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Younger adults with acute myeloid leukemia in remission for 3 years have a high likelihood of cure: the ECOG experience in over 1200 patients

Justin M. Watts¹, Xin Victoria Wang^{2,3}, Mark R. Litzow⁴, Selina M. Luger⁵, Hillard M. Lazarus⁶, Peter A. Cassileth^{7,*}, Hugo F. Fernandez⁸, Dan Douer¹, Lynette Zickl², Elisabeth Paietta⁹, Jacob M. Rowe¹⁰, and Martin S. Tallman¹

¹Leukemia Service, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, New York

²Dana-Farber Cancer Institute, Boston, Massachusetts

³Harvard School of Public Health, Boston, Massachusetts

⁴Mayo Clinic, Rochester, Minnesota

⁵University of Pennsylvania, Philadelphia, Pennsylvania

⁶Case Western Reserve University, Cleveland, Ohio

⁷University of Miami, Miami, Florida

⁸H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

⁹Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

¹⁰Shaare Zedek Medical Center, Jerusalem, Israel

Abstract

We examined 1229 younger patients with acute myeloid leukemia who achieved CR1 on Eastern Cooperative Oncology Group trials. We defined late relapse as occurring after 3 years of CR1. With median follow-up of 11.3 years, there were 14 late relapses (1.1% of CR1 patients; 3.3% of 3-year CR1 patients). Eight achieved second CR and median overall survival after late relapse was 3.2 years. Most patients tested (9/11) had a normal karyotype at diagnosis; none had new

Corresponding author: Justin Michael Watts, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, Box 8, New York, NY 10065, Phone: 212-639-6442, Fax: 212-639-3841, watts@mskcc.org.

*deceased prior to publication

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AUTHORSHIP CONTRIBUTIONS

JMW analyzed and interpreted data and wrote the manuscript. XVW analyzed and interpreted data, performed statistical analysis, and revised the manuscript. MRW, SML, HML, HFF, and DD analyzed and interpreted data and revised the manuscript. LZ analyzed and interpreted data, performed statistical analysis, and revised the manuscript. EP analyzed and interpreted data and revised the manuscript. JMR and MST conceived the study, analyzed and interpreted data, and revised the manuscript.

PC was deceased prior to manuscript preparation but served as the Principal Investigator for 3 of the 4 ECOG clinical trials analyzed in this manuscript and was included as a co-author.

CONFLICT OF INTEREST DISCLOSURES

All authors have no conflict of interest to report.

cytogenetic abnormalities at relapse. Late relapse is rare and nearly all 3-year CR1 patients are cured. If late relapse occurs, outcomes are relatively favorable.

Keywords

acute myeloid leukemia; late relapse; outcomes; clinical trials; normal cytogenetics

INTRODUCTION

For the last 25 years, 5-year overall survival (OS) in younger adults with newly diagnosed acute myeloid leukemia (AML) has been approximately 35–40%. [1] While most younger patients (60–80%) achieve complete remission (CR), many relapse, regardless of the type or duration of post-remission therapy. Most relapses occur early, usually within 12–18 months of achievement of first CR (CR1), and these patients have poor outcomes. [2–5] Relapse after longer remission durations has been reported and may be associated with better outcomes compared to early relapse [6], but to our knowledge few studies have systematically examined late relapse and none have done so in a cooperative group setting.

While previous reports have considered patients in remission for 3 or more years to be “potentially cured” [7,8], past studies have used various CR1 durations to define late relapse, most commonly 18 months [2,5] or 5 years [3,4], making it difficult to compare studies, assess the overall risk of late relapse, and determine potential risk factors and outcomes in late relapse patients. We have examined the long-term follow-up data of a large cohort of newly diagnosed AML patients treated on Eastern Cooperative Oncology Group (ECOG) protocols over the last 25 years, focusing on the incidence of late relapse and the characteristics and outcomes of these patients.

METHODS

Patient Population

The ECOG database includes large numbers of AML patients treated at major university and community hospitals across the United States and abroad. Detailed medical records are maintained and routinely updated on these patients, including follow-up for relapse, survival, second cancers, and adverse events. We examined the long-term follow-up data from newly diagnosed AML patients treated on 4 different ECOG clinical trials conducted from 1984 to 2008: E3483, PC486, E3489, and E1900. [9–12] A total of 2122 patients were enrolled on these protocols and 1882 were considered eligible and evaluable [Table 1, Figure 1]. Two hundred and forty patients were excluded from the original protocols because of wrong or unconfirmed diagnosis on pathology review, loss of eligibility or withdrawal from study prior to receiving induction chemotherapy, or inadequate documentation of CR.

