Outcome of refractory and relapsed acute myeloid leukemia in children treated during 2005–2011 – experience of the Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG)

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Aim of the study: Recent studies showed relatively better outcome for children with refractory (refAML) and relapsed acute myeloid leukemia (relAML). Treatment of these patients has not been unified within Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG) so far. The goal of this study is to analyze the results of this therapy performed between 2005–2011.

Material and methods: The outcome data of 16 patients with refAML and 62 with relAML were analyzed retrospectively. Reinduction was usually based on idarubicine, fludarabine and cytarabine with allogenic hematopoietic stem cell transplant (alloHSCT) in 5 refAML and 30 relAML children.

Results: Seventy seven percent relAML patients entered second complete remission (CR2). Five-year OS and disease-free survival (DFS) were estimated at 16% and 30%. The outcome for patients after alloHSCT in CR2 (63%) was better than that of those not transplanted (36%) with 5-year OS of 34% vs. 2-year of 7% and 5-year DFS of 40% vs. 12.5%. Second complete remission achievement and alloHSCT were the most significant predictors of better prognosis (p = 0.000 and p = 0.024). The outcome of refAML children was significantly worse than relAML with first remission (CR1) rate of 33%, OS and DFS of 25% at 3 years and 53% at 2 years, respectively. All survivors of refAML were treated with alloHSCT after CR1.

Conclusions: The uniform reinduction regimen of the documented efficacy and subsequent alloHSCT in remission is needed to improve the outcome for ref/relAML children treated within PPLLSG. The focus should be on the future risk-directed both front and second line AML therapy.

Key words: acute myeloid leukemia, relapse, stem cell transplantation, children.

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Introduction

Childhood acute myeloid leukemia (AML) is resistant to therapy (refAML) in 5–10% or recurs (relAML) in 30–40% of patients [1, 2]. Recent trials have shown a higher cure rate, providing an insight into current therapeutic strategies for these children with poor prognosis [3, 4].

Treatment of ref/relAML children within the Polish Pediatric Leukemia/Lymphoma Study Group (PPLLSG) has not been unified so far. The improved outcome among consecutive BFM AML studies encouraged the PPLLSG to adopt the modified BFM relapsed AML 2001/01 protocol [5]. The objective of this retrospective report is to analyze the outcomes to date in comparison

with other groups and to establish a benchmark for analysis of future therapy.

Material and methods

Between 2005 and 2011, 16 children (8 boys, 8 girls) with refAML and 62 children (38 boys, 24 girls) with relAML were treated at PPLLSG institutions.

The median time from the date of the first complete remission (CR1) to relapse was 10 months (range 1–77.4). Forty (64%) relAML patients had early (≤ 1 year) and 22 (35%) late relapse (> 1 year). Table 1 shows the characteristics of the patients in this cohort.

Reinduction treatment

Informed consent and ethical approval were obtained before the therapy was performed. There was no single reinduction chemotherapy performed. The management varied according to different institutions. IdaFlag (fludarabine, high-dose cytarabine and granulocyte colony-stimulating factor with addition of idarubicin) was the most common basis of the administered regimens: refAML $n = 11$, relAML $n = 43$.

After reinduction chemotherapy, 35 (5 refAML, 30 relAML) patients underwent allogeneic hematopoietic stem cell transplantation (alloHSCT): 24 (68%) from a matched unrelated donor (MD), 5 (14%) from a matched sibling donor (MSD), 3 (8%) from a mismatched donor (MMD), 1 (3%) from a haploidentical donor, and for 2 (6%) there were no data concerning donor type. The majority of children were conditioned for alloHSCT with the busulfan plus cyclophosphamide-based regimen.

Definitions

Primary refAML, first relapse AML, and risk group at the initial diagnosis were defined according to the AML-BFM Interimphase 2004 protocol. Early treatment response, postreinduction complete remission and second relapse were defined according to the Relapsed AML 2002/01 protocol [5].

