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Late relapses in acute myeloid leukemia: analysis of characteristics and outcome

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Abstract

Relapse after 5 years of complete remission (CR) is uncommon in acute myeloid leukemia (AML). Among 2347 patients seen between 1980 and 2008, 1366 achieved CR; 942 relapsed. Eleven (1.16% of all relapses) relapsed after a CR of >5 years. The median age was 66 years (range, 37–79). Initial therapy was cytarabine plus anthracycline in six, amsacrine-based in three, and other in two. The median CR1 duration was 81 months (range, 60–137). At relapse, the karyotype was different from the initial finding in five of eight (63%) patients with available data. Treatment for relapse included cytarabine with anthracycline in eight, and other in three patients, with a second CR (CR2) achieved in four (36%). The median CR2 duration was 1 month (range, 0–37), and median survival after relapse was 6.4 months (range, 1–39). Late relapses in AML are infrequent, with poor response to therapy. Karyotype at relapse is frequently different, raising the question of second AML versus relapse with the original clone.

Keywords

AML; late relapse; acute myeloid leukemia

Introduction

Intensive combination chemotherapy regimens for acute myeloid leukemia (AML) have improved the outcome of patients, and about 80% of younger patients with newly diagnosed AML may achieve complete remission (CR) [1, 2]. The majority of patients who achieve CR with initial chemotherapy will eventually relapse. Most relapses occur in the first 3 years, and rare patients relapse after being in CR for more than 5 years [3–11]. Previously published literature has defined late relapse in AML as a relapse happening more than 18 months to 5 years after the day that complete remission (CR) is determined [8, 11], with anecdotal reports of patients relapsing 11–18 years after achieving CR [9, 10]. The outcome

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of patients with very late relapse (>5 years after CR) is unknown, as there are very few available studies. In one study, 5-year relapse-free survival and overall survival rates of 59% and 51%, respectively, were reported [8].

We analyzed the medical records of adult patients with AML treated with various chemotherapeutic regimens at The University of Texas MD Anderson Cancer Center (UT-MDACC), to describe the clinical experience in patients with AML relapsing after 5 years, and to analyze the biological and clinical characteristics and identify any predictors for late relapse.

Materials and methods

Patients

Adult patients (age, ≥18 years) with newly diagnosed AML treated at UT-MDACC from January 1998 to December 2008 and enrolled in various clinical trials were included in this analysis. We selected patients diagnosed before July 2003 to allow the possibility of at least 5 years of follow-up. Patients with the M3 subtype (acute promyelocytic leukemia, APL) were excluded from this analysis. The studies were approved by the institutional review board, and all patients signed an informed consent according to institutional guidelines.

Evaluation of patients and statistical methods

CR was defined using the criteria from the International Working Group [12], and included a bone marrow examination showing normal maturation of all cellular components with <5% leukemic blast cells, a peripheral blood absolute neutrophil count $1 \times 10^9/L$, and a platelet count $100 \times 10^9/L$, with complete disappearance of all clinical and/or radiologic evidence of disease. Complete remission without platelet recovery (CRp) consisted of identical bone marrow findings with neutrophil recovery, as for CR, but with platelets $<100 \times 10^9/L$ and $20 \times 10^9/L$. Partial remission was defined as peripheral blood counts as for CR, but with bone marrow blasts of 6–25% and a decrease in marrow blasts of ≥50% compared with baseline before therapy. Overall survival (OS) was calculated from the time of initial AML diagnosis to death from any cause or until last follow-up. The duration of CR was calculated from the time of achieving CR until there was evidence of AML relapse.

Results

We identified 2347 adult patients with newly diagnosed AML who had undergone treatment at UT-MDACC. The patients were diagnosed between January 1980 and July 2003, and were followed until December 2008. A total of 1366 of the 2347 patients achieved CR; 215 patients had been in CR for >5 years, and 1151 had a CR duration <5 years. Among the 1151 patients with CR <5 years, 220 remain in CR and 931 have relapsed. Of the 215 with CR >5 years, 204 remain in CR while 11 patients have relapsed. Therefore, overall, 11 of the 942 total relapses (1.16%) or 11 of the 1366 patients who achieved CR (0.8%) developed late relapse. For the whole cohort of 2347 patients, the median age was 59 years (range, 15–89), median white blood cell (WBC) count $10.5 \times 10^9/L$ (range, 0.2–433), and median platelet count $49 \times 10^9/L$ (range, 1–229). Their median follow-up was 79.7 months (range,

1–296), with a median CR duration of 12.4 months (range, 0–295), and median survival of 9 months (range, 0–296).

