Genetic alteration patterns and clinical outcomes of elderly and secondary acute myeloid leukemia

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Abstract
To illustrate the clinical and genetic features of elderly and secondary acute myeloid leukemia (AML) patients, we compared 145 elderly AML (e-AML) and 55 secondary AML (s-AML) patients with 451 young de novo AML patients. Both e-AML and s-AML patients showed lower white blood cell (WBC) and bone marrow (BM) blasts at diagnosis. NPM1, DNMT3A, and IDH2 mutations were more common while biallelic CEBPA and IDH1 mutations were less seen in e-AML patients. s-AML patients carried a higher frequency of KMT2A-AF9. In treatment response and survival, e/s-AML conferred a lower complete remission (CR) rate and shorter duration of event-free survival (EFS) and overall survival (OS) compared with young patients. In multivariate analysis, s-AML was an independent risk factor for OS but not EFS in the whole cohort. Importantly, intensive therapy tended to improve the survival of e/s-AML patients without increasing the risk of early death, and hematopoietic stem cell transplantation (HSCT) could rescue the prognosis of s-AML, which should be recommended for the treatment of fit patients.

KEYWORDS
acute myeloid leukemia, elderly, genetic, prognosis, secondary

1 | INTRODUCTION

Acute myeloid leukemia (AML) is a group of biological and clinical heterogeneous hematologic malignancies, whose prognosis is strongly associated with underlying genetic alterations and clinical factors, especially the history of antecedent hematological diseases or cytotoxic treatment, which is called secondary acute myeloid leukemia (s-AML). In addition, age is another important clinical feature, which exerts negative effect on the disease. More importantly, AML is increasingly considered as a senile disease, which was reported of a median age of 66 in the United States and 71 in Sweden. With the development of high dose chemotherapy, hematopoietic stem cell transplantation (HSCT) and even tailored therapy, the treatment outcome of AML has improved significantly in the last decades; however, the prognosis of elderly AML (e-AML) and s-AML remains dismal. Both elderly and secondary AML (e/s-AML) patients present with increased age, poor performance status, more comorbidities, depleted hematopoietic reserves, and more importantly, the disease-associated factors, such as unfavorable cytogenetic and molecular abnormalities, leading to insufficient treatment and poor treatment outcome.

It was reported that e/s-AML patients harbored less favorable cytogenetics such as CBF-rearrangements but more unfavorable cytogenetics especially abnormalities involving 5 or 7 chromosome at diagnosis. Genetic landscape of AML has been widely studied in the
past decades, however, most of previous studies focused on de novo AML especially those patients with young age,\textsuperscript{7,8} while reports regarding genetic alterations and their prognostic significance in e/s-AML are still rare.

More importantly, the treatment of e/s-AML remains controversial. Various modalities, such as hypomethylation agents as exemplified as decitabine and azacitidine, and low doses chemotherapy were tried in this group of patients; however, no therapeutic regimen was proved to be significantly superior to traditional chemotherapy. To some extent, the treatment decision was strongly dependent on the fitness of AML patients.

In this study, we examined genetic alterations and post-treatment minimal residual diseases (MRD) in order to illustrate their distribution and prognostic impact in e/s-AML and to provide treatment recommendations for those patients.

2 | METHODS

2.1 | Patients

From January 2013 to December 2017, a total of 651 adult patients (18 years old or above) with newly diagnosed non-M3 AML at Shanghai Institute of Hematology (SIH) were executively enrolled in this study, among which, 55 patients were diagnosed as s-AML (34 patients had an antecedent hematological disease [AHD-AML] and 21 patients were diagnosed as therapy-related AML [t-AML]). Cytogenetic risk stratification was based on 2017 European LeukemiaNet (ELN) recommendations.\textsuperscript{9}

This study was approved by the ethic committee of Ruijin Hospital. All patients had given informed consent for both treatment and cryopreservation of bone marrow (BM) and peripheral blood according to the Declaration of Helsinki.

