died due to toxicity and those who died due to disease in terms of the factors analyzed (groups 2 and 3).

#### 4. Discussion

The treatment of childhood ALL is based on risk stratification. By understanding the factors that affect the prognosis we can classify

children into standard, intermediate, or high-risk groups. This leads to a differentiation in the intensity of chemotherapy. Thus, identifying the risk factors that affect treatment outcomes is very important.<sup>[3,6]</sup>

Despite increasing concerns about treatment-related deaths, the main cause of therapy failure is disease relapse. In the Nordic countries, the relapse rate was approximately 40% between 1981 and 1993, and over the last two decades reported relapse rates were 15% to 20% in developed countries.<sup>[7,8]</sup>

Oskarsson et al evaluated outcomes following ALL relapse to validate currently used risk stratifications and identify additional prognostic factors for overall survival. The authors reported that a total of 516 of 2735 patients (18.9%) relapsed between 1992 and 2011. This study demonstrated that unfavorable cytogenetics (hypodiploidy, t(1;19), *MLL* rearrangement, t(9;22)

*BCR/ABL1*), the age of 10 years or over, T-cell immunophenotype with hyperleukocytosis and Down's syndrome were all additional individual prognostic factors in relapsed ALL.<sup>[9]</sup>

In our study, unfavorable cytogenetics (*BCR/ABL1* and *KMT2A/AFF1*) was not an adverse prognostic factor for first-line therapy failure. Positive status for *BCR/ABL1* was identified in 27/384 (7%) patients who experienced treatment failure compared to 39/1488 (2.6%) who were in the CR1. Similarly, positivity for *KMT2A/AFF1* was identified in 9/384 (2.3%) patients who experienced treatment failure and 12/1488 (0.8%) who were in the CR1. This discrepancy may be because imatinib had been used previously, in addition to chemotherapy, in the cases positive for *BCR/ABL1*, which was not included in our protocol.

Stary et al published a large, intercontinental study, which included a total of 5060 evaluable patients aged 1 to 18 years with newly diagnosed non-B-cell ALL treated from November 2002 to November 2007. A total of 255 patients (5.3%) died due to treatment-related events in CR. Authors reported a 5% rate of death in CR, ranging from 3% in the standard risk group to 13% in the HRG. The incidence of death in CR was significantly higher in children older than 10 years vs younger children, in girls versus boys, and in T-ALL versus B-cell precursor ALL. In this study, the 5-year cumulative incidence of relapse was 19%.<sup>[5]</sup> Nguyen et al analyzed survival following relapse among 9585 pediatric patients enrolled in Children's Oncology Group clinical trials from 1988 to 2002. A total of 1961 (20.5%) patients experienced relapse. Adjusting for both time and relapse site, the multivariate analysis showed that age (10 years and older), the presence of CNS disease at diagnosis, male sex, and T-ALL were significant predictors of inferior post-relapse survival.<sup>[10]</sup>

In our study, we found that factors that were prognostic in the first-line therapy failure, were also valid for relapsed patients: older age, a high WBC, immunophenotype at the time of diagnosis and belonging to the HRG were all adverse factors for survival after relapse.

Despite the development of more effective treatments for ALL, 2% to 5% of children still die from causes other than relapse. In the ALL-BFM 90 trial, the Berlin-Frankfurt-Münster (BFM) group demonstrated a 1% induction death (ID) rate and 1.6% CR1 death rate.<sup>[2]</sup> Similarly, in a study published by Toft et al, ID rates are at 1% and CR1 death rates at 2.6%.<sup>[11]</sup>

In the NOPHO ALL-92 study, TRD frequency was found at 3%, of which 1% was IDs and 2% CR1 deaths. The risk factors for TRD were high-risk leukemia, T-cell immunophenotype, high WBC and female sex. In this study, a higher number of girls than those expected, particularly in the lower risk groups, died of treatment-related infections and this was attributed to sex-specific differences in the immunological response to infections or differences in toxicity during chemotherapy. Other reasons included differences between boys and girls in body mass index, liver function and related pharmacokinetics. The authors of the study were most interested to find out whether sex differences were detectable in other ongoing protocols.<sup>[1]</sup>

In the study presented by Schrappe et al, the age of 10 years or older, T-cell leukemia, the presence of 11q23 rearrangement, and 25% or more blasts in the bone marrow at the end of induction therapy were associated with a particularly poor outcome.<sup>[2]</sup>

Similar to previous published reports, in our study, patients who died due to complications of treatment were characterized by T-ALL or AHL, an older age, high WBC, and belonged to the HRG. However, in our analysis, we identified male sex as the

high-risk feature, in contrast to results of the NOPHO ALL-92 study.

Taken together, our results indicate that age should be considered a risk-factor of first-line treatment failure and a modification in supportive care for older children should be considered.

Structural and numeric chromosomal aberrations in childhood ALL are studied as disease markers and indicators of outcomes. Gene rearrangements, such as *ETV6-RUNX1* or high hyperdiploidy are associated with a significantly better outcome. However, *KMT2A/AFF1*, intrachromosomal amplification of chromosome 21 and hypodiploidy are associated with an increased risk of relapse. *TCF3/HLF* fusion gene is typically linked to relapse and death within 2 years from diagnosis.<sup>[12,13]</sup> Currently, new genetic markers are analyzed (deletions in *IKZF1*, *CDKN2A/B*, *PAX5*, *PAR1* regions) and the results will provide important insights into the genetic basis of treatment failure in childhood ALL.<sup>[14-17]</sup> However, research involving new genetic stratification tools are expensive and must be planned in a cost-effective way.

In conclusion, this is the largest retrospective study of first-line treatment failure in children with ALL in the Polish population. Our analysis shows that age older than 10 years is a particular risk-factor for the failure of first-line of treatment, both in terms of relapse and treatment-related mortality.

## Author contributions

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