Table 1. Characteristics of the disease and the patients with refAML and refAML

	Primary refractory AML ($n = 16$)	First relapse AML ($n = 62$)
Age	1.2–17.1 years (median 12.7)	0.1–17.5 years (median 10.9)
Risk group at primary diagnosis		
SR		17 (27%)
HR	16 (100%)	45 (72%)
Initial protocol		
AML-BFM 2004 Interim	15	53
ANLL98		9
Site of primary disease/ relapse		
isolated BM	13	43
BM + CNS	2	10
BM + other	1	4
isolated CNS		4
other isolated		1

Statistical analysis

Surviving patients were censored on the 31st of December 2011. For statistical analysis, the Kaplan-Meier and the log-rank test were used. The Cox proportional-hazards regression model allowed us to determine significant time-dependent factors. Results were considered to be statistically significant if the p value was under 0.05.

Results

Primary refAML outcome

Of 16 children, one patient died before reinduction. Fifteen (93%) children underwent reinduction chemotherapy and the early good response rate was 40% ($n = 6$). Five (33%) children, including one poor early responder, entered first complete remission.

Of the patients who remitted, one had a relapse 9 days after CR1 and died 3.5 months later. Four remaining patients underwent alloHSCT at a median of 1.5 months (range 1.1–1.9) from CR1.

One of the transplanted children relapsed after MSD alloHSCT. The three remaining grafted patients (2 MD, 1 MSD) were the only survivors at the time of the last follow-up (Table 2).

One child who failed to enter CR1 on second-line chemotherapy received matched unrelated donor (MUD) alloHSCT and died 9 days later of progressive disease. By December 31, 2011, three (18.7%) of 16 refAML children, including 1 poor early responder, were alive, with a median time from CR1 of 33.2 months (range 14.9–34.2).

Relapse AML outcome

Four children died before reinduction. Among the 58 patients who received chemotherapy, 37 (63%) were good early responders with missing data in 14 cases. Second complete remission (CR2) was attained in 44 (75%) children, including 5 poor early responders. One other patient achieved CR2 after MD alloHSCT performed in relapse, resulting in a CR2 rate of 77% ($n = 45$). The CR2 rate among children treated initially according to protocols AML-BFM 2004 Interim and ANLL98 was 70% ($n = 35$) and 88% ($n = 8$) respectively.

AlloHSCT was performed in 28 (63%) children in CR2, at median time of 2.5 months (range 0.2–5.5) from second

Table 2. Treatment follow-up in children with refAML after CR1 according to the consolidation with alloHSCT

	AlloHSCT after CR1 ($n = 4$)	No alloHSCT after CR1 ($n = 1$)
Death/TRM		
Relapse	$n = 1$, 26 months*	$n = 1$, 0.3 months*
Survival in CR1	$n = 3$, 33.2 months** (range 14.9–34.2)	

**time from CR1 in months; **median time from CR1*

Table 3. Treatment follow-up of relAML children in CR2, according to the consolidation with alloHSCT

	AlloHSCT in CR2; median time to HSCT: 2.5 mo (range 0.2–55)	No alloHSCT in CR2
Number of patients	28	16
Age	0.2–17.4 years (median 8.9)	0.1–17.3 years (median 11.3)
Boys/girls	13/15	10/6
Death/TRM	8 (28%) 1.7 months* (range 0.4–12)	6 (37%) 2.1 months* (range 0.7–7)
Second relapse	7 (25%) 10 months* (range 5–16)	7 (43%) 2 months* (range 0.6–3.2)
Survival in CR2	13 (46%) 30.4 months* (range 4.6–87.6)	3 (18%) 30.4 months* (range 0.03–32)
pDFS	5 years 0.408 ±0.104	5 years 0.125 ±0.083
	log rank 0.002	
pEFS	5 years 0.352 ±0.104	2 years 0.074 ±0.103
	log rank = 0.000	
pOS	5 years 0.348 ±0.16 median follow up 20.2 mo (range 3.5–88.3)	2 years 0.073 ±0.07 median follow up 4 mo (range 0.6–32.7)
	log rank 0.000	

**median time from CR2*

remission. Of 44 children in CR2 after reinduction chemotherapy, 16 (36%) did not undergo alloHSCT. Table 3 shows the follow-up of the children in CR2, according to the subsequent alloHSCT therapy.

Among the transplanted children 8 died of toxic complications – 3 due to graft-versus-host disease, 2 due to multiorgan failure, and one each from sepsis, CNS hemorrhage, and lymphoproliferative disease. In 6 non-transplanted patients treatment-related mortality was caused by multiorgan failure, sepsis and CNS hemorrhage in 3, 2 and one case respectively.