Among the 11 patients with late relapse, four were females and seven were males. Their median age was 66 years (range 37–79), and their median presentation WBC count was $2.3 \times 10^9/\text{L}$ (range, 1.1–92.3). The characteristics of these patients at initial diagnosis are shown in Table I. The initial treatment was with a variety of combination chemotherapy regimens, with the majority of patients (91%) receiving cytarabine (Ara-C) based therapy, including six patients (55%) who received Ara-C with an anthracycline. The treatment details are summarized in Table I. All patients except one achieved a CR after one induction course; one patient needed two cycles of VAD (vincristine, adriamycin, dexamethasone) induction to achieve CR. Some patients received prolonged maintenance therapy, and these prolonged therapies reflect ongoing studies at the time examining the role of daily maintenance Ara-C or other low-dose maintenance strategies. None of these patients underwent an allogeneic stem cell transplant (Allo SCT) in first CR due to lack of a suitable donor and/or decision by patient and physician not to proceed with a transplant. The median duration of CR was 81 months (range, 60–137).

At the time of relapse, the median age was 74 years (range, 44–83); the median WBC count was $4.4 \times 10^9/\text{L}$ (range, 1.7–48.8). There were eight patients in whom karyotype was available both at the time of initial diagnosis and at the time of relapse. In these eight patients, three (37%) had the same cytogenetic abnormality at both time points [diploid in two, der(13;14) in one], and five (63%) had different cytogenetic aberrations at relapse than at initial diagnosis. The characteristics of patients at the time of relapse are shown in Table II, and none had evidence of myelodysplasia (MDS). At relapse, the patients were treated with a combination of high-dose Ara-C with various agents, as depicted in Table II.

The response to treatment after development of late relapse is also shown in Table II. Four patients (36%) achieved a second CR (CR2), two (18%) achieved partial remission, four (36%) were resistant, and one (10%) patient died during salvage therapy. No patient underwent an Allo SCT in CR2 due to lack of a suitable donor and/or inter-current illness. The median duration of CR2 was 1 month (range, 0–37). The median OS after relapse was 6.4 months (range, 1–39), and median OS from initial diagnosis of AML was 107 months (range, 68–143) (Figure 1). One patient in CR2 is alive, 32 months after the diagnosis of relapse.

Discussion

With increased understanding of the molecular abnormalities associated with AML and with the availability of newer targeted agents, the proportion of patients who may be offered specific therapy based on cytogenetic and/or molecular aberrations is likely to increase. However, despite such advances, the treatment of patients with relapsed AML remains difficult, with a median CR2 duration 14 months and median overall survival 12 months [13]. The prognosis of relapsed AML is affected by the age of the patient, duration of CR1, and cytogenetics. Patients with CR1 duration 12 months or 18–24 months have CR2 rates

of 10–17% and 50–64%, respectively [11, 14]. A favorable or unfavorable cytogenetic finding may result in CR2 rates of 88% vs. 36%, respectively [15].

Medeiros *et al.* [8] reported 15 cases of late relapse AML (3% of all relapses) in their patient population, in whom the median age was 48 years and median CR1 duration was 104.5 months. Six patients had cytogenetics data available at both the initial diagnosis and at relapse; the cytogenetics were the same at both time points in these six patients. CR2 was achieved in 87% of patients, with a median CR2 duration of 12.1 months, and 5-year disease-free survival and OS rates of 59% and 51%, respectively. In our cohort, the median CR2 rate, median CR2 duration, and median survival after late relapse were lower at 36%, 1 month, and 6.4 months, respectively.

Although all the patients in our cohort received high-dose Ara-C based regimens at relapse, fewer patients achieved a second CR, and their outcome was inferior to that reported by Medeiros *et al.* [8]. This may potentially be related to the extensive post-remission consolidation/maintenance that was administered to the patients in our series, thus rendering them less sensitive to salvage chemotherapy at relapse. Our patients were older (median age, 66 years), 63% had intermediate cytogenetic risk group at initial diagnosis and relapse, and 63% had different karyotype at relapse from that at initial diagnosis. These cytogenetic findings are in contrast to the report by Medeiros *et al.*, where they found similar cytogenetics at initial diagnosis and relapse in all six patients in whom the karyotype was available at both time points. Surprisingly, none of our patients underwent a SCT in CR2. This may reflect an inability to find donors, and can further account for the differences between our cohort and those reported by Medeiros *et al.* Despite this, the duration of CR2 in those who achieved it was long, indicating that a prolonged second CR can be achieved with chemotherapy alone in a proportion of these patients.

It is not clear whether these late relapses represent a new therapy-related leukemia or a delayed relapse of the original leukemia clone [16]. This may be due to the presence of a common leukemia stem cell with the initial leukemic clone responding to the treatment and the minor, more resistant clone acquiring further mutations leading to relapse [17]. Due to the small number of patients in our analysis, we were unable to identify any specific risk factors that might predispose to the development of relapse.

In conclusion, our analysis shows that late relapses in AML (>5 years after CR) are infrequent (0.8% of all patients who achieve CR or 1.16% of all relapses). The response to treatment is poor, and best treatment responses are with a regimen similar to the initial induction therapy, although it is possible to have a long CR2 duration in a proportion of patients. Karyotype at late relapse is frequently different from that at initial diagnosis. It remains unclear whether these late relapses are a second AML, or relapse with the original clone.

