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Brief Communication

Outcomes of Patients With Acute Myeloid Leukemia Who Relapse After 5 Years of Complete Remission

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Leukemia relapse 5 years after achieving first complete remission (CR1) is uncommon in patients with acute myeloid leukemia (AML). In this study, we evaluated the outcomes of AML patients with late relapse at our institution and reviewed the literature for these patients. The study cohort consisted of nine AML patients with late relapse. The median interval between CR1 and AML relapse was 6.1 years (range: 5.1–16.2 years). At relapse, the karyotype was different from the initial AML diagnosis in 50% of patients. At the time of AML relapse, seven patients received induction chemotherapy and two patients received hypomethylating agents with an overall CR rate of 66%. The median time to relapse after achieving second CR (CR2) was 16.5 months [95% confidence interval (CI): 9.4, NA]. The median overall survival after first relapse was 28.6 months (95% CI: 7.3, 3.4–66.5 months). Despite initial CR after reinduction therapy, relapse rates are still high, suggesting that alternative strategies for postremission therapies are warranted in CR2. These approaches include the use of allogeneic hematogenic cell transplantation and the use of newly approved AML agents as maintenance therapy in nontransplant eligible patients.

Key words: Acute myeloid leukemia (AML); Late relapse; Prognostic factors; Survival

Acute myeloid leukemia (AML) is a heterogeneous disease with significant variation in prognosis and outcomes[1]. Although 80% of adult AML patients achieve complete morphologic remission (CR) after initial induction chemotherapy, many patients will eventually relapse. With standard chemotherapy, long-term survival for patients with AML is 35%–45% in patients younger than 60 years of age and 10%–15% in patients 60 years and older[1]. Relapsed disease and treatment-related complications are the most common causes of death. The clinical outcomes for patients with relapse AML are poor, with overall survival (OS) estimated at less than 10% at 3 years[2]. Leukemia relapse occurs in most patients with AML within 3 years after initial diagnosis[3]. The major determinants of outcome after relapse are a short duration of remission, adverse genetic factors, older age, and poor general health status[4]. Late relapse, arbitrarily defined as relapse after 5 years of achieving first CR, is uncommon, occurring in less than 3% of AML patients[5–7]. It remains under investigation whether late relapse is therapy related or associated with the reemergence of a dormant leukemic clone. Outcomes of AML patients with late relapse have not been extensively investigated. In this study, we evaluated the outcomes of patients with late relapse at our institution and reviewed the literature for these patients.

In this analysis, we used the Medical Archival Retrieval System (Medical Archival Retrieval System Inc., Pittsburgh, PA, USA), a repository for information derived from University of Pittsburgh Medical Center clinical, administrative, and financial systems, to identify patients who underwent diagnostic bone marrow biopsies at least 5 years apart after January 1, 2000[8]. Using the

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International Classification of Diseases, Ninth Revision (*ICD*-9) CM diagnosis codes for myeloid neoplasms (*ICD-9* diagnosis codes 204–208), we identified 144 patients. Chart review of these patients identified nine patients with a diagnosis of AML who experienced late leukemia relapse. Cytogenetic abnormalities and criteria for response were defined based on published criteria[9].

OS was defined as elapsed time from first relapse to death or last follow-up; median survival was estimated by the Kaplan–Meier method. Clinical and demographic parameters were examined for association with OS with proportional hazards (Cox) regression. The study was reviewed by the University of Pittsburgh Institutional Review Board and was approved according to institutional guidelines.

The study cohort consisted of nine AML patients who were determined to have late relapse. At the time of initial AML diagnosis, the median age was 58.8 years (range: 13–68 years). Cytogenetic data were available for seven patients at AML diagnosis. Five patients had a normal karyotype, one patient had translocation 9;11, and one patient had trisomy 11. All patients were treated with induction chemotherapy consisting of cytarabine and idarubicin, and all patients received consolidation therapy with high-dose cytarabine. None of the patients underwent allogeneic hematopoietic cell transplantation (allo-HCT) in first complete remission (CR1).

The median interval between CR1 and AML relapse was 6.1 years (range: 5.1–16.2 years). Patient demographics and baseline characteristics at AML relapse are presented in Table 1. Cytogenetic data were available for eight patients at AML relapse; six patients had a normal karyotype, and two patients had a complex karyotype. Four patients with a normal karyotype at AML diagnosis had concordant karyotype at relapse, and the one patient with trisomy 11 had relapse with trisomy 1. One patient with normal cytogenetics at diagnosis and a patient with translocation 9;11 had complex cytogenetics at relapse.

