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Treatment outcome and prognostic factors in relapsed pediatric acute myeloid leukemia

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Background
Despite improved outcomes for pediatric patients with acute myeloid leukemia (AML), the prognosis for relapse remains poor. This study aimed to examine the clinical factors associated with prognosis in relapsed pediatric AML.

Methods
We conducted a chart review of pediatric patients with AML who experienced their first relapse and received treatment at our institution between 2008 and 2019. Risk stratification at diagnosis was performed according to the definition suggested by the ongoing AML 2012 study in Korea, and the clinical factors associated with prognosis were analyzed.

Results
A total of 27 pediatric patients with relapsed AML were identified. The 5-year overall survival (OS) and event-free survival (EFS) rates were 32.9% and 32.9%, respectively. A duration ≥12 months from diagnosis to relapse had a favorable impact on survival outcomes (5-yr OS, 64.0% vs. 15.7%; P=0.007). Patients who achieved complete remission (CR) after 1 course of chemotherapy following relapse (N=15) had a 5-year OS rate of 59.3%, while none of the other patients survived (P<0.0001). Additionally, the 5-year OS differed significantly based on the risk group at initial diagnosis (62.3% [favorable and intermediate prognosis groups, N=11] vs. 13.3% [poor prognosis group, N=15]; P=0.014).

Conclusion
Patients with a longer duration of CR before relapse, who achieved CR following 1 course of reinduction chemotherapy, and were in the favorable or intermediate prognosis group at diagnosis demonstrated better outcomes. These findings emphasize the importance of tailoring treatment strategies based on the expected prognosis at relapse in pediatric patients with AML.

Key Words Acute myeloid leukemia, Pediatric, Relapse, Prognosis

INTRODUCTION

The incidence of pediatric acute myeloid leukemia (AML) is estimated to be 6.6 to 8.4 per million children, making it the second most common leukemia [1, 2]. Compared to the early 1980s, when only 40% of children with AML survived, the current survival rate has increased to approximately 70% [3, 4]. However, even after treatment with chemotherapy and hematopoietic stem cell transplantation (HSCT), approximately 24% to 41% of pediatric patients with AML still experience relapse [5-10]. The probability of long-term survival for relapsed AML in pediatric patients is around 30% to 40% [11-13]. Poor outcomes in pediatric patients with relapsed AML have highlighted the need for extensive research. However, due to the relatively small size of this patient population, only a limited number of studies have focused on relapsed pediatric AML. We con-

ducted a retrospective study to understand treatment outcomes and clinical factors associated with prognosis in relapsed pediatric AML.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of pediatric patients with a first relapse of AML who were treated at the Samsung Medical Center between 2008 and 2019. Patients with Down syndrome or acute promyelocytic leukemia were excluded from the study. To assess the prognosis after a first relapse of pediatric AML, we collected the following data from the patients' medical records: sex, white blood cell (WBC) count at the time of initial AML diagnosis, age at the time of relapse, interval from initial diagnosis to first relapse, time point of achieving complete remission (CR) after relapse, prognosis group at initial diagnosis, site of relapse, and molecular abnormalities. The risk group at the time of initial diagnosis was classified as favorable, intermediate, or poor, with the prognosis based on the risk stratification of the AML 2012 protocol (Fig. 1), which is currently undergoing a prospective multicenter clinical trial in Korea. This study was reviewed and approved by the Institutional Review Board of the Samsung Medical Center (approval no. 2023-05-103).

An event was defined as relapse or death from any cause, whichever occurred first. Survival rates after relapse were estimated using the Kaplan-Meier method, and the sig-

Table 1. Patient characteristics.

