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Acta Haematologica Polonica

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DOI: 10.5603/AHP.a2023.0036

Article type: Original research article

Submitted: 2023-04-10

Accepted: 2023-05-02

Published online: 2023-07-17

Relapsed childhood acute myeloid leukemia: prognostic factors and outcomes: experience from a single oncology center

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Abstract

Introduction: Over recent decades, significant progress in the treatment of childhood acute myeloid leukemia (AML) has been made. However, the relapsed disease remains a challenge. The aim of this study was to analyze therapy results in pediatric patients treated for relapsed AML in a single oncology center, with a particular focus on prognostic factors.

Materials and methods: Data from patients younger than 19 years with AML diagnosed between January 1994 and December 2020 treated in the Department of Pediatric Hematology and Oncology in Bydgoszcz, Poland was analyzed, with detailed analysis of patients with relapsed disease.

Results: A total of 77 children were diagnosed with AML in the analyzed period and 21 had a relapsed disease (27.3%). Bone marrow relapse was the most common. The risk factors of relapse included white blood cells >100 G/L at initial diagnosis and classification to the high risk group. Late relapse was related to poorer outcomes. The 5-year probability of overall survival for the entire group was 28.6%, and this was significantly higher in patients who

achieved second remission compared to those who did not (44.9% vs. 0.0%, p <0.001). The main reason for death was progression of disease, which occurred in 10 patients.
Conclusions: Outcomes in relapsed AML in children are still dismal. Lack of second remission suggests the need for experimental therapy.
Key words: acute myeloid leukemia, relapse, children, survival

Introduction

Despite the significant progress in pediatric acute myeloid leukemia (AML) treatment, minimal improvement had been made in the therapy of relapsed disease [1]. While complete remission (CR) rates in first line treatment have reached c.90% with modern therapy regimens, relapse still occurs in 30–40% of pediatric patients [1–3]. Relapsed disease remains one of the most important risk factors in children with AML, with long-term survival of c.30% [1, 4].

Several prognostic factors have been identified in relapsed AML, such as time to relapse, early response to salvage therapy, French–American–British (FAB) and cytogenetics subtypes of blast cells alike in acute lymphoblastic leukemia [4, 5]. Moreover, modern diagnostic tools, such as whole exome sequencing analyses, are revealing new potentially actionable mutations [2, 4].

One of the main challenges that limit the development in therapy of relapsed AML is — the small number of patients and a lack of consistent second line therapy guidelines [1]. Treatment is usually based on intensive reinduction regimens followed by allogeneic hematopoietic stem cell transplantation (allo-HCT) [6]. There is an urgent need for new therapeutic options because chemotherapy intensification is limited by the risk of toxicity totals rising related to previous treatment. Even so, between 2006 and 2016 only <25% of children with relapsed disease were enrolled into clinical trials [7]. To date, the largest analysis of therapy results in relapsed pediatric AML contains only 12 studies with only a single one describing the results of a clinical trial [1].

In this study, we analyze therapy results in pediatric patients treated because of relapsed AML in a single oncology center, with a particular focus on prognostic factors related to the patient and the disease itself.

Material and methods

Design of study

We retrospectively analyzed outcomes of pediatric AML patients treated in a single oncology center in Poland with detailed analysis of data from patients who entered remission and subsequently experienced a first relapse. The study was performed after approval by the Ethics Committee of *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz (KB 577/2021).

Patients

The study included patients younger than 19 years with AML diagnosed between January 1994 and December 2020 who were treated in the Department of Pediatric Hematology and Oncology in Bydgoszcz, Poland. Patient demographic and clinical data related to the initial diagnosis and subsequent relapses was collected from medical records. All patients diagnosed with AML were included in the analysis. Ineligible patients included those 19 or older at initial diagnosis and patients with insufficient or missing data.

Treatment

Children were treated according to five therapeutic protocols: AML NOPHO 88 from March 1994 to March 1998 [8]; ANLL 98 from March 1998 to November 2005 [9]; BFM AML 2004 from November 2005 to August 2013 [10]; BFM AML 2012 from August 2013 to January 2020 [11]; and BFM AML 2019 from January 2020. Allo-HCT has been performed since 2005.

Diagnosis

Patients were diagnosed with de novo AML and relapsed disease based on a bone marrow biopsy with cell morphology according to the FAB classification and immunophenotyping. In all cases, diagnostic work-up with complete blood count, ultrasonography of the abdomen with liver and spleen measurement, lumbar puncture with cerebrospinal fluid analysis, chest X-ray and echocardiography were performed.