All 1882 patients treated on protocol received standard induction with 1 or 2 courses of fixed doses of infusional cytarabine and an anthracycline (2 different doses of daunorubicin were administered on E1900). All patients who achieved CR on study were randomized or assigned to post-remission therapy except for 26 patients on E3483 who were randomized to

observation. These 26 patients all relapsed and were included in our analysis. Patients with a suitably matched sibling donor were offered allogeneic hematopoietic cell transplantation (HCT) on all 4 protocols. Other post-remission therapies included autologous HCT, a single or multiple courses of high-dose cytarabine (HiDAC), and 2 years of maintenance chemotherapy with 6-thioguanine and subcutaneous cytarabine (E3483 only). On E3483 and PC486, all patients had *de novo* AML. E3489 did not specify whether patients with an antecedent hematologic disorder were eligible, but patients who had received prior radiotherapy or chemotherapy were excluded. Most patients on E1900 had *de novo* AML except for 22 who had a documented antecedent hematologic disorder.

We evaluated all protocol patients for AML relapse if they were 60 years of age or younger at trial registration and achieved CR1 with 1 or 2 courses of induction chemotherapy. We excluded 71 CR1 patients from protocols E3483, PC486, and E3489 who had acute promyelocytic leukemia (APL), as defined by the presence of t(15;17)/PML-RAR α or French-American-British classification M3 morphology (if genetic data unavailable). We assessed for AML recurrence from the day that CR1 was confirmed, and defined late relapse as occurring after 3 or more years of CR1. All studies required reporting of relapses including late relapses. Disease characteristics of late relapse patients that were assessed included: age, race, gender, white blood cell (WBC) count, and cytogenetic status at both diagnosis and relapse. We assessed the long-term outcomes of patients after late relapse, including achievement of second CR (CR2) and OS. Details regarding the type of therapy after late relapse and cause of death when unrelated to treatment or relapse were not always available on the older studies.

Statistical Methods

Achievement of CR was determined using standard International Working Group criteria. All patients who achieved CR had complete hematologic recovery. Response categories such as CRi, or CR with incomplete hematologic recovery, and CRp, CR with incomplete platelet count recovery, were not used. Duration of CR is the time from the date of CR to the date of relapse. Disease-free survival (DFS) is defined as the time from CR to relapse or death without relapse. Cases without relapse or death are censored at the date of last contact. The Kaplan-Meier method is used to estimate DFS. OS is defined as the time from the date of trial registration to the date of death from any cause. OS from relapse is the time from the date of relapse to the date of death from any cause. Patients still alive were censored at the date of last contact.

RESULTS

We identified 1229 younger AML patients who underwent induction and achieved CR1 on an ECOG protocol [Table 1]. Of these patients, 273 (22%) received autologous HCT and 183 (15%) allogeneic HCT in CR1. Of the remaining 773 protocol patients, 326 received consolidation with 1 or more courses of HiDAC, 78 received maintenance chemotherapy, 23 were observed, 1 underwent syngeneic HCT, and 345 did not receive post-remission therapy on protocol. The median age at diagnosis was 42 years (range 15–60). The median follow-up of all CR1 patients was 11.3 years (range 0.1–19.7). PC486 had the longest median

follow-up at 17.4 years and E1900 the shortest at 5.7 years (follow-up on E1900 still ongoing). Only 20 patients (1.6%) were lost to follow-up before 3 years; 33 additional patients (2.7%) were lost to follow-up after 3 years [Table 2].

Of the 1229 CR1 patients, 542 (44%) relapsed [Table 1]. The median CR1 duration of relapsed patients was 0.67 years. The rate of relapse decreased sharply after 3 years of CR1 [Figure 2]. Using 3 years of CR1 to define late relapse, 528 patients relapsed early and 14 patients relapsed late. DFS of patients achieving CR1 at 18 months, 2.5 years, 3 years, 4 years, and 5 years was 46%, 38%, 36%, 34% and 33%, respectively. Of the 1229 CR1 patients, 426 (35%) were alive, in follow-up, and still in CR1 at 3 years (3-year CR1 patients). The 14 late relapse patients comprised 1.1% of all patients achieving CR1 (1229), 2.6% of all relapses (542), and 3.3% of 3-year CR1 patients (426). Two of the 14 late relapses occurred after 5 years of CR1 (very late relapse) [Table 3]. The median follow-up of late relapse patients was 12.3 years from protocol registration (diagnosis) and 8.8 years from relapse.