	N (%)/median (range)
Sex	
Male	15 (55.6)
Female	12 (44.4)
Initial WBC count, median (/μL)	20,400 (1,650–265,800)
Age at relapse, median (yr)	6.0 (1.0–18.0)
Interval from diagnosis to first relapse (mo)	7 (2–33)
Remission after 1 course of reinduction	
Yes	15 (53.6)
No	12 (46.4)
Prognosis group at initial diagnosis	
Favorable	4 (14.8)
Intermediate	7 (25.9)
Poor	15 (55.6)
Not available	1 (3.7)
Relapsed site	
BM only	21 (77.8)
EM only	5 (18.5)
BM+EM	1 (3.7)
Molecular abnormality	
FTL3-ITD	4 (14.8)
c-KIT in CBF AML	1 (3.7)
CEBPA	2 (7.4)
Others	20 (74.1)

Abbreviations: BM, bone marrow; CBF, core-binding factor; EM, extramedullary.

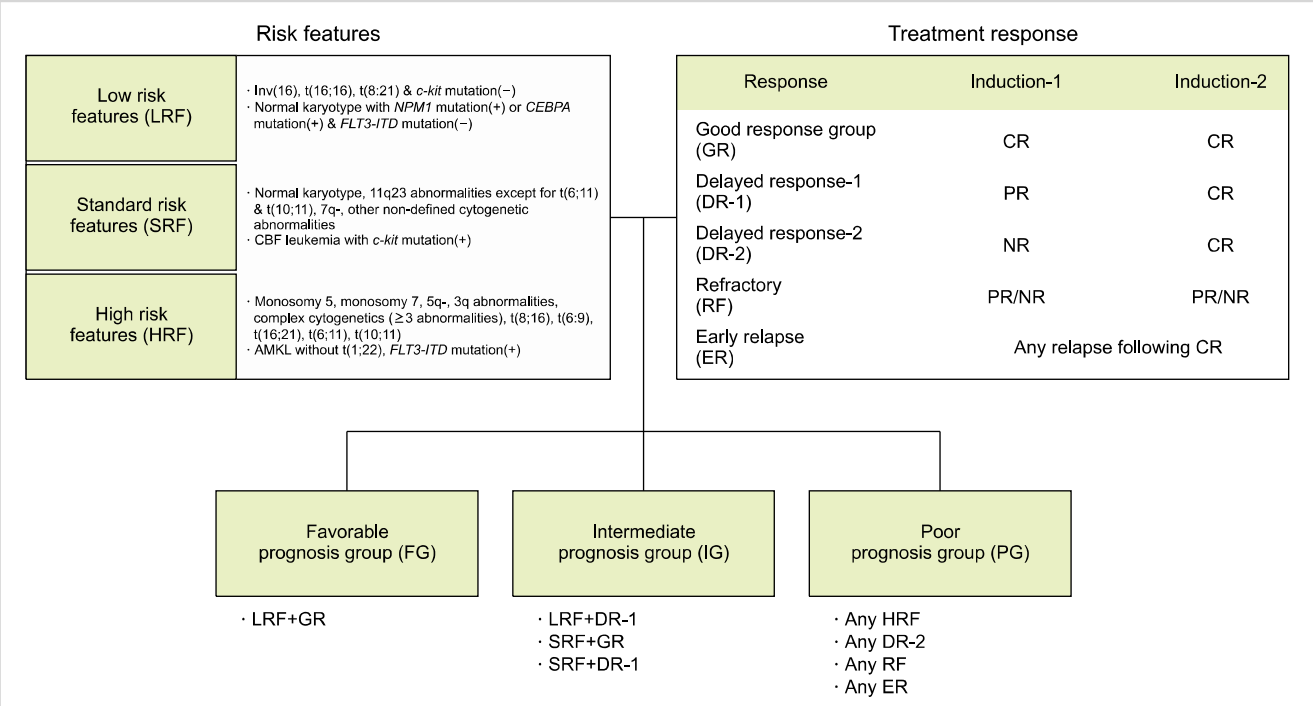

Fig. 1. Determination of prognosis groups in AML 2012 trial. Both risk features and treatment response were taken into account in determining the prognostic group.
Abbreviations: AMKL, acute megakaryocytic leukemia; CBF, core-binding factor; CR, complete remission; NR, no response; PR, partial response.

