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Changing risk factors in childhood acute lymphoblastic leukemia: experience from Kujawsko-Pomorski region 1976–2018

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. Risk factors in childhood ALL have changed during recent decades, mostly due to treatment personalization.

The aim of this study was to analyze therapy results and prognostic factors in childhood ALL in the Kujawsko-Pomorski region of Poland between 1976 and 2018.

Material and methods: Data from 495 patients (0–18 years old) diagnosed with ALL from the Kujawsko-Pomorski region between 1976 and 2018 was analyzed. Prognostic factors were analyzed separately in specific therapeutic groups, which were defined by several therapy protocols.

Results: Prognostic factors have changed over the course of consecutive therapeutic periods. Between 1976 and 1988 (the first and second therapeutic protocols), central nervous system involvement was the most important risk factor. During the third therapeutic period, an unsatisfactory treatment response on days 8 and 14 was related to a poor outcome. In 1995–2002, the risk factors were hepatomegaly, splenomegaly, lymph nodes involvement, and unsatisfactory therapy response on days 15 and 33. Between 2002 and 2011, immunophenotype other than 'common' and hemoglobin level at diagnosis were the risk factors, and a lack of BCR-ABL aberration was related to better therapy results. During the final analyzed period (2011–2018), failure to achieve remission on day 33 was a risk factor, and patients classified as non-high risk group and those aged <6 years had better outcomes.

Conclusions: The changing profile of risk factors in ALL has reflected progress in ALL therapy, with the gradual elimination of factors related to poor outcomes, mostly due to modifications in treatment and the development of diagnostic methods as well as therapy monitoring.

Key words: acute lymphoblastic leukemia, prognostic factors, risk factors, children, therapeutic era

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and represents more than 20% of all malignancies in patients aged 0–18 years. Each year, c.200–220 children are diagnosed with ALL in Poland [1]. Therapy outcomes have improved significantly over recent decades — the probability of five-year overall survival has increased from 31% in 1975 to c.85% with current therapy protocols [2, 3]. The identification of prognostic factors was undoubtedly one of the milestones in ALL therapy: the presence of risk factors enabled risk group stratification and therapy adjustment. Patients with factors related to a poor outcome have received more intensive treatment, whereas in children with more favorable features, treatment has been modified to avoid severe toxicity and short-term as well as long-term side effects [4].

Prognostic factors in ALL can be divided into three groups: factors related to patient characteristics, factors related to disease features, and factors related to treatment response. Age at diagnosis, race and sex are prognostic factors related to patient characteristics. Factors related to disease include leukocytes count at diagnosis, blasts immunophenotyping, chromosomal aberrations in blast cells, and the presence of extramedullary infiltrations. Prognostic factors related to therapy include response to treatment on days 8, 15 and 33 and the presence of minimal residual disease (MRD) at later timepoints [5].

The aim of this study was to analyze therapy results and the significance of prognostic factors in childhood ALL in the Kujawsko-Pomorski region between 1976 and 2018.

Material and methods

Design of study

In this study, data from 495 patients (0–18 years old) diagnosed with ALL from the Kujawsko-Pomorski region of Poland between 1976 and 2018 was analyzed. Children were treated in the Department of Children's Hematology and Oncology of Antoni Jurasz University Hospital in Bydgoszcz. Prognostic factors were analyzed separately in specific therapeutic groups, which were defined by several therapy protocols.

Definitions

Treatment response was assessed on days 8, 14/15 and 28/33. Prednisone good response (PGR) was defined as absolute blast count in peripheral blood <1,000/μL on day 8 of therapy. Prednisone poor response (PPR) was defined as absolute blast count in peripheral blood ≥1,000/μL on day 8. MRD was calculated as blast cells count according to cells immunophenotyping. Patients stratified to the standard risk (SR) group should have MRD <0.1% on day 14/15 to remain in the SR group. In a case of MRD between 0.1% and 10%, they were stratified to the intermediate risk group, and in a case of MRD above 10% they were stratified to the high risk group. Response definition on day 28/33 was divided into three groups, based on blast count in the bone marrow:

- **M1** <5% of blasts in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis;
- **M2** 5 <25% of blasts in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis;
- **M3** ≥25% of blasts in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis.

Hepatomegaly and splenomegaly was defined as enlargement of liver and spleen above the value normal for the patient's age. Central nervous system (CNS) involvement was defined as clinical or imaging findings of CNS disease and the presence of blasts on cytospin preparation in cerebrospinal fluid. Complete remission (CR) was achieved when the following criteria were fulfilled on day 33 of therapy: <5% blast cells (M1) in representative bone marrow with sufficient cellularity and signs of regeneration of normal myelopoiesis; ≤5 nucleated cells/μL and no evidence of blasts in cytospin and no evidence of leukemic infiltrates as evaluated clinically and by imaging; and a preexisting mediastinal mass must have decreased to at least one third of the initial tumor volume.