2.2 | Treatment protocols

For young de novo patients (younger than 60 years old), standard intensive “3 + 7” induction regimens (idarubicin 10-12 mg/m\(^2\) or daunorubicin 45-60 mg/m\(^2\), D1-3; cytarabine 100 mg/m\(^2\) D1-7) were given as the initial induction therapy. If CR was achieved, four cycles of high-dose cytarabine (2 g/m\(^2\)) was given as consolidation. For e-AML (60 years and older) and s-AML patients, the treatment was mainly decided by the physician in consideration of the fitness of patients and risk of disease. Fit patients received treatment similar to young patients but reduced cycles of consolidation to 2 cycles of high-dose cytarabine; unfit patients received “3 + 7” regimens with reduced dose, hypomethylation treatment or palliative treatment according to the physician’s decision.

2.3 | Molecular events and MRD

Genetic alterations including FLT3-ITD/TKD, KMT2A-PTD, NPM1, NRAS, CKIT, CEBPA, DNMT3A, IDH1, IDH2, RUNX1-RUNX1T1, CBF-β-MYH11, KMT2A rearrangements were detected as previously reported.\textsuperscript{10} Bone marrow aspirate samples were processed according to the standard procedure of our institution as previously reported.\textsuperscript{11} Detection of MRD after induction therapy was based on leukemia-associated immunophenotype (LAIP) at diagnosis and performed by ten-color multiparametric flow cytometry. MRD was considered positive when leukemia cells were greater than or equal to 0.01%.

2.4 | Statistical analyses

Complete remission (CR) was defined by the criteria of the International Working Group.\textsuperscript{12} Early death (ED) was defined as death within 30 days after diagnosis. Overall survival (OS) was measured from the date of disease diagnosis to death from any cause, and patients alive at last follow-up were censored. Event-free survival (EFS) was defined as the time from diagnosis to the date of relapse (if achieved CR) or death from any cause, whichever occurred first, with patients still alive censored at the date of last follow-up. Patients who received HSCT were censored at the time of HSCT to eliminate its impact on EFS and OS. The Kaplan-Meier method was used to calculate the distribution of OS and EFS. A log-rank test was performed to compare the difference in survival time. Multivariate analyses were conducted by using binary logistic regression for CR and ED, and Cox proportional hazard model for OS and EFS. All of the above statistical procedures were carried out by using the SPSS Version 24.0 statistical software package.

3 | RESULTS

3.1 | Characteristics of patients

The baseline characteristics of patients were shown in Table 1. Patients with s-AML presented female predominance (P = .041), most of whom had a previous history of breast carcinoma (43%). Older age (P < .001), lower white blood cell (WBC) count (P = .031), hemoglobin (HB, P = .004), and BM blasts (P < .001) were observed in s-AML as compared with young patients. Similarly, elderly patients showed lower WBC (P = .036) and BM blasts (P = .009) at diagnosis. In WHO subtype distribution, higher frequency of pure erythroid leukemia was seen in s-AML (P = .013). Both e-AML and s-AML patients received less intensive induction, but more hypomethylation treatment and palliative treatment than younger patients (all P < .001).

3.2 | Cytogenetic and genetic alterations

In cytogenetic classification, elderly patients had a significantly higher proportion of intermediate risk cytogenetics (P = .011). Favorable cytogenetic alterations were less frequent in both elderly and secondary patients (P = .008 and .014, respectively) as compared with young patients.

With regard to genetic abnormalities, the incidence of CBF leukemia was significantly lower in e/s-AML patients as compared with young patients (7.1% vs 14.7%, P = .013 for RUNX1-RUNX1T1 and 2.6% vs 7.4%, P = .038 for CBF-β-MYH11). A higher frequency of
As for the association between genetic abnormalities and clinical features, NPM1 mutations were associated with higher WBC in elderly patients \((P = .037)\). Moreover, s-AML patients with KMT2A-AF9 were prone to having higher BM blasts \((P = .068)\) (Table S1).