Characteristics of patients with late relapse

For the 14 late relapse patients, median age at initial diagnosis was 40 years (range 19–54) [Table 3]. Seven (50%) were male. The median WBC count at diagnosis was 11,800/ μ l (range 1,300–230,000). The late relapse patients were treated as follows after achieving CR1 on protocol: 1 received allogeneic HCT, 2 autologous HCT, 7 HiDAC consolidation, and 4 went off protocol prior to receiving post-remission therapy.

Of the 11 late relapse patients with cytogenetic testing performed at diagnosis, 10 had an intermediate-risk karyotype (9 normal karyotype and 1 trisomy 8), 1 had a favorable karyotype [inv(16)], and none had an unfavorable karyotype [Table 3]. All 7 patients with cytogenetic testing performed at diagnosis and late relapse had a normal karyotype (NK) at both time points. Molecular genetic data from diagnosis were available on 2 of the 3 late relapse patients from E1900: 1 patient had mutated *DNMT3A* and *NPM1* genes and was wild type for 17 other genes including *FLT3* and *MLL*; the second was *NPM1*, *FLT3*, and *MLL* wild-type and did not have further testing performed. Molecular testing was not performed on E3483, PC486, or E3489 as the technology was not available when these trials were conducted.

Outcomes of patients with late relapse

The median CR1 duration was 4 years (range 3–7.7) [Table 3]. Eight late relapse patients (57%) are deceased. The 2 patients who relapsed very late, after CR1 durations of 6 and 7.7 years, died within 6 months of relapse. Six late relapse patients (43%) were still alive at a median follow-up of 8.2 years (range 2.5–14.1) after relapse. Eight patients achieved CR2 and 7 had sustained CR2 durations based on survival data: 6 patients are still living with very long follow-up and 1 patient died 10 years after relapse of unknown causes. The remaining patient who achieved CR2 died approximately 10 months after late relapse of other causes (neither relapse nor treatment-related complications). Median OS of late relapse patients was 8 years from diagnosis and 3.2 years from relapse [Figure 3]. Five of the 6 surviving late relapse patients had cytogenetic testing performed at diagnosis: 4 had a NK

and 1 had inv(16). Three of the 4 surviving patients with normal cytogenetics at diagnosis had cytogenetic testing done at relapse and were still NK. Detailed follow-up information was available on the 3 late relapse patients from E1900: 1 patient died from cerebral hemorrhage related to his disease and 2 patients are still living after receiving allogeneic HCT in CR2.

DISCUSSION

AML recurrence after 3 years of CR1 (late relapse) was rare. Only 14 of 1229 younger patients with very long follow-up relapsed late (1.1% of CR1 patients; 3.3% of 3-year CR1 patients). Interestingly, most of these patients (9 of 11 tested) had a NK at diagnosis. AML recurrence after 5 years of CR1 was extremely rare (2/1229) and these patients can almost certainly be considered cured, with the caveat that a slight risk of t-AML may remain. Our cohort was composed almost exclusively of younger, *de novo* AML patients receiving established induction and post-remission regimens (including allogeneic HCT) on cooperative group protocols, and patient outcomes on these trials were consistent with modern OS rates for younger AML patients.[1] Interestingly, none of the 25 3-year CR1 patients with unfavorable cytogenetics at diagnosis had late relapse, suggesting that high-risk patients who survive for 3 years or more also have a high likelihood of cure (10 of these 25 had allogeneic HCT).

We chose 3 years of CR1 to define late relapse. When examining the cumulative proportion of relapses against time, the change point in the curve was between 2.5 and 3 years [Figure 2]. For the first 2 years, the rate of relapse is relatively constant, after 2 years it begins to decline, and by 3 years it has plateaued (97.4% of relapses had occurred by 3 years). Therefore, it appears that CR1 durations of 18 months (too early) or 5 years (too late) are sub-optimal for defining late relapse. This observation is also reflected in the DFS of CR1 patients, which plateaus at approximately 3 years.

Of the 426 3-year CR1 patients, 60 (14%) subsequently died of other causes without relapse. This group of 60 patients was older than the remainder of the cohort (median age 46 versus 40 years at diagnosis), had median follow-up of 6.5 years after achievement of CR1, and 10 had received allogeneic HCT. While the exact cause of death was not specified or known in each case, and it is therefore possible that some of these patients could have had undocumented relapse, the ECOG database is routinely updated and investigators are required to report both relapse and mortality data for all patients. Lack of information on exact cause of death may be an inherent limitation of long-term follow-up studies examining late outcomes.