Treatment protocols

According to therapy protocols, patients were divided into six groups:

1. 1976–1983 — MEMPHIS V–VII (56 patients) [6];
2. 1983–1988 — BFM-83 (33 patients) [7];
3. 1988–1995 — NOPHO-86 (81 patients) [8];
4. 1995–2002 — BFM-90 (96 patients) [7] and New York I–II (19 patients) [9];
5. 2002–2011 — ALL-IC-2002 (115 patients) [10];
6. 2011–2018 — ALL-IC-2009 (95 patients) [11].

Risk factors

Prognostic factors analyzed in the entire group included age at diagnosis, sex, CNS involvement, lymph nodes involvement, mediastinal mass, splenomegaly >4 cm, hepatomegaly >4 cm, risk group according to the Berlin–Frankfurt–Munster (BFM) protocol, leukocyte count at diagnosis, hemoglobin (Hgb) level at diagnosis, and treatment response (GPR vs. PPR) on day 8 of therapy.

From 1990 onwards, additional prognostic factors were analyzed: blasts morphology according to the French–American–British (FAB) classification; blasts immunophenotyping; and treatment response on days 14/15 and 28/33. From 1996 onwards, chromosomal aberrations BCR-ABL, TEL-AML1, MLL-AF4, and the presence of hypodiploidy or hyperdiploidy were evaluated.

Table I. Prognostic factors analyzed in respective therapeutic groups

Group	Years	Prognostic factors
1	1976–1983	Age at diagnosis, sex, leukocyte count and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass)
2	1983–1988	Age at diagnosis, sex, leukocyte count, hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8
3	1988–1995	Age at diagnosis, sex, leukocyte count and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 14 and 28
4a/4b	1995–2002	Age at diagnosis, sex, leukocyte count and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 15 and 33, blast immunophenotyping, FAB classification, hypodiploidy, BCR-ABL rearrangement
5	2002–2011	Age at diagnosis, sex, leukocyte count, platelets number and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 15 and 33, MRD on day 15, blast immunophenotyping, FAB classification, hypodiploidy, hyperdiploidy, BCR-ABL, TEL-AML1 and MLL-AF4 rearrangement, risk group
6	2011–2018	Age at diagnosis, sex, leukocyte count, platelets number and hemoglobin level at diagnosis, extramedullary involvement (liver, spleen, CNS, lymph nodes, mediastinal mass), treatment response on day 8, count of blast cells in bone marrow on days 15 and 33, MRD on day 15, blast immunophenotyping, FAB classification, hypodiploidy, hyperdiploidy, BCR-ABL, TEL-AML1 and MLL-AF4 rearrangement, risk group

CNS — central nervous system; FAB — French–American–British; MRD — minimal residual disease

Risk factors analyzed in the respective therapeutic groups are set out in Table I.

Statistical methods

The probability of overall survival (pOS), probability of event-free survival (pEFS), and probability of relapse-free survival (pRFS) were calculated with the Kaplan–Meier method, and compared by log-rank test. An 'event' was defined as relapse, death or secondary malignancy. Cox regression model was used to calculate univariate and multivariate analysis of prognostic factors. Factors with *p*-value <0.1 in univariate analysis were included into the multivariate model. Odds ratio (OR) was calculated with 95% confidence interval.

Results

For each therapeutic group, pOS, pEFS and pRFS were calculated. Risk factors of death, event and relapse were analyzed separately in each group. Results of multivariate analysis are shown in Tables II, III and IV.

Group 1

Group 1 includes patients treated between 1976 and 1983 according to the St. Jude Memphis therapeutic protocol. 5-year pOS was 19.6% (±5.3%). None of the evaluated factors achieved statistical significance in pOS analysis. 5-year pEFS was 7.4% (±3.4%). Event occurred in 92.9% of patients. The only factor with a significant impact on pEFS in univariate analysis was CNS involvement. Relapse occurred in 80.4% of patients and the 5-year pRFS was 11.2% (±4.9%). In both univariate and multivariate analysis, CNS involvement had a significant impact on pRFS and was related to a more than 20-fold increased risk of relapse. Other important adverse prognostic factors included mediastinal mass and Hgb level <8 g/dL at diagnosis.