**TABLE 1**  
**Clinical characteristics of AML patients**

| Factor                        | s-AML, N = 55 | P* | de novo AML           | Young, N = 451 | Elderly, N = 145 | P* |
|-------------------------------|---------------|----|-----------------------|----------------|------------------|----|
| **Age, y**                    |               | .001|                       |                |                  | .001|
| Median                        | 57            |     | 43                    | 65             |                  |    |
| Range                         | 21-77         |     | 18-59                 | 60-81          |                  |    |
| **Male gender, n (%)**        | 22 (40.0)     | .041| 246 (54.5)            | 76 (52.4)      |                  | .654|
| **WBC count, \( \times 10^9/L \)** | | .031|                       |                |                  | .036|
| Median                        | 6.8           |     | 16.83                 | 10.56          |                  |    |
| Range                         | 0.8-144.1     |     | 0.77-419.9            | 0.5-241.94     |                  |    |
| **HB, g/L**                   |               | .004|                       |                |                  | .338|
| Median                        | 69            |     | 85                    | 82             |                  |    |
| Range                         | 34-143        |     | 30-171                | 15-142         |                  |    |
| **PLT count, \( \times 10^9/L \)** | | .074|                       |                |                  | .099|
| Median                        | 60            |     | 41                    | 44             |                  |    |
| Range                         | 3-752         |     | 2-1726                | 3-512          |                  |    |
| **BM blasts, %**              |               | <.001|                       |                |                  | .009|
| Median                        | 39.5          |     | 69                    | 60.5           |                  |    |
| Range                         | 16.5-95       |     | 7-98.5                | 17.5-96.5      |                  |    |
| **WHO category, n (%)**       |               |     |                       |                |                  |    |
| AML with recurrent genetic abnormalities | |     |                       |                |                  |    |
| AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1 | 2(3.6) | .042| 59(13.1)              | 10(6.9)        |                  | .043|
| AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); CBFB-MYH11 | 0(0) | .112| 28(6.2)              | 4(2.8)         |                  | .109|
| AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A | 4(7.3) | .013| 6(1.3)               | 1(0.7)         |                  | .857|
| AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM | 0(0) | 1   | 1(0.2)               | 1(0.7)         |                  | .428|
| Provisional entity: AML with BCR-ABL1 | 0(0) | 1   | 1(0.2)               | 0(0)           |                  | 1   |
| AML with mutated NPM1 | 7(12.7) | .436| 76(16.9)             | 39(26.9)       |                  | .008|
| AML with biallelic mutations of CEBPA | 3(5.5) | .048| 69(15.3)            | 11(7.6)        |                  | .018|
| **AML, NOS**                  |               |     |                       |                |                  |    |
| AML without maturation        | 0(0)          |     | 1                     | 2(1.4)         |                  | .148|
| AML with maturation           | 0(0)          | .45 | 12(2.7)              | 6(4.1)         |                  | .532|
| Acute myelomonocytic leukemia | 9(16.4)       | .837| 69(15.3)             | 18(12.4)       |                  | .392|
| Acute monoblastic/monocytic leukemia | 6(10.9) | .387| 69(15.3)            | 25(17.2)       |                  | .577|
| Pure erythroid leukemia       | 4(7.3)        | .013| 6(1.3)               | 2(1.4)         |                  | 1   |
| Not classified                | 20(36.4)      | <.001| 54(12.0)            | 26(17.9)       |                  | .067|
| **Therapy**                   |               |     |                       |                |                  |    |
| Intensive induction           | 23 (41.8)     | <.001| 422 (93.6)           | 79 (54.5)      |                  | <.001|
| Hypomethylation               | 12 (21.8)     | <.001| 5 (1.1)              | 15 (10.3)      |                  | <.001|
| Palliative treatment          | 20 (36.4)     | <.001| 24 (5.3)             | 51 (35.2)      |                  | <.001|

Abbreviation: AML, acute myeloid leukemia; BM, bone marrow; HB, hemoglobin; NOS, not otherwise specified; PLT, platelet; WBC, white blood cell; WHO, The World Health Organization.