Definitions

Patients were considered to have achieved CR if they had <5% blasts in the bone marrow aspirate with no evidence of circulating blasts or extramedullary disease, and with recovery of peripheral counts. Relapse was defined as the reappearance of leukemic blasts in the peripheral blood, re-infiltration of bone marrow (BM) with ≥5% blasts or leukemic

infiltration elsewhere following CR lasting at least four weeks. Probability of overall survival (pOS) was defined as the time from AML diagnosis until death from any cause or until the time of the final follow-up, but no later than 1 January, 2022. Probability of relapse free survival (pRFS) was defined as the time from AML diagnosis until relapse occurrence. Early relapse was defined as relapse that occurred during the first year after CR.

Statistical methods

The statistical analysis was performed with univariate and multivariate logistic regression analysis. Differences between groups were calculated using Chi-squared test, and in specific subgroups relative odds ratio (OR) was determined, with 95% confidence interval (CI). The Kaplan-Meier method was used to estimate survival rates with comparisons based on the two-sided log-rank test. P-values were considered statistically significant when $p < 0.05$. Analyses were conducted using MedCalc 20.100 statistical software (MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

A total of 77 children were initially diagnosed with AML and treated in the period 1994–2022. CR was achieved in 67 patients (87.0%). Overall, 21/77 children had a relapsed disease (27.3%). Table I shows the clinical characteristics of the patients with recurrence of AML. Five-year pRFS was 62.7% for the entire group. Classification to the high risk (HR) group was an independent risk factor of relapse (OR 4.35, 95% CI: 1.23–15.44, $p = 0.023$). In univariate analysis, a white blood cells (WBC) count above 100 G/L at diagnosis also conferred an increased risk of relapse (OR 3.9, 95% CI: 1.16–4.68, $p = 0.042$). According to the FAB classification, the best outcomes were observed in patients with the M3 subtype (5-year pRFS 100%) and the differences between respective FAB subtypes were statistically significant ($p < 0.001$).

Table I. Characteristics of patients in study group

Variable	Number of patients	[%]
Gender		
Male	11	52
Female	10	48
Age at diagnosis		
<10 years	11	52
≥10 years	10	48
WBC at diagnosis		
<100 G/L	15	71
≥100 G/L	6	28
PLT at diagnosis		
<20 G/L	5	24
≥20 G/L	16	76
Hb at diagnosis		
<8 g/L	10	48
≥8 g/L	11	52
CNS involvement	4	19
Extramedullary organs involvement	18	86
FAB types		
M0	1	5
M1	6	28
M2	8	38
M3	0	0
M4	1	5
M5	3	14
M6	1	5
M7	0	0
NA	1	5
Time to relapse		
<1 year	11	52
1–2 years	7	34
≥2 years	3	14

WBC — white blood cells; PLT — platelet count; Hb — hemoglobin; CNS — central nervous system; FAB — French–American–British

Relapse

Most patients (15/21) had isolated bone marrow relapse); two children had isolated central nervous system (CNS) relapse; in two cases relapse occurred both in BM and CNS; and another two had BM and localized extramedullary relapse (nasopharyngeal mass in both cases). Median time to relapse was 1.0 year (range 0.1–12.5). Early relapse occurred in 10

patients (47.6%), and was related to poorer outcomes compared to late relapse (5-year pOS 57.1% vs. 20.5%, $p = 0.050$).

Therapy and role of HCT

First line therapy has changed several times during the c.28-year analyzed period and patients have been treated according to five therapeutic protocols. The 5-year pRFS for consecutive therapeutic protocols is shown in Figure 1. Differences in the 5-year pRFS between therapy protocols was statistically significant ($p = 0.010$). 6/21 patients who subsequently relapsed received allo-HCT in first line-therapy. Patients treated without allo-HCT in the first remission had almost a three times greater chance of second remission achievement [odds ratio (OR) 2.75, 95% confidence interval (CI): 0.38–19.67, $p = 0.313$]. Reinduction regimens differed relevantly between patients. Second line therapies as well as further outcomes are shown in Table II. After the first relapse, 12 of the children received allo-HCT. The other nine patients received chemotherapy only and did not undergo allo-HCT because of a progressive disease or the lack of suitable donor. The 5-year pOS was 33.3% in the group treated with HCT in relapse, and 22.2% in the group who received chemotherapy only ($p = 0.135$).