In 1988, Kantarjian and colleagues defined late relapse as AML recurrence after 18 months of CR1.[2] More recent studies defining late relapse as recurrence after 5 years have reported much lower rates of late relapse (0.8% of CR1 patients in 1 study).[3,4] Our study is unique in that we define late relapse as occurring after 3 years of CR1 and report the number of late relapses in terms of all patients in follow-up and still in CR1 at 3 years—14 of 426 (3.3%). Reporting late relapses solely in terms of all patients achieving CR1—1.1%

of patients in our study—may not reflect the true rate of late relapse since many patients relapse early, die of other causes, or are lost to follow-up before 3 years.

Estey has shown that patients who relapse after longer CR1 durations (1–2 years versus <1 year) have higher response rates to re-induction and improved survival.[6] Our data show that patients who relapse after very long CR1 durations (>3 years) have relatively favorable outcomes, with most late relapse patients achieving CR2 and median OS of 3.2 years after late relapse. Although the number of patients with late relapse was small, it may follow that remission durations beyond 2 years are associated with further improvements in survival after relapse.

In previous reports, OS rates after late relapse have varied considerably. For example, median OS after late relapse was 6.4 months in 1 study [4], compared to significantly longer survival times reported by us and Medeiros and colleagues.[3] This may be related to differing rates of t-AML versus true late relapse. In the study by Verma and coworkers, 5 of 8 patients tested had new cytogenetic abnormalities at late relapse (>5 years of CR1), including 3 patients with complex cytogenetics, del(5q), and monosomy 7.[4] A study using CR1 duration of 18 months to define late relapse found new cytogenetic abnormalities in only 3 of 15 patients.[5]

In our study, 10 of 11 late relapse patients with diagnostic cytogenetic data available had intermediate-risk cytogenetics, 9 of which were NK. No patients with cytogenetic testing at relapse had new abnormalities (all 7 had a NK at both diagnosis and relapse). These data demonstrate that the timing of late relapse may predict the likelihood of 2 distinct events: relapse of the original clone versus the emergence of a new leukemia. In patients who relapse very late, or after 5 years, it is possible that the risk of t-AML eclipses that of true relapse. Furthermore, given that most patients with late relapse had normal cytogenetics in our study, there may be specific mutational profiles or epigenetic alterations associated with late relapse that have not yet been defined. On E1900, neither of the 2 late relapse patients with molecular testing performed had high-risk mutations. The patient with 19-gene targeted sequencing had co-occurring *DNMT3A* and *NPM1* mutations (suggesting an intermediate prognosis for survival).[13] These findings highlight the importance of examining integrated cytogenetic and molecular data at diagnosis and relapse to better differentiate true late relapse from a new primary or therapy-related leukemia.

In summary, late relapse is rare and the vast majority of younger patients in remission for >3 years are cured. In the rare instance that late relapse does occur, outcomes are relatively favorable, supporting the hypothesis that most cases of late relapse represent re-emergence of a temporarily quiescent leukemic clone, not t-AML. This observation is also supported by the high percentage of long-term survivors after late relapse and the lack of therapy-related cytogenetic abnormalities in most patients with late relapse. A detailed genetic assessment of late relapse patients at initial diagnosis and relapse is warranted and may be critical for determining prognosis and treatment strategy, as patients with late relapse appear to have better outcomes than those with a secondary leukemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Late relapse of AML is rare after 3 years of first remission, and the majority of these patients can be considered cured
- Most cases of late relapse appear to represent re-emergence of the original clone, not a new therapy-related leukemia
- Most of the 14 late relapse patients tested had a normal karyotype at diagnosis
- If late relapse does occur, outcomes are relatively favorable (median OS after late relapse 3.2 years)

Figure 1.

Figure 2.

Late Relapses (n=14) **Figure 3.**

Table 1

Summary of the newly diagnosed AML patients treated on protocols E3483, PC486, E3489, and E1900, including follow-up data, number of relapses and late relapses, and characteristics of late relapse patients.

	E3483	PC486	E3489	E1900	Total
No. of patients enrolled	534	123	808	657	2122
No. of patients eligible and evaluable	449	111	740	582	1882
No. of patients achieving CR1 ^a	255	69	493	412	1229
No. of CR1 patients who received auto HCT ^b	0	29	94	150	273
No. of CR1 patients who received allo HCT ^b	24	11	111	37	183
Median follow-up of CR1 pts (yr)	14.8	17.4	12.8	5.7	11.3
Range of follow-up of CR1 pts (yr)	3.9–17.5	7.0–19.7	0.6–16.3	0.1–9.1	0.1–19.7
Total number of relapses	47	37	268	190	542
Late relapses	2	1	8	3	14 ^c
Late relapses post-auto HCT	0	0	0	2	2
Late relapses post-allo HCT	0	0	1	0	1
Late relapses deceased	2	0	5	1	8
Median time [range] to late relapse (yr)	4.7 [3.3–6.0]	4.5	4.0 [3.0–7.7]	3.3 [3.3–4.9]	4.0 [3.0–7.7]
Median age [range] at diagnosis (yr)	26 [19–33]	31	42.5 [20–50]	50 [33–54]	39.5 [19–54]
Median WBC [range] at diagnosis (k/μl)	116 [1.3–230]	26.3	10.8 [2.4–37.3]	37 [9.7–55]	13 [1.3–230]