nificance of factors related to survival was analyzed using the log-rank test. A *P*-value of <0.05 was considered statistically significant. Multivariate analysis was conducted using the Cox regression analysis. All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 27.0, Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 27 pediatric patients with relapsed AML were identified; their characteristics are presented in Table 1. There were 15 males and 12 females, the median WBC count at diagnosis was 20,400/μL (range, 1,650–265,800/μL), median age at relapse was 6.0 years (range, 1.0–18.0 yr), and the median time between diagnosis to relapse was 7 months (range, 2–33 mo). At initial diagnosis, a majority of patients (N=16) had AML, not otherwise specified (NOS), followed by AML with recurrent genetic abnormalities (N=6), AML with myelodysplasia-related changes (N=4), and myeloid sarcoma (N=1). Diagnoses were made according to the AML 2016 World Health Organization (WHO) classification. Based on the clinical risk factors at the time of initial diagnosis, the patients were stratified into 3 prognostic groups: 4 patients in the favorable group, 7 in the intermediate group, and 15 in the poor group. The one remaining patient could not be stratified due to a lack of information. Among the 27 patients, 21 experienced bone marrow relapse, 5 had isolated extramedullary relapse, and 1 had a combined relapse. Molecular abnormalities were identified in 7 patients: 4 with a *FTL3/ITD* mutation, 1 with a core-binding factor AML with a *c-KIT* mutation, and 2 with a *CEBPA* mutation. The remaining 20 patients had either no clinically relevant molecular abnormalities or did not undergo molecular testing.

Treatment after relapse

Most patients (N=23, 85.2%) received the FLAG regimen (fludarabine, cytarabine, and granulocyte-macrophage stimulating factor) as reinduction therapy after the first relapse. Following relapse, 18 patients (66.7%) achieved a second