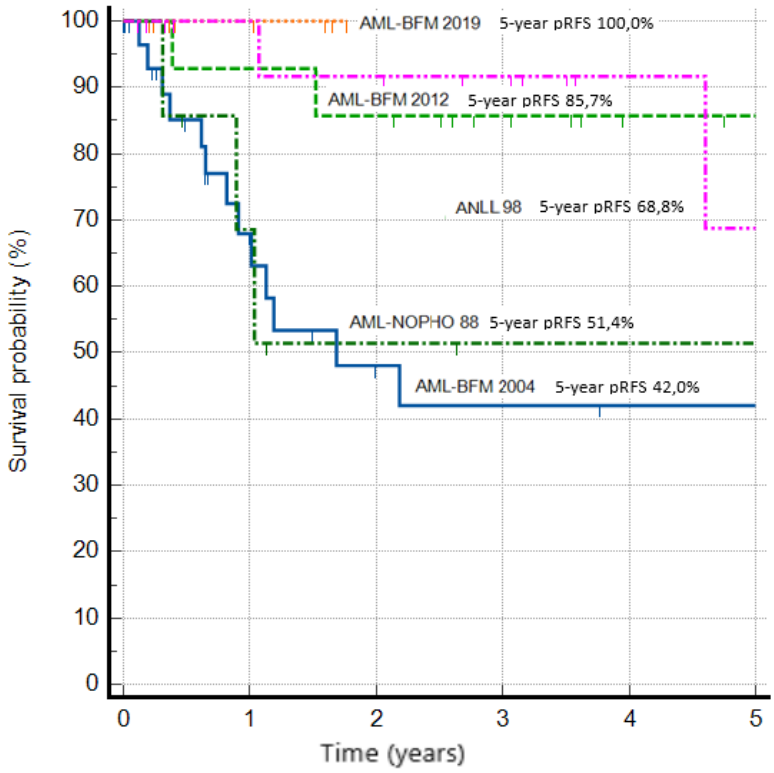

Figure 1. 5-year probability of relapse free survival (pRFS) for acute myeloid leukemia (AML) children treated 1994–2022 according to five consecutive protocols

Table II. Clinical outcomes of patients with relapsed disease

PN	**Age**	**Sex**	**Relapse site**	**Initial treatment**	**Second-line treatment**	**CR2**	**HCT in relapse**	**Outcome**	**Follow-up [m]**
1	7.6	M	BM	AML-NOPHO 88	ANNL 98	1	1	Alive	83
2	13.8	M	CNS	AML-NOPHO 88	AML-BFM 88	1	0	Lost in follow-up	25
3	11.7	M	BM	AML-NOPHO 88	IDA-FLAG	1	1	2nd relapse, CR3, 3rd relapse, death in progression	22
4	5.2	F	BM	AML-	IDA-FLAG	0	0	Death in	4

				NOPHO 88				progression	
5	11.9	F	BM	ANLL 98	CDE+FLAG	1	1	2nd relapse, death in progression	14
6	5.3	M	BM	ANLL 98	FLAG	1	1	2nd relapse, death in progression	87
7	1.1	F	BM + CNS	AML-BFM 2004	FLAG	1	0	2nd relapse, CR3, 3rd relapse, death in progression	10
8	18.0	M	BM	AML-BFM 2004	IDA-FLAG	0	0	Death — infection during treatment	2
9	0.3	F	CNS	AML-BFM 2004	FLAG	1	0	Alive	149
10	16.8	M	BM + NS	AML-BFM 2004	IDA-FLAG	1	1	Alive	36
11	13.4	M	BM + NS	AML-BFM 2004	IDA-FLAG	0	0	Death — treatment toxicity	4
12	17.8	M	BM	AML-BFM 2004	IDA-FLAG	1	1	2nd relapse, death — infection during treatment	28
13	4.9	F	BM	AML-BFM 2004	FLAG	1	1	Alive	139
14	18.5	F	BM	AML-BFM 2004	FLAG	1	1	Death — GvHD	8
15	5.4	M	BM	AML-BFM 2004	FLAG	0	1	Death in progression	6
16	4.9	M	BM	AML-BFM 2004	FLAG	1	1	2nd relapse, CR3, 3rd relapse, death in progression	12
17	1.6	F	BM	AML-BFM 2004	DLI	0	0	Death in progression	5
18	16.9	F	BM	AML-BFM 2004	IDA-FLA	0	1	Death in progression	14
19	13.6	F	BM	AML-BFM 2012	IDA-FLAG	1	1	Alive	15
20	0.5	F	BM+ CNS	AML-BFM 2012	IDA-FLAG	0	0	Death in progression	0
21	5.7	M	BM	AML BFM 2004	FLAG + Aza-C	0	0	Death — infection during treatment	10