CR1 indicates first complete remission; pts, patients; yr, years; HCT, hematopoietic cell transplantation; n/a, not available; k/μl, 1,000 per microliter.

^aThese numbers include all AML patients 60 years of age or younger at trial registration who did not have APL and achieved CR1. Patients >60 years of age and with APL were removed.

^bThese patients were transplanted in CR1 on protocol (all donors matched or single-antigen—mismatched siblings).

^cThe 14 late relapse patients represent 1.1% of 1229 CR1 patients, 2.6% of 542 total relapses, and 3.3% of 426 patients alive and still in CR1 at 3 years.

Table 2

Outcomes of AML patients achieving CR1

Events within 3 years and after 3 years of CR1: the categories are mutually exclusive. Within 3 years of CR1, patients can fall into 4 categories: early relapse, death, lost to follow-up, or no events. Patients still in follow-up and without relapse after 3 years of CR1 can fall into 4 categories: late relapse, death without relapse, lost to follow-up, or still in follow-up.

	E3483	PC486	E3489	E1900	Total
Patients achieving CR1	255	69	493	412	1229
Early relapses (within 3 yr of CR1)	45	36	260	187	528 (43%)
Death from other causes before 3 yr	134	8	52	61	255 (21%)
Lost to follow-up before 3 yr	0	0	2	18	20 (2%)
No events at 3 yr	76	27	179	146	426 (35%)
CR1 patients alive at 3 yr	76	27	179	146	426
Late relapses (after 3 yr of CR1)	2	1	8	3	14 (3%)
Death from other causes after 3 yr ^a	24	4	21	11	60 (14%)
Lost to follow-up after 3 yr	4	4	20	5	33 (8%)
Still in follow-up	46	16	130	127	319 (75%)

CR1 indicates first complete remission; yr, years; pts, patients.

^aThese patients died without evidence of relapse.

Table 3

Demographics, outcomes, and diagnostic and relapse cytogenetics of AML patients with late relapse (relapse after 3 years of CR1).

Patient	Trial	Age (yr)	Gender	NCI race	CR1 duration (yr)	Survival (yr)	Vital status	COD	Diagnostic karyotype	Relapse karyotype
1	E3483	19	female	Pre-NCI	3.3	6.2	dead	unknown	n/a	n/a
2	E3483	33	male	Pre-NCI	6.0 ^a	6.5	dead	unknown	n/a	n/a
3	PC486	31	female	White	4.5	18.8	alive	alive	n/a	n/a
4	E3489	32	male	White	4.0	13.9	dead ^b	unknown	46,XY	46,XY
5	E3489	50	female	Black	3.8	4.0	dead	AML	47,XX,+8	n/a
6	E3489	49	male	White	7.7 ^a	8.0	dead	unknown	46,XY	n/a
7	E3489	48	female	White	4.0	12.9	alive	alive	46,XX	46,XX
8	E3489	40	male	White	4.7	12.3	alive	alive	46,XY	n/a
9	E3489	39	male	White	3.8	4.6	dead	other causes ^c	46,XY	46,XY ^d
10	E3489	20	male	Other	3.0	12.3	alive	alive	inv(16)	n/a
11	E3489	45	female	White	4.0	7.4	dead	unknown	46,XX	46,XX ^e
12	E1900	50	male	White	3.3	3.4	dead	AML	46,XY	46,XY ^d
13	E1900	54	female	White	4.9	7.8	alive	alive	46,XX	46,XX ^d
14	E1900	33	female	White	3.3	5.9	alive	alive	46,XX	46,XX

CR1 indicates first complete remission; yr, years; COD, cause of death; NCI, National Cancer Institute.

^aVery late relapse patients (5 years of CR1).

^bThis patient died 10 years after late relapse of unknown causes.

^cThis patient died of other causes (neither treatment nor disease).

^dRandom loss/non-clonal marker observed in 1 metaphase.

^eExtramedullary relapse.