Two children received MD alloHSCT in relapse resulting in one CR2 attained. Both of them died, one due to hemorrhagic complications in CR2, the other because of progressive disease, 47 and 37 days from alloHSCT respectively.

By December 31, 2011, 16 (35%) of 62 relAML children, including 1 poor early responder[1] and 3 non-grafted patients, were alive, with a median time from CR2 of 30.4 months (range 0.03–87.6). One of the non-transplanted survivors was a 17-year-old boy with SR AML FAB M4 inv16, with 2 years CR1 duration. The other one was a 2-year-old boy at diagnosis, with AML FAB M4E, delayed CR1 (HR), early CNS relapse, and a good response to one Flag course and CNS radiotherapy. The third one was a 15-year-old boy with HR AML BCR/ABL positive (FAB data missing), late marrow relapse, and remission entry after IdaFlag plus dasatinib. The time of follow-up of these 3 boys was 0.6, 32 and 4 months respectively.

Table 4 shows the comparison of the therapy results in refAML and relAML.

Prognostic factors

The impact of selected prognostic factors (age, risk group, early response to chemotherapy, duration of CR1, HSCT in relapse) for CR2 rate and survival was analyzed in the group of relAML.

Early relapse was significantly correlated with lower remission rates (62% vs. 90% $P = 0.046$; Table 5) and both 5-year pDFS ($P_{\text{log-rank}} = 0.03$) and pOS ($P_{\text{log-rank}} = 0$).

There was a marginally significant difference in overall survival between high and standard risk patients ($P_{\text{log-rank}} = 0.035$). A significant effect of alloHSCT on survival was identified in the log-rank test (pDFS: $P_{\text{log-rank}} = 0.02$; pOS: $P_{\text{log-rank}} = 0$).

In a Cox regression model using age, risk group, CR1 duration, achievement of CR2 and HSCT in relapse, only HSCT after CR2 showed a strong impact on survival (Tables 6 and 7; Fig. 1).

The variety of postreinduction chemotherapy regimens used in our group precludes the evaluation of the impact of any one therapeutic schedule.

Discussion

The 5-year OS of 16% for children with relAML in this report reflects the poor prognosis for these patients. The survival rates in childhood relAML have increased over time with intensified and uniform reinduction concepts and improved supportive care. They range from 12% to 34% at 2–5 years in other studies [6] with recent relatively good outcome of 38% at 4 years in Relapsed BMF AML 2001/01 and 38% at 5 years in Nordic Society for Pediatric Hematology and Oncology (NOPHO) AML93 trials [3, 5]. Results presented here fit the lower range of these limits but the comparability may not be accurate due to methodological discrepancies between the trials.

Whereas the survival of the patients in the presented cohort was unsatisfactory, the second remission rate of 77% was comparable with those shown by the leading

[1]One poor early responder, who entered and remained in CR2 on the last follow-up, afterwards had the next relapse.

Table 4. Summary of outcome and follow-up of children with refAML and relAML

	refAML (*n* = 16)	relAML (*n* = 62)
Postreinduction CR rate	*n* = 5 (33%)	*n* = 45 (77%)
First/second relapse	*n* = 2/5 (0.3 and 26 months)*	*n* = 14/45 (31%) 16.4 months (range 0.6–16.4)**
Survival in CR1/CR2	*n* = 3/5 33.2 months (range 17.8–34.2)**	*n* = 16/45 (35%) 30.4 months (range 0.03–87.6)**
pDFS	2 years, 0.533 ±0.248	5 years, 0.305 ±0.07
pEFS	3 years, 0.167 ±0.093	5 years, 0.177 ±0.05
pOS	3 years, 0.25 ±0.108 median follow-up 37.3 months (range 17.8–37.4)	5 years, 0.164 ±0.079 median follow-up 19.8 months (range 0.6–88.3)

**time from remission; **median time from remission*

groups: 77% (NOPHO) [3], 71% (French Leucémie Aique Myeloide Enfant 89/91 protocol-LAME) [4]. This observation can be explained with the low quality of the remissions and directs the attention toward the need for optimal chemotherapy choice. Prospective monitoring of minimal residual disease (MRD) is supposed to be a more accurate technique to evaluate the disease status than remission rate [1, 9].