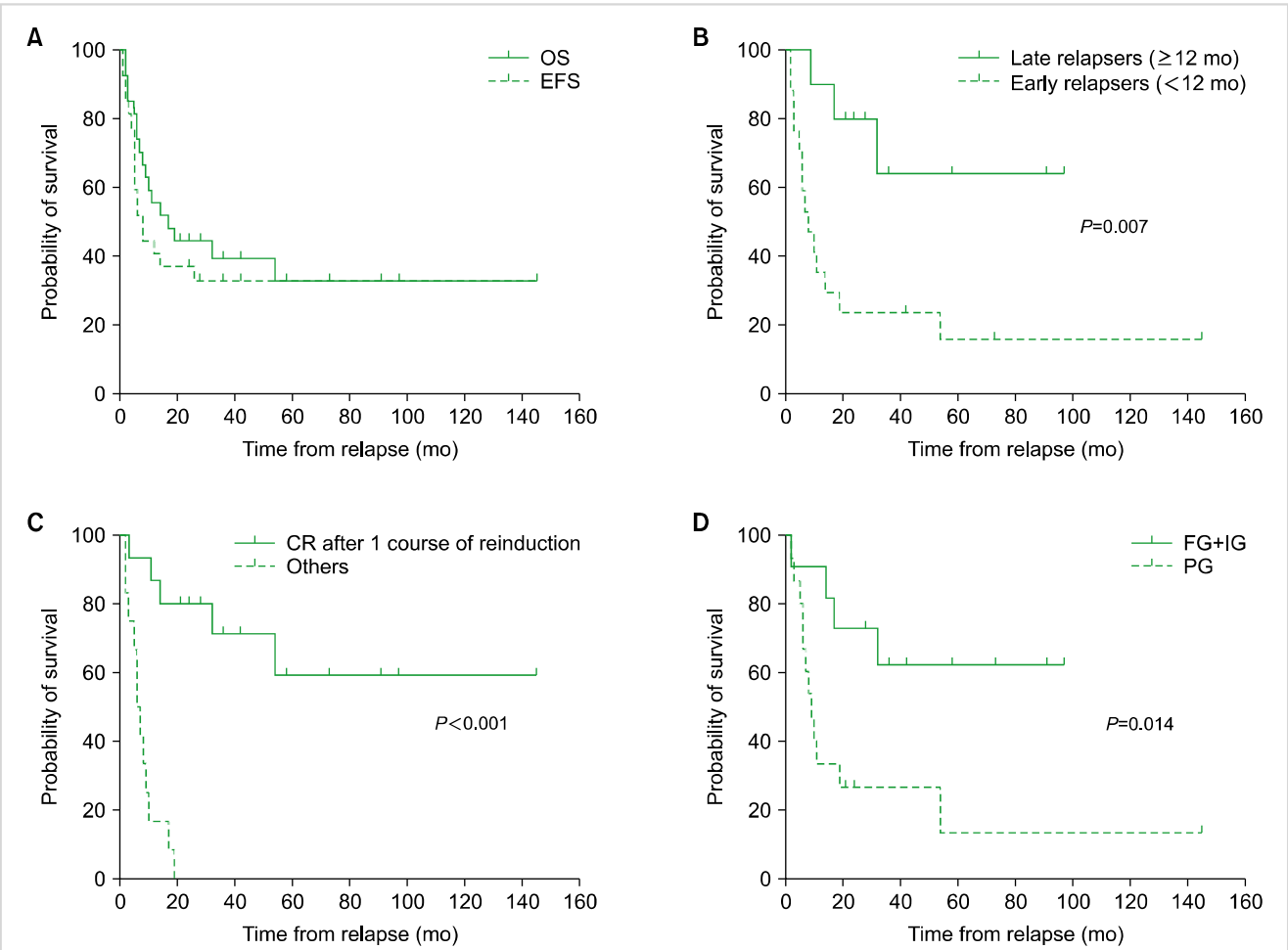

Fig. 2. Overall survival (OS) and event-free survival (EFS) rates. OS and EFS of all patients with first relapse of pediatric AML **(A)**. Comparisons of OS rates between the early vs. late relapsers **(B)**, those who achieved CR after 1 course of reinduction chemotherapy vs. others **(C)**, and those in the favorable or intermediate prognosis groups (FG+IG) vs. poor prognosis group (PG) **(D)**.

CR, with 15 (55.6%) achieving it after 1 course of reinduction chemotherapy. HSCT was recommended for all patients, irrespective of their response to reinduction chemotherapy or history of prior transplantation. However, 5 patients did not undergo HSCT due to: death from infectious complications (N=3), parental refusal (N=1), and isolated central nervous system relapse with poor general condition (N=1).

The conditioning regimens for HSCT varied depending on the patients' conditions, history of previous transplantation, and the graft source. Transplant recipients (N=11) received a myeloablative total body irradiation (TBI)-based regimen, 10 received combination busulfan and fludarabine, and one received low-dose TBI (3 Gy) in combination with busulfan and fludarabine.

Survival outcomes

The 5-year overall survival (OS) and event-free survival (EFS) rates were 32.9% and 32.9%, respectively (Fig. 2A). Two-thirds (N=18) of patients experienced an event; these were a second relapse before (N=1) or after (N=13) transplantation, death from infectious complications before transplantation (N=3), and a transplant-related mortality due to infection (N=1). Among the 5 patients who did not undergo HSCT, only 1 who had an isolated central nervous system relapse survived. As shown in Table 2, there were no statistically significant differences in survival rates according to sex (P=0.745), initial WBC count (P=0.989), or age at relapse (P=0.782). However, an interval time of >12 months from diagnosis to first relapse was identified as a favorable prognostic factor (P=0.007). The 5-year OS rate in this group was 64.0% (Fig. 2B). Among the 15 patients who achieved CR after 1 course of reinduction chemotherapy, the 2-year and 5-year OS rates were 80.0% and 59.3%, respectively. However, none of the patients who achieved CR after 2 or more courses or were refractory to chemotherapy survived (P<0.0001) (Fig. 2C). Among those patients who achieved CR after 1 course of reinduction chemotherapy, only one did not undergo HSCT but survived with chemotherapy after an isolated central nervous system relapse. Survival outcome was not affected by the relapse site (P=0.258). The 5-year OS rates for patients with *FLT3/ITD* mutations (N=4), *c-KIT* mutations in core-binding factor AML (N=1), *CEBPA*

Table 2. Univariate analysis of prognostic factors.