Table 1. Patients' Characteristics at Late Acute Myeloid Leukemia (AML) Relapse

Characteristic	
Total number	9
Median age (range), years	64 (23–75)
Gender	
Male	5 (55%)
Female	4 (45%)
Cytogenetic risk category at AML relapse	
Unfavorable	6 (75%)
Intermediate	2 (25%)
WBC count ($\times 10^9$/L; range)	4.3 (2.1–10.2)
% blasts in bone marrow (range)	32 (20–67)
Hemoglobin at AML diagnosis (g/dl; range)	12.6 (10.3–13.8)
Platelet count ($\times 10^9$/L; range)	73 (43–145)
LDH count (range)	192 (123–1163)
Total bilirubin (mg/dl; range)	0.6 (0.6–1.3)
Creatinine (mg/dl; range)	0.7 (0.6–1.3)

At the time of AML relapse, seven patients received induction chemotherapy. Four patients were treated with idarubicin/cytarabine, one patient with topetecan/cytarabine, one patient with idarubicin/cytarabine and fludarabine/cytarabine, and one patient with idarubicin/cytarabine and mitoxatrone/etoposide. Two patients received therapy with the hypomethylating agent, decitabine.

Six (66%) of the seven patients treated with chemotherapy achieved CR2. The two patients treated with decitabine did not achieve CR. Five of the CR patients subsequently received consolidation therapy with cytarabine. No patient underwent allo-HCT in CR2.

Eight of the nine patients had died by the time of analysis. The median time to relapse after achieving CR2 was 16.5 months [95% confidence interval (CI): 9.4, NA]. The median OS after first relapse was 28.6 months (95% CI: 7.3, 3.4–66.5 months) (Fig. 1). Three patients underwent allo-HCT after achieving CR3 following induction chemotherapy. OS from first relapse was related to platelets at relapse (hazard ratio: 0.85, $p = 0.01$) and white blood cell count at relapse (hazard ratio: 0.25, $p = 0.03$) (Table 2).

Although the outcome of patients with AML has improved due to the use of anthracycline-based chemotherapy, newly approved agents such as FLT3 inhibitors, and advanced supportive care, relapse continues to represent the leading cause of death in the majority

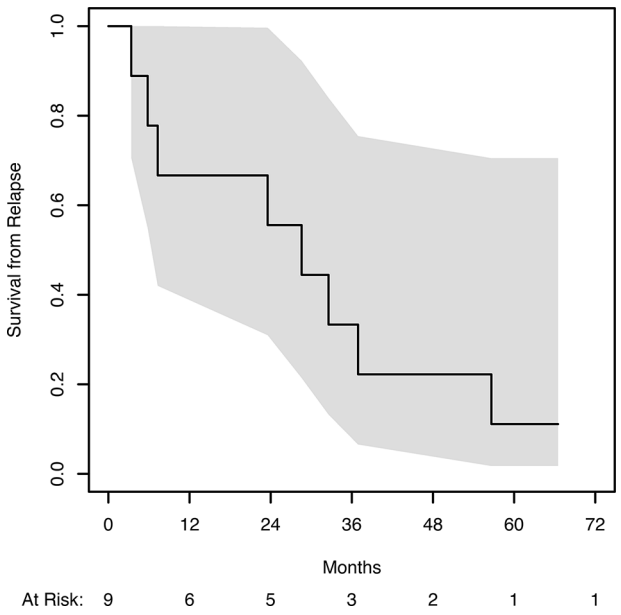

Figure 1. Overall survival.

Table 2. Factors Associated With Overall Survival

	HR	95% CI	*p*
Age at AML relapse	1.04	(0.98, 1.10)	0.10
Blasts at AML relapse	1.02	(0.98, 1.07)	0.25
WBC at AML relapse	1.06	(0.84, 1.34)	0.03
Hemoglobin at AML relapse	0.95	(0.45, 2.04)	0.90
Platelets at AML relapse	0.97	(0.94, 1.00)	0.04
Years from diagnosis to relapse	0.93	(0.69, 1.27)	0.67

HR, hazard ratios; CI, confidence interval. The *p* value is from a likelihood ratio test.

of patients[10]. The probability of relapse depends on risk factors such as age, pretreatment cytogenetics, molecular abnormalities, and the number of cycles of induction chemotherapy required for attaining the first CR. The risk of relapse in patients younger than 60 years ranges from 35% to 80%, and for AML patients older than 60 years, the cumulative incidence of relapse approaches 60% at 3 years for favorable risk category patients and exceeds 85% for those in the unfavorable risk category[11].