Group 2

The second group was treated between 1983 and 1988 according to the BFM-83 therapeutic protocol. 5-year pOS was 54.5% (±8.7%) and pEFS was 53.2% (±8.8%). CNS involvement was a risk factor of death and event in univariate and multivariate analysis of both parameters. Additionally, age <1 year and >6 years at diagnosis had a significant impact on pOS; patients of this age had a 3-fold higher risk of death during this therapeutic era. Relapse occurred in 12 patients (36.4%) and 5-year pRFS was 61.0% (±9.2%). None of the analyzed factors achieved statistical significance in either univariate or multivariate analysis of pRFS.

Group 3

Between 1988 and 1995, patients were treated according to the NOPHO-86 protocol. In this group, 5-year pOS was 58.0% (±5.5%) and 37 children died during the observational period, which represented 45.7% of the entire group. The most important prognostic factor on pOS was treatment response on day 8. Patients with PPR at this timepoint had a 3-fold higher risk of death. In univariate analysis also Hgb level <8 g/dL had a significant impact on pOS, although this effect was not shown in multivariate analysis. 5-year pEFS was 51.9% (±5.6%). In univariate analysis, therapy response on days 8 (PPR) and 14 (M3) as well as Hgb level

Table II. Multivariate analysis of prognostic factors for probability of overall survival

Group	Years	Prognostic factors	OR* (95% CI)	*p*
1	1976–1983	No parameter reached statistical significance	–	–
2	1983–1988	CNS involvement	10 (1.7–64)	*p* = 0.010
		Age at diagnosis <1 year or >6 years	3.8 (1.1–13)	*p* = 0.033
3	1988–1995	Treatment response on day 8 (PPR)	3.1 (1.6–6.2)	*p* = 0.001
4a	1995–2002	Risk group — HR	5.6 (2.21–14)	*p* <0.001
		Hepatomegaly	4.6 (1.7–12)	*p* = 0.002
		Treatment response on day 33 (bone marrow morphology — M2)	10 (1.03–96)	*p* = 0.047
4b	1995–2002	No parameter reached statistical significance	–	–
5	2002–2011	Immunophenotype other than 'common ALL'	3.1 (1.2–8.2)	*p* = 0.019
		Lack of BCR-ABL arrangement	0.1 (0.02–0.3)	*p* < 0.001
6	2011–2018	Risk group — non-HR	0.2 (0.1–0.5)	*p* < 0.001

*Odds ratio (OR) >1 means an increased risk of failure; CI — confidence interval; CNS — central nervous system; PPR — prednisone poor response; HR — high risk; ALL — acute lymphoblastic leukemia

Table III. Multivariate analysis of prognostic factors for probability of event-free survival

Group	Years	Prognostic factors	OR* (95% CI)	*p*
1	1976–1983	CNS involvement	8.3 (1.6–43.7)	*p* = 0.012
2	1983–1988	CNS involvement	8.6 (1.5–49)	*p* = 0.015
3	1988–1995	Treatment response on day 14 (M3)	2.6 (1,2–5.9)	*p* = 0.018
4a	1995–2002	Risk group — HR	3.5 (1.5–7.9)	*p* = 0.003
		Splenomegaly	2.9 (1.3–6.3)	*p* = 0.008
4b	1995–2002	Lymph nodes involvement	4.2 (1.3–13)	*p* = 0.011
		Treatment response on day 15 (M2)	23 (1.6–100)	*p* = 0.022
5	2002–2011	Hgb <8 g/dL at diagnosis	2.3 (1.1–4.8)	*p* = 0.028
6	2011–2018	Failure to achieve CR on day 33	10.7 (1.0–114)	*p* = 0.049
		Age <6 at diagnosis	0.2 (0.1–0.9)	*p* = 0.031

*Odds ratio (OR) >1 means an increased risk of failure; CI — confidence interval; CNS — central nervous system; HR — high risk; Hgb — hemoglobin; CR — complete remission

Table IV. Multivariate analysis of prognostic factors for probability of relapse-free-survival

Group	Years	Prognostic factors	OR* (95% CI)	*p*
1	1976–1983	CNS involvement	34 (4.2–270)	*p* = 0.001
		Mediastinal mass	4.9 (1.04–23)	*p* = 0.044
		Hgb <8 g/dL at diagnosis	2.8 (1.1–7)	*p* = 0.029
2	1983–1988	No parameter reached statistical significance	–	–
3	1988–1995	Treatment response on day 8 (PPR)	1.8 (0.8–4.2)	*p* = 0.019
4a	1995–2002	Splenomegaly	5.0 (1.7–14)	*p* = 0.002
		T-cell immunophenotyping	4.3 (1.4–13)	*p* = 0.009
4b	1995–2002	Treatment response on day 15 (M2)	7.7 (1.04–56)	*p* = 0.042
5	2002–2011	Hgb >8 g/dL at diagnosis	3.9 (1.5–10.4)	*p* = 0.007
6	2011–2018	Failure to achieve remission on day 33	24 (1.4–402)	*p* = 0.027
		Age <6 at diagnosis	0.1 (0.01–0.7)	*p* = 0.027