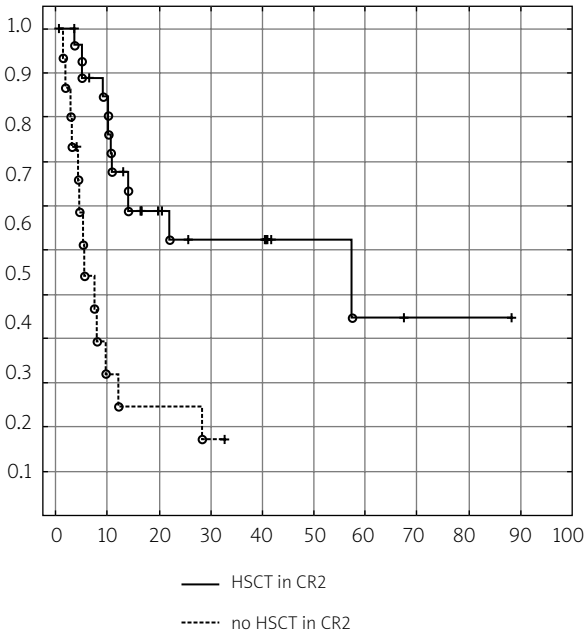
In accordance with other reports, in the presented group the second remission rate and survival differed according to the first remission duration [3, 4, 7, 8, 13]. Early relapse was associated with a statistically significantly lower CR2 rate (62% vs. 90%) and worse 5-year pOS (11% vs. 27%) than late relapse. Presented survival in early relapse was similar to 3-year pOS of 24% in the MRC AML10 trial; however, NOPHO 93 and LAME 89/91 studies reported 21% and 24% at 5 years.

The prognosis in the analyzed refAML group was dismal, with CR1 rate, disease-free survival (DFS), event-free survival (EFS) and overall survival (OS) of 33%, 53% at 2 years, 16% at 3 years and 25% at 3 years vs. 77%, 30% at 5 years, 17% at 5 years and 16% at 5 years in relAML respectively. In contrast to relAML, among the presented 16 children with refAML, no one had standard risk AML, the CR1 rate was half the level of the CR2 rate in relAML, and the final prognosis was much worse. These findings show that probably refAML should be evaluated as a distinct entity.

There are few reports describing treatment outcomes in cohorts of children with refAML. Of 11 refAML patients in the DCOG study, no one attained CR1 [6]. Gorman *et al.* reported 2-year DFS of 0% in a group of 7 refAML children [10]. Due to the small numbers, these children are incorporated into cohorts of relAML or poor responder AML patients. Warenham *et al.* have just reported (NOPHO-AML 2004) the outcome of early alloHSCT in 14 refAML patients. Two of them were transplanted in persistent disease and 9 with positive MRD. These 11 patients became long-term survivors (3-year follow-up), recommending early alloHSCT regardless of the disease state in such cases [11].

In the presented ref/relAML cohort, patients who were transplanted in postreinduction remission had the best prognosis and accounted for 100% of refAML and 84% of relAML survivors. AlloHSCT in CR2 was statistically the leading predictor of better outcome in relAML children. This is consistent with the literature data [3, 4, 7, 10] and the documented graft versus leukemia effect which is the basis of the established consensus to advocate alloHSCT to all ref/relAML patients in postreinduction remission [1, 2]. This therapy gives the chance of 5-year survival of up to 49–62% in different studies [12], compared with 35% in the presented cohort. It shows that details of the transplant procedure, toxicities and supportive care modalities should be analyzed, which is planned to be done in a separate paper.