Late relapse occurring more than 5 years after achievement of first CR is rare, occurring in fewer than 3% of AML patients. It is not known whether late leukemia relapse is therapy related or due to reemergence and evolution of an originally quiescent clone or even the development of a new primary leukemia in a high-risk population. To better understand the mechanisms of late relapse, Yilmaz et al. performed whole exome sequencing in bone marrow samples obtained at diagnosis and late relapse in 10 AML patients[7]. A total of 41 driver mutations were identified, of which 11 were primary tumor specific, 17 relapse specific, and 13 shared (detected both in primary and relapsed tumor samples). In 8 of 10 cases, primary–relapse tumor pairs revealed that the founder clone persisted after frontline therapy and relapsed after a median of 7 years. Loss of primary tumor subclones was identified in five of eight cases, suggesting that some of the subclones were eliminated with chemotherapy. In all cases except one, relapsing tumors acquired at least one relapse-specific mutation. These data suggest that, in most cases, the founder leukemic clone persists after chemotherapy and establishes the basis for relapse years later.

Medeiros et al. reported the clinical outcomes of 15 AML patients with late relapse (Table 3)[5]. Among the 15 patients, 5 patients had undergone allo-HCT, and 3 patients autologous HCT in CR1 prior to the late relapse. Cytogenetic studies were available in 12 patients at relapse, and 9 patients had normal karyotypes. Six patients had concordant karyotypes at diagnosis and relapse. The median duration of CR1 was 9 years (range: 5.2–11.5 years). Thirteen patients (86%) achieved CR2 with reinduction therapy. Seven patients underwent allo-HCT after achieving CR2. The 5-year relapse-free survival and OS rates of this cohort were 59% and 51%, respectively. Verma et al. reported the outcomes of 11 patients with late relapse (Table 3)[6]. None of these patients underwent allo-HCT in CR1. At relapse, the karyotype was different from the initial finding in five of eight (63%) patients. After reinduction chemotherapy, CR2 was achieved in four patients (36%). The median CR2 duration was 1 month (range: 0–37), and median survival after relapse was 6.4 months (range: 1–39). No patient underwent allo-HCT in CR2 due to lack of a suitable donor and/or intercurrent illness.

In the current study, reinduction with intensive chemotherapy was associated with relatively high CR rates (66%) and with an OS after first relapse of 28.6 months. At relapse, the karyotype was different from the initial finding in four of the eight (50%) patients. Because of existing comorbidities, organ dysfunction, donor availability, and patients' wishes, no patient in our cohort underwent allo-HCT in CR2. An inherent limitation of this retrospective study is the small sample size, which precluded us to perform subgroup analyses to determine outcomes according to different treatment strategies (e.g., hypomethylating agents vs. reinduction chemotherapy). In addition, patients initially diagnosed with AML and treated at our institution may have been lost to follow-up and not identified by the retrieval system and thus escaped inclusion into the study after the 5-year landmark of initial diagnosis. In addition, because of the lack of pair molecular samples at AML diagnosis and late relapse, we did not perform next-generation sequencing to determine clonal persistence or the development of new mutations.

Given the rarity of late-relapse AML and the lack of prospective clinical trials, it is challenging to develop treatment guidelines. However, we and others have reported acceptable CR rates from reinduction chemotherapy, specifically in those patients whose performance

Table 3. Outcomes of AML Patients With Late Leukemia Relapse

No. of AML Patients	Median Age [Years (Range)]	Median Duration of First CR1 [Years (Range)]	Patients (%) Achieving CR2	Survival	Ref.
15	48 (13–77)	9 (5.2–11.5)	86%	51%, 5-year OS probability	5
11	66 (37–79)	6.7 (5.5–11.4)	36%	6.4 months	6
9	64 (23–75)	6.1 (5.1–16.2)	66%	2.3 years	Current study

status allows them to tolerate reinduction. Despite initial CR, however, relapse rates are still high, suggesting that alternative strategies for postremission therapies are warranted in CR2. These approaches include the use of allo-HCT and the use of newly approved agents, such as FLT3 inhibitors, as maintenance therapy in nontransplant eligible patients.

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