*A all compared with young patients.

NPM1 \((P = .003)\), DNMT3A \((P = .015)\), and IDH2 \((P = .004)\) mutations, but lower frequency of biallelic CEBPA (BiCEBPA, \(P = .029\)) and IDH1 \((P = .038)\) mutations were observed in elderly patients. In addition, s-AML patients carried KMT2A-AF9 \((P = .007)\) more frequently when compared with young de novo patients (Table 2).
3.2.1 Treatment responses

In total cohort, CR rate and ED rate were 76.1% and 10.5%, respectively. Both s-AML and e-AML patients conferred reduced CR rate as compared with young patients (s-AML vs young: 58% vs 83%, \( P < .001 \); e-AML vs young, 60.7% vs 83%, \( P < .001 \)). Additionally, a higher frequency of ED (e-AML vs young: 16.6% vs 8%, \( P = .003 \)) was observed in e-AML (Table 3). In order to find significant factors that can independently predict ED and CR, we conducted univariate and multivariate analyses (Tables S1 and 4).

Among patients achieving CR, 258 young, 56 elderly, and 23 secondary AML patients had a definite LAIP feature before treatment, and the MRD of whom could be monitored. The frequency of positive MRD was higher in s-AML than in young patients (\( P = .039 \), Table 3).

When e-AML and s-AML patients were put together, those who were treated with intensive therapy had a higher CR rate (74.2% vs 44.3%, Table 2).

### Table 2: Cytogenetic and genetic alteration patterns of acute myeloid leukemia (AML) patients

| Variable         | Number/Total (%) | \( P^a \) | de novo AML             |
|------------------|------------------|----------|-------------------------|
|                  | s-AML, N = 55    | Young, N = 451 | Elderly, N = 145 | \( P^a \) |
| Cytogenetics     |                  |           |                        |
| Favorable        | 3/49 (6.1)       | .014     | 84/404 (20.8)          | .008    |
| Intermediate     | 38/49 (77.6)     | .076     | 262/404 (64.9)         | .011    |
| Unfavorable      | 8/49 (16.3)      | .712     | 58/404 (14.4)          | .639    |
| Genetic Alterations |              |           |                        |
| RUNX1-RUNX1T1    | 2/46 (4.3)       | .052     | 59/401 (14.7)          | .063    |
| CBFβ-MYH11       | 0/37 (0)         | .170     | 28/378 (7.4)           | .139    |
| FLT3-ITD         | 4/44 (9.1)       | .416     | 54/402 (13.4)          | .759    |
| FLT3-TKD         | 3/44 (6.8)       | .932     | 21/400 (5.2)           | .856    |
| KMT2A-fusion     | 5/44 (11.4)      | .193     | 21/400 (5.2)           | .870    |
| KMT2A-AF9        | 4/44 (9.1)       | .007     | 6/400 (1.5)            | .896    |
| KMT2A-PTD        | 2/44 (4.5)       | .956     | 24/399 (6.0)           | .604    |
| NPM1             | 7/44 (15.9)      | .618     | 76/400 (19.0)          | .003    |
| CKIT             | 2/41 (4.9)       | .354     | 42/387 (10.9)          | .457    |
| NRAS             | 7/44 (15.9)      | .669     | 54/398 (13.6)          | .789    |
| BICEBPA          | 3/45 (6.7)       | .070     | 69/403 (17.1)          | .029    |
| DNMT3A           | 7/46 (15.2)      | .373     | 43/397 (10.8)          | .015    |
| IDH1             | 2/23 (8.7)       | .971     | 28/314 (8.9)           | .038    |
| IDH2             | 1/22 (4.5)       | .996     | 22/314 (7.0)           | .004    |

\( ^a \)All compared with young patients.