	N	5-yr OS (%)	*P*	5-yr EFS (%)	*P*	Hazard ratio (95% CI)
Sex						
Male	15	38.9	0.745	33.3	0.810	1.175 (0.445–3.052)
Female	12	27.8		27.3		
Initial WBC count (/μL)						
<20,000	13	34.6	0.989	33.3	0.951	1.007 (0.378–2.683)
>20,000	13	30.8		27.7		
Age at relapse (yr)						
0–10	16	35.0	0.782	30.0	0.908	1.144 (0.430–3.046)
>10	11	34.1		30.0		
Interval from diagnosis to first relapse (mo)						
≥12	10	64.0	0.007	60.0	0.008	4.636 (1.792–12.000)
<12	17	15.7		12.5		
Remission after 1 course of reinduction						
Yes	15	59.3	<0.0001	59.3	<0.0001	7.206 (2.403–21.610)
No	12	0.0		0.0		
Prognostic group						
FG+IG	11	62.3	0.014	60.0	0.002	3.640 (1.360–9.743)
PG	15	13.3		10.0		
Relapsed site						
BM only	21	33.3	0.258	33.0	0.676	
EM only	5	40.0		40.0		
BM+EM	1	0.0		0.0		
Molecular abnormality						
FTL3-ITD	4	0.0	0.019	0.0	0.109	
c-KITin CBF AML	1	100.0		100.0		
CEBPA	2	100.0		100.0		
Others	20	30.9		30.7		
Previous transplant						
No	15	26.8	0.382	25.7	0.511	1.557 (0.584–4.150)
Yes	12	43.8		41.7		

Abbreviations: BM, bone marrow; CBF, core-binding factor; EFS, event-free survival; EM, extramedullary; OS, overall survival; FG, favorable prognosis group; IG, intermediate prognosis group; PG, poor prognosis group.

Table 3. Multivariate analysis of prognostic factors affecting survival.

	Odds ratio	95% CI	*P*
Interval from diagnosis to first relapse	2.799	0.763–10.267	0.121
Remission after 1 course of reinduction	16.674	3.490–79.658	0.001
Prognostic group	1.199	0.227–6.339	0.831

mutations (N=2), and the remaining 20 patients were 0%, 100%, 100%, and 30.9%, respectively. The 5-year OS rates for the favorable or intermediate prognosis groups (N=11) and poor prognosis group (N=15) were 62.3% and 13.3%, respectively (P=0.014) (Fig. 2D).

Among the prognostic factors with a P-value <0.1 by univariate analysis, CR after 1 course of reinduction chemotherapy was the only independent prognostic factor on multivariate analysis (Table 3).

DISCUSSION

Contemporary clinical trials involving relatively large numbers of pediatric patients with AML have shown OS and EFS rates between 60% to 75% and 50% to 65%, respectively [5-10]. Nevertheless, relapse remains the primary cause of initial treatment failure, occurring in 24% to 41% of patients. In our study, the 5-year OS rate was 32.9%, consistent with the results of previous reports.

Relapsed AML in pediatric patients poses several challenges to both patients and healthcare professionals. Limited treatment options are available, leading to poor outcomes for many patients. Chemotherapy resistance is a common issue among these patients and significantly limits the efficacy of standard treatments. Moreover, limited access to clinical trials can restrict experimental and personalized treatment options.

In a study by the Therapeutic Advances in Childhood Leukemia (TACL) Consortium on pediatric relapsed or refractory AML, the 5-year EFS and OS rates were <30% [11]. However, the disease-free survival rate was 43% in the 56% of patients who achieved CR after reinduction therapy, highlighting the importance of achieving CR through reinduction chemotherapy for these patients to survive. Consistent with this finding, our data demonstrated that only those patients who achieved CR after 1 course of reinduction therapy survived.