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Figure 1.
Survival of patients after late relapse of acute myeloid leukaemia.

Table I

Overview of late relapse acute myeloid leukemia (AML) patients at initial AML diagnosis.

Patient no.	Age, sex	AML f/u (survival from Dx) (months)	WBC ($\times 10^9/L$)	FAB	Cyto	Induction therapy (no. of courses to CR1)	Consolidation/maintenance Rx type (no. of courses)	Consolidation/maintenance course duration (months)	CR1 duration (months)
1	58M	108	1.2	M5	IM	Amsac + OAP (1)	Amsac + OAP (10), POMP (3)	15	70
2	66M	107	2	NA	IM	Amsac + OAP (1)	Amsac + OAP (10), POMP (3)	15	105
3	70F	122	1.2	M2	IM	VAD (2)	Ara-C (13), VAD (9)	24	81
4	46F	102	2.3	M1	der(13;14)	Amsac + Ara-C (1)	Amsac + Ara-C (4), Amsac (2)	6	101
5	39M	125	52.8	M2	Dip, -Y	Dnr + Ara-C (1)	Dnr + Ara-C (2)	2	123
6	72M	140	91.3	M4	Diploid	Ida + Ara-C (1)	Ara-C (3), Ida + Ara-C (4)	12	137
7	56M	131	1.1	M6	Diploid	Ida + Ara-C (1)	Ida + Ara-C (7)	—	125
8	68M	75	92.3	M5	Diploid	Ida + Ara-C (1)	Ida + Ara-C + ATRA (9)	11	67
9	72M	104	5.3	M2	Diploid	Ida + Ara-C + F (1)	Ida + Ara-C + F (5), IFN + Ara-C (20), Ara-C (10)	41	73
10	79F	67	3.3	M2	Diploid	CAT (1)	Ida + Ara-C (1), Ara-C (48)	57	60
11	37F	103	1.8	M2	del(7q)	Dnr + Ara-C (1)	Dnr + Ara-C (3), IFN-A + Ara-C (22)	27	76

f/u, follow-up; Dx, diagnosis; WBC, white blood cell count; FAB, French American British classification; NA, not available; Cyto, cytogenetics; IM, insufficient metaphases; CR1, first complete remission; Amsac, amsacrine; OAP, Oncovin (vincristine), Ara-C, prednisone; VAD, vincristine, adriamycin, dexamethasone; Ara-C, cytarabine; Dnr, daunorubicin; Ida, idarubicin; F, fludarabine; CAT, cyclophosphamide, Ara-C, topotecan; Rx, treatment; POMP, prednisone, Oncovin (vincristine), methotrexate, 6-mercaptopurine; ATRA, all-trans retinoic acid; IFN, interferon.

Table II

Overview of patients at late relapse of AML.

Patient no.	Relapse age, sex	AML f/u (survival from Dx) (months)	WBC ($\times 10^9/L$)	Cyto	Induction therapy (no. of courses)	Consolidation/maintenance Rx type (no. of courses)	Maintenance course duration (months)	Rx result	CR2 duration (months)	Survival after late relapse (months)
1	64M	108	12.7	6q+	Dnr + Ara-C (1)	Ara-C (2), IFN (4)	6	CR	35	36
2	75M	107	1.4	NA	Ara-C + Eto + Carbo (1)	—	—	Died	0	1
3	77F	122	1.7	inv(9qh)	Ida + Ara-C + F (1)	Ida + Ara-C + F (3), Ida (4)	12	CR	37	39
4	55F	102	3	der(13;14)	Ara-C + F + ATRA (1)	—	—	Resis	0	1
5	49M	125	26.5	2q+	Ida + Ara-C (1)	—	—	Resis	0	1
6	83M	140	48.8	+9, +13, +21, +22	Ida + Ara-C (1)	—	—	CRp	1	5
7	67M	131	4.4	+8	Ida + Ara-C (2)	—	—	Resis	0	4
8	74M	75	40.6	6q-, -77	Ida + Ara-C (1)	—	—	Resis	0	7
9	78M	104	1.7	Diploid	Ida + Ara-C (1)	Ara-C (22)	26	CR	27	31
10	85F	67	6.2	Diploid	Ida + Ara-C (1)	Ara-C (1)	1	PR	6	6
11	44F	103	3.3	del(5q), del(7q)	Ida + Ara-C (1)	Ida + Ara-C (4)	4	CR	29+	32+

f/u, follow-up; Dx, diagnosis; WBC, white blood cell count; Cyto, cytogenetics; NA, not available; Dnr, daunorubicin; Ara-C, cytarabine; Eto, etoposide; Carbo, carboplatin; Ida, idarubicin; F, fludarabine; ATRA, all-trans retinoic acid; Rx, treatment; IFN, interferon; CR, complete remission; Resis, resistant to treatment; CRp, complete remission without platelet recovery; CR2, second complete remission.