PN — patient's number; M — male; F — female; BM — bone marrow; CNS — central nervous system; NS — nasopharynx; CR2 — 2nd complete remission; HCT — hematopoietic cell transplantation; IDA-FLAG — idarubicin, fludarabine, cytarabine, G-CSF; FLAG — fludarabine, cytarabine, G-CSF — granulocyte colony-stimulating factor; CDE — cytarabine, daunorubicin, etoposide; DLI — donor lymphocyte infusion; Aza-C — azacitidine; GvHD — graft-versus-host disease; m — months

Outcome after relapse

One patient died because of a rapid progression of disease without receiving any treatment. Among the remaining 20 patients, the second CR rate achieved by heterogeneous reinduction regimens was 65.0%. The 5-year pOS for the entire group was 28.6%, and was significantly higher in patients who achieved second remission compared to those who did not (44.9% vs. 0.0%, p <0.001). The results are shown in Figures 2 and 3. Second relapse occurred in six cases with median time to second relapse of 0.98 years (range 0.3–1.8) and five of them were bone marrow relapses. The main reason for death was progression of disease which occurred in 10 patients. Treatment-related mortality was observed in five cases, of which three died because of infections, one because of graft-versus-host disease after HCT, and one because of treatment toxicity.

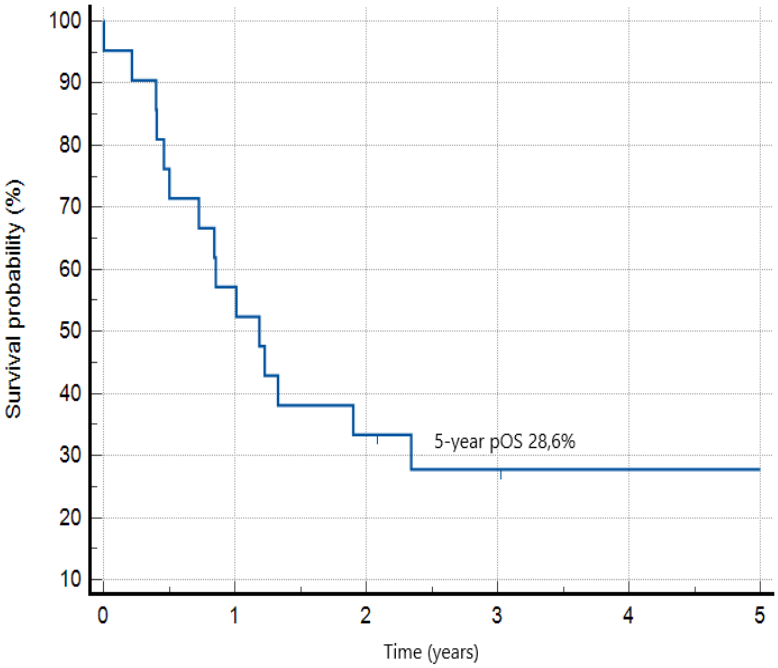

Figure 2. 5-year probability of overall survival (pOS) for acute myeloid leukemia children with relapsed disease

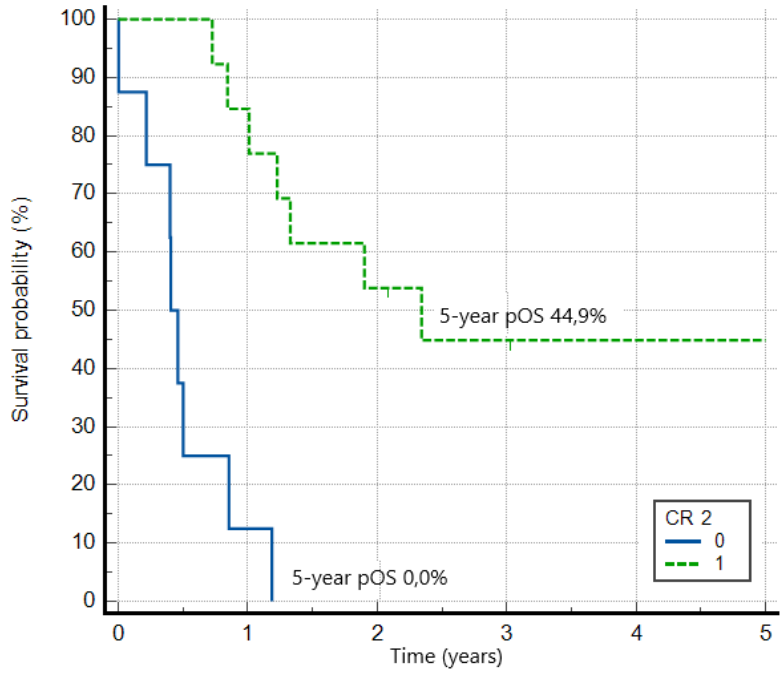

Figure 3. 5-year probability of overall survival (pOS) for acute myeloid leukemia children with relapsed disease in groups with and without second remission achievement; CR2 — 2nd complete remission