*Odds ratio (OR) >1 means an increased risk of failure; CI — confidence interval; CNS — central nervous system; Hgb — hemoglobin; PPR — prednisone poor response;

lower than 8 g/dL had significant impacts on pEFS, but in multivariate analysis only therapy response on day 14 was related to a worse outcome and doubled the risk of event. 5-year pRFS was 66.2% (±6.9%). The only risk factor related to pRFS was therapy response on day 8.

Group 4

Group 4 was divided into two subgroups due to different therapeutic protocols: the BFM-90 protocol (group 4a) and the NEW YORK I–II protocol (group 4b).

In group 4a, 5-year pOS was 77.9% (±4.3%) and 5-year pEFS was 68.8% (±4.7%). The most important prognostic factor in both pOS and pEFS was treatment response on day 8, which was correlated with a 10-fold increased risk of event and a more than 3-fold higher risk of death in patients with PPR. Other factors that achieved statistical significance in univariate analysis in pOS and pEFS were risk group, hepatomegaly or splenomegaly at diagnosis, leukocyte count at diagnosis >20,000/μL, blasts phenotype, and treatment response on days 15 and 33 (bone marrow classified as M2). Relapse occurred in 16 children (16.7%) and mean time to relapse was 2.5 years. Among factors significant in univariate analysis, only T-cell blasts phenotype and splenomegaly proved significant in multivariate analysis.

In group 4b, 5-year pOS was 73.7% (±10.1%). None of the analyzed factors had an impact on pOS. 5-year pEFS was 68.4% (±10.7%). Involvement of lymph nodes and treatment response on day 15 had significant impacts on pEFS. Relapse was observed in five cases (26.3%) and four patients in this group died. Treatment response on day 15 was the only prognostic factor related to pRFS.

Group 5

Group 5 included 115 patients treated between 2002 and 2009 according to the IC-BFM 2002 protocol. 5-year pOS was 79.1% (±3.8%). Mean OS was 7.4 years [95% confidence interval (CI): 6.8–7.8 years). The most important factor with a significant negative impact on patient pOS was the presence of BCR-ABL fusion gene [as a result of translocation t(9;22)]; children with this mutation had a more than 7-fold lower pOS. In univariate analysis, hepatomegaly and splenomegaly at diagnosis had a significant impact on pOS as well. 5-year pEFS was 71.1% (±4.2%). Relapses occurred in 27 (23.5%) children and 5-year pRFS was 79.3% (±3.9%). Only Hgb <8 g/dL at diagnosis had a significant impact on both pEFS and pRFS, with a 2.3-fold higher risk of event and an almost 4-fold higher risk of relapse in patients with this feature.

Group 6

In group 6, data from children treated according to the ALL IC-BFM2009 protocol was analyzed. 5-year pOS was 90.7% (±3.4%). Mean OS was 4.1 years (95% CI: 2.7–6.5 years). In univariate analysis, only hypodiploidy had a significant impact on pOS. 5-year pEFS was 86.6% (±4.1%). Among prognostic factors related to lower pEFS, only Hgb level at diagnosis <8 g/dL was statistically significant. Relapses occurred in nine patients and 5-year pRFS was 90.1% (±3.6%). In univariate analysis, patients who did not achieve remission on day 33 had a more than 35-fold higher risk of relapse (data not shown). Other factors related to a worse pRFS were hepatomegaly, splenomegaly, and age <10 years at diagnosis.

Discussion

Decades of research into childhood ALL have resulted in the identification of several clinical and laboratory features which have had significant impacts on therapy outcomes. The best-known factors include age, leukocyte count at diagnosis, immunophenotype and chromosomal abnormalities in blasts, and response to initial therapy. The presence of prognostic factors has enabled risk group stratification and led to therapy intensification in patients at risk of treatment failure [4, 12]. The present data reflects improvements in therapy outcomes in childhood ALL as well as developments in diagnostic methods achieved due to international collaboration and great research effort.