### Table 3: Treatment responses

| Factor            | s-AML, N = 55 | \( P^a \) | de novo AML             |
|-------------------|---------------|----------|-------------------------|
|                   |               | Young, N = 451 | Elderly, N = 145 | \( P^a \) |
| CR status         | <.001         |          |                        |
| CR, % (n)         | 58 (29)       | 83 (356) | 60.7 (82)               | <.001 |
| Missing/unknown   | 5             | 22       | 10                      |       |
| Early death       | 0.172         |          |                        |
| Yes, % (n)        | 14.5 (8)      | 8 (36)   | 16.6 (24)               | .003  |
| Missing/unknown   | 0             | 2        | 0                       |       |
| MRD               | 0.039         |          |                        |
| <0.01%, % (n)     | 17.4 (4)      | 39.1 (101)| 37.5 (21)               | .819  |
| Missing/unknown   | 32            | 193      | 89                      |       |

Abbreviation: AML, acute myeloid leukemia; CR, complete remission; MRD, minimal residual disease.

\( ^a \)All compared with young patients.
P < .001) and tended to have a lower incidence of positive MRD (60.8% vs 82.1%, P = .051) than those treated with other therapy categories. In addition, e/s-AML patients receiving intensive therapy tended to have a lower ED rate than those who were treated with palliative treatment (12.7% vs 22.5%, P = .090).

3.3 Impact of prognostic factors on survival

The median follow-up in all patients was 27 months (range, 0-66 months). Generally, e/s-AML patients had inferior EFS and OS compared with young patients (elderly vs young: 9 vs 18 months for EFS, P < .001, and 12 vs 44 months for OS, P < .001; s-AML vs young: 7 vs 18 months for EFS, P < .001, and 11 vs 44 months for OS, P < .001, respectively) (Figure 1A,B). In the stratification of patients who received intensive therapy, e/s-AML patients also conferred shorter EFS and OS than young patients (elderly vs young: 12 vs 20 months for EFS, P < .001, and 15 vs 44 months for OS, P < .001; s-AML vs young: 9 vs 20 months for EFS, P = .022, and 14 vs 44 months for OS, P = .026, respectively) (Figure 1C,D). However, there was no difference in EFS and OS between young and e/s-AML patients who received less intensive therapy (Figure 1E,F). In elderly patients, the median EFS and OS were significantly longer in patients who received intensive therapy, as compared with other treatment modalities (12 vs 6 months for EFS, P = .025, and 15 vs 6 months for OS, P = .04, respectively). A similar tendency was observed in s-AML (9 vs 5 months for EFS, P = .35 and 14 vs 5 months for OS, P = .149). Combining e-AML and s-AML patients together, patients receiving intensive therapy were prone to having a longer EFS and OS than those treated with decitabine-based hypomethylation therapy (10 vs 6 months for EFS, P = .093, and 15 vs 7 months for OS, P = .067, respectively) and palliative treatment (10 vs 6 months for EFS, P = .048, and 15 vs 6 months for OS, P = .057, respectively) (Figure 1G,H).

Univariate analysis for EFS and OS was shown in Table S3. In order to explore the prognostic significance of increased age and s-AML after accounting for other recognized prognostic factors, we conducted multivariate analysis (Table 4). In whole cohort, s-AML relative to de novo AML was an independent risk factor for OS (P = .009), while it was not associated with EFS. Notably, the independent prognostic impact of s-AML on OS was lost when HSCT was not regarded as a censored event, suggesting that HSCT may abrogate the adverse impact of s-AML on survival to a certain extent (Table S4).

4 DISCUSSION

Acute myeloid leukemia is a hematologic malignancy with a relative high incidence rate especially in high Human Development Index (HDI) countries. The incidence of AML increases with age, which makes AML a tumor of the elderly population. As a separate type of AML, s-AML becomes more and more common due to the aging population and the increasing use of leukemogenic cytotoxic therapy.

Our study demonstrated that e/s-AML patients have distinct clinical features compared with young de novo AML patients, such as lower WBC and BM blasts at diagnosis, which indicate that both