Discussion

The significant progress in recent decades in therapy results of pediatric AML is due to therapeutic protocol improvement, supportive care development, and experience in managing emergencies. Although all of these aspects reduce mortality and have a great impact on patients' overall survival, relapsed disease remains one of the main challenges in the therapy of AML in children [12]. In our analysis, relapse occurred in over 27% of patients, and children with a recurrence of disease had a highly unfavorable prognosis, with the 5-year pOS being below 30%. This result was slightly lower compared to outcomes reached by modern therapeutic approaches reported by other authors [13–15].

Considering that relapse is the most significant risk factor, several attempts have been made to establish factors associated with a higher risk of disease recurrence in first remission [16–18]. In our study, WBC >100 G/L diagnosis was a risk factor of relapse. Significant leukocytosis not only corresponds to higher blast cells load at diagnosis, but is also considered to be a factor related to unfavorable genetic mutations, such as *FLT3* internal tandem duplication (*FLT3*-ITD) [18]. In the analyzed group we cannot compare laboratory and genetic tests results, because genetic diagnostics was not available in the early period of the analysis.

Time to relapse proved to be an important prognostic factor in the analyzed cohort, with an almost three times greater pOS in children who relapsed later than one year after their first complete remission. In a systematic review of therapy outcomes, length of first remission has been strongly correlated with overall survival according to 10 out of 12 studies [1].

Achievement of a second complete remission was another factor with a significant impact on the 5-year pOS. A good response to initial therapy in children with *de novo* diagnosed AML is a well known favorable prognostic indicator. A comprehensive analysis of 546 patients under the age of 21 with relapsed AML showed that patients who achieved second remission had 4-year survival of 53 ± 3% compared to 13 ± 3% in the group of patients without CR. In that study, the achievement of second remission was correlated with other favorable prognostic factors such as late relapse and cells favorable morphology and cytogenetics [6].

The role and indication for allo-HCT in first CR of AML remains a topic of intense debate [19]. In the analyzed group, children treated with allo-HCT in first remission tended to

have lower CR-rates after relapse compared to children treated with chemotherapy only, but the difference was not statistically significant. Numerous other studies have described similar results [20–23]. The reason for this correlation is unclear, but it is worth noting that allo-HCT in first line treatment is dedicated for children with high risk factors, that are themselves related to a higher risk of relapse. On the other hand, in relapsed disease the 5-year pOS was 33.3% for patients treated with HCT and 22.2% in the group who received chemotherapy only. Allo-HSCT in second remission has been also related to significantly superior outcomes in several studies [22–24].

In the analyzed group, induction regimens have differed between patients. Similar problems have been described in other studies, where some induction regimens have included new drugs and therapies, while others have been based on conventional chemotherapy only [25]. Considering the poor outcome and high toxicity of salvage treatment, currently great expectations are resting on targeted therapies. Several therapies for relapsed AML have been under investigation, but the main challenge of evaluating novel agents for children is that pediatric relapsed AML is a relatively rare disease. The optimal way to incorporate new agents into therapy is still under investigation [2, 25, 26].

Clearly there are some limitations of this study. Our analysis was based on retrospective data and the described group was small. Therapeutic regimens in second line therapy differed between patients. However, relapsed AML remains a rare disease and we lack large, multicenter studies.

Conclusion

Our analysis has identified several prognostic factors in relapsed childhood AML. Unfortunately, as relapse is the most important risk factor in childhood AML, a group of patients with favorable characteristics dedicated to treatment reduction cannot yet be defined. The aim of identifying prognostic factors is to define high risk patients who may benefit from innovative therapy regimens and clinical trials, because treatment intensification in the highly pretreated group is limited by severe toxicity. There is a great need for international collaboration with clinical trials specifically for children with relapsed acute myeloid leukemia.

Authors' contributions

JS — data collection and interpretation, statistical analysis, description of results; ED, AJG, 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 — 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.

Financial support

None.

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