In the analyzed study the median time between CR2 and second relapse or treatment-related death in the non-transplanted patients was 2 and 2.1 months respectively. These time periods were shorter than the median time to transplant (2.5 months) in the grafted children. It suggests that these circumstances precluded HSCT and



HSCT – hematopoietic stem cell transplantation

Fig. 1. Probability of survival according to consolidation in CR2

Table 5. Evaluation of the impact of selected prognostic factors on CR2 rate in relAML children

Factor		*n*	CR2 (*n* = 44)	Univariate analysis	
				z	*p*
age	< 10 years	27	70%	0.205106	0.837489
	> 10 years	35	74%		
risk group	SR	17	94%	1.51033	0.130960
	HR	45	64%		
early response	< 20%	37	83%	0.223753	0.822950
	> 20%	7	71%		
CR1 duration	≤ 1 year	40	62%	1.99513	0.046030
	> 1 year	22	90%		

Table 6. Evaluation of the impact of selected prognostic factors on DFS in relAML children

Factor		*N*	pDFS	log-rank	Cox regression	
					HR (95%CI)	*p*
age	< 10 years	19	5 years, 0.307 ±0.113	0.709	1.578	0.323692
	≥ 10 years	26	5 years, 0.305 ±0.094			
risk group	SR	16	5 years, 0.499 ±0.13	0.153	2.328	0.083611
	HR	34	5 years, 0.218 ±0.078			
CR1 length	≤ 1 year	25	5 years, 0.24 ±0.08	0.030	0.465	0.104055
	> 1 year	20	5 years, 0.382 ±0.122			
HSCT after CR2	HSCT	28	5 years, 0.408 ±0.083	0.002	2.751	0.01458
	no HSCT	16	2 years, 0.125 ±0.083			

Table 7. Evaluation of the impact of selected prognostic factors on OS in relAML children

Factor		*n*	pOS	log-rank	Cox regression	
					HR (95%CI)	*p*
age	< 10 years	27	5 years, 0.258 ±0.096	0.502	1.962	0.057
	≥ 10 years	35	5 years, 0.121 ±0.095			
risk group	SR	17	5 years, 0.238 ±0.184	0.035	2.119	0.090
	HR	45	5 years, 0.182 ±0.063			
CR1 length	< 1 year	40	5 years, 0.119 ±0.057	0.000	1.44	0.467
	≥ 1 year	22	5 years, 0.272 ±0.202			
CR2	CR2	45	5 years, 0.228 ±0.108	0.000	5.326	0.000
	no CR2	17	0.48 year 0 ±0			
HSCT	HSCT	30	5 years, 0.324 ±0.150	0.000	2.989	0.024
	no HSCT	32	2 years, 0.070 ±0.047			

shows the need for optimal care to avoid delay in proceeding to transplant.

The question may be raised whether further relapses are due to delay of HSCT or to a more aggressive type of leukemia or suboptimal first line treatment. On the other hand, favorable long-term outcomes after chemotherapy alone have also been reported. Goemans *et al.* in 2008 summarized from the literature 34 of them [6]. In our cohort there was one survivor with 32 months of follow-up after chemotherapy alone.

Genetic profiling and MRD monitoring are currently the modalities which, if performed after primary diagnosis, might provide insight into these doubts concerning AML heterogeneity. Specific genetic predictors and MRD strongly correlate with the treatment outcome [1, 2, 9] and may guide risk-stratified therapeutic decisions. The impact of the genetic characteristics on the management individualization was shown in the Relapsed AML 2001/01 trial. The patients with core binding factor acute myeloid leukemia (CBF-AML) treated with DaunoFlag had an OS of 82% at 4 years in contrast to 58% in those treated with FLAG only [5]. This risk-directed strategy may also be extended to the frontline AML therapy as it is proposed in the AML-BFM 2012 study: whereas HSCT in children in CR1 has been considered controversial so far, in this trial it is offered to subgroups with unfavorable genetics, assuming relapse rate reduction [1, 13].

In our nationwide study none of the refAML patients and nearly none of relAML ones presented the potential to survive a long time without HSCT in postreinduction

remission. The key issue of current management of ref/relAML is the reinduction regimen to achieve and maintain remission and optimal care to support the patient for early HSCT using the best genomic typing technology to select the best matched available donor [1, 2]. There is no standard reinduction chemotherapy protocol [1, 2]. The concern should focus on the optimal balance between efficacy and toxicity of the chosen regimen and the unified rules of the therapy which allow to derive conclusions on future solutions. The development of highly sensitive MRD techniques standardized for all patients, genetic profiling and identification of other predictors are required for future more individualized treatment.

Authors declare no conflict of interest.

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