The optimal reinduction regimen for relapsed pediatric AML remains uncertain. A recent report by the AML- Berlin–Frankfurt–Munster (BFM) group indicated that 88% of children with relapsed AML received a fludarabine plus cytarabine-based combination, with or without an anthracycline and granulocyte-colony stimulating factor (G-CSF) [14]. They observed that 42% of late relapsers (defined as relapse >1 year from initial diagnosis) survived event-free, whereas only 14% of early relapsers (defined as relapse <1 year from initial diagnosis) survived. In our study, in which most patients received a fludarabine plus cytarabine-based reinduction chemotherapy, the survival difference between late and early relapsers was even more pronounced than in the AML-BFM study (14.0% vs. 68.6%, respectively).

Allogeneic HSCT is generally recommended for pediatric patients with relapsed AML. Additionally, reducing the disease burden as much as possible prior to HSCT is important for the treatment of malignant diseases. To achieve this, clinical trials exploring new combinations of therapy (e.g., clofarabine-based regimens) and various targeted agents are underway. Some studies have reported that clofarabine-based reinduction chemotherapy could lead to an approximately 50% OS rate in pediatric patients with relapsed or refractory AML, whereas non-responders exhibit much lower OS rates [15, 16]. However, these outcomes cannot be considered optimal, given the comparable ones in other studies, including ours.

Targeted therapies are gaining attention due to their improved response rates in pediatric AML. However, developing targeted therapies for pediatric AML faces challenges due to the relatively small population of pediatric patients with AML and the limited potential for financial return; these may discourage pharmaceutical companies from investing in development of such drugs. Despite these challenges, several targeted therapies for the treatment of pediatric AML—particularly for relapsed or refractory cases, are currently undergoing clinical trials. Gemtuzumab ozogamicin (GO), an antibody-drug conjugate against CD33, is the only targeted therapy currently approved for pediatric AML, while others are in early-phase clinical trials or preclinical studies [17]. A recent Children's Oncology Group trial showed promising results when GO was added to chemotherapy, leading to improved EFS by reducing relapse rates in newly-diagnosed pediatric AML [8]. In a retrospective BFM study of pediatric relapsed or refractory AML, GO, with or without cytarabine, successfully bridged 49 of 76 patients to HSCT [18]. Similarly, in a French retrospective study that used a single dose of GO added to a fludarabine plus cytarabine plus anthracycline regimen in 26 patients with first relapse and 3 with refractory disease, 24 (83%) achieved CR, with an OS rate of 49% [19]. Notably, the OS rates for low-, intermediate-, and high-risk patients in that study were 56%, 51%, and 0%, respectively. These findings further highlight that the initial risk group is a highly significant prognostic factor in pediatric relapsed and refractory AML, similar to the findings in our study. Given the small number of patients in the favorable prognosis group (N=4) of our study, we compared the OS rates between the favorable and intermediate prognosis groups and the poor prognosis group. The higher OS rates in the favorable and intermediate prognosis groups and extremely poor outcomes in the poor prognosis group were consistent with the findings of other studies. They clearly underscore the predictive value of initial prognostic factors in determining clinical outcomes after relapse.

The small number of patients is a major limitation of

our study. However, our study demonstrated that only patients who achieved CR after 1 course of reinduction therapy survived, and this was the only independent factor affecting survival outcomes. In line with our findings, several groups have reported that early achievement of CR is a strong prognostic factor [11, 20]. Given that rapid responders to therapy may have a higher chance of being salvaged, inducing early CR is a major primary endpoint for future clinical trials.

In conclusion, we showed that patients in the favorable or intermediate prognosis group at diagnosis, those with a longer duration of remission before relapse, and those who achieved CR after 1 course of reinduction chemotherapy demonstrated better outcomes. These findings support the need to tailor treatment strategies based on the expected prognosis at relapse in pediatric patients with relapsed AML. Future clinical trials using targeted therapies should be highly encouraged, especially in patients who are likely to be resistant to standard reinduction therapies.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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