During the first two analyzed periods, CNS involvement was one of the most important factors related to a poor outcome. Patients with CNS involvement had a 34-fold higher risk of relapse in the period 1976–1984 ($p = 0.001$) and a 10-fold higher risk of death between 1983 and 1988 ($p = 0.010$). This impact was also observed in international therapy protocols analysis, and resulted in the introduction of CNS prophylaxis and the introduction of the administration of high doses of methotrexate, which improved 5-year pEFS from 9% to 36% [6]. In other research, CNS prophylaxis with intrathecal methotrexate and cranial irradiation reduced the risk of CNS relapse from 32.5% to 1.4% after hematological remission [13]. Further efforts have been made towards limiting the side effects of CNS prophylaxis, and currently only a strictly limited group of patients who are at the highest risk of CNS relapse are treated with cranial irradiation.

Another feature early identified as a risk factor was age at diagnosis. Infants, especially in the first year of life, have significantly worse outcomes compared to children aged between one and six. In our analysis, patients aged <1 year treated between 1983 and 1988 had significantly lower pOS ($p = 0.033$) and pEFS ($p = 0.082$). This effect is caused by the different leukemia biology in this particular group and the high risk of long-term side effects [14]. The answer for issues related to infant ALL was the development of dedicated therapy protocols, conducted by three large collaborative groups — the Children's Oncology Group (COG), the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), and the Interfant Study Group [14].

Infant-dedicated protocols, as well as previous observations, resulted in better understanding of infant ALL genetic background and the identification of risk factors in this group, and provided necessary information about treatment toxicity [14].

The role played by Hgb concentration at diagnosis is unknown, with a significant impact of Hgb <8/dL on EFS and RFS. This phenomenon was also reported by Schrappe et al. [15] in their analysis of BFM-90 protocol results. This is difficult to explain, but hypothetically it might correspond to marrow blasts involvement or cellular sensitivity.

One of the most important prognostic factors in childhood lymphoblastic leukemia is early response to treatment. It has been proved that the hematological response to prednisone on day 8 of therapy, and the bone marrow response at later timepoints, have crucial impacts on long-term outcomes [2, 16, 17]. In our study, this effect was mostly seen in children treated in the period 1988–1995, when PPR was related to a more than 3-fold higher risk of death (p = 0.001) and an almost 2-fold higher risk of relapse (p = 0.019). Due to this observation, patients with PPR were stratified into a high risk group with therapy intensification, which led to an improvement in therapy outcome in this particular group [18]. Furthermore, in our analysis, the response to treatment was one of the most important risk factors during subsequent therapeutic periods [4, 19]. That resulted in the development of diagnostic methods related to therapy response assessment, and the implementation of MRD monitoring. This in turn enabled the early identification of patients at risk of relapse, even at times when the disease seems to be in remission. Moreover, it allows us to reduce therapy in standard-risk patients with a low level of MRD [20].

Genetic aberrations in blast cells proved to be crucial to the proper understanding of ALL biology and therapy response. One of the first genetic aberrations identified as a risk factor was the BCR-ABL mutation, and patients with this feature were thus stratified into a high risk group [21]. In our cohort, genetic diagnostics become available in 1996. In the period 2001–2011, a lack of the BCR-ABL mutation was the most important factor related to a better pOS (p <0.001). Unsatisfactory therapy results in this group resulted in treatment modification, with the introduction of targeted therapy with tyrosine kinase inhibitors (TKI), which have dramatically improved patients' outcomes. The success of TKI drove further research into targeted therapy in childhood ALL [21].

Conclusions

Prognostic factors in ALL have changed during the last few decades, and the development of diagnostic methods have led to a better understanding of the underlying causes of the disease. Medicine has become more aware of ALL's genetic background, and this has triggered further research in the field of genetic diagnostics and contributed to its accessibility. Furthermore, the changing landscape of risk factors in ALL has reflected sustained progress in ALL therapy, with the gradual elimination of features related to poor outcomes, mostly due to modifications in treatment and developments in diagnostic methods as well as therapy monitoring.

The modern era of immunotherapy and treatment focused on molecular pathways facilitates a more targeted approach, with new opportunities regarding the high risk group of patients [22]. Moreover, targeted therapy has had a great impact on treatment toxicity reduction in specific subgroups. New therapy protocols should bring answers regarding the efficiency and side effects of novel therapies in ALL.

Authors' contributions

JS — data collection and interpretation, statistical analysis, description of results. ED, AJG — data collection and interpretation, statistical analysis. NB, AK, SK, KC, MRP, RD, MP, BT, PK, JC, ME, AM, AD, AU, EG, KJ, EW, DK, MŁ, MA, SW, OG, ST, MM, MD, MK, BKR, ED, AM — data collection and interpretation. JS — thesis draft, critical review and important intellectual content, acceptance of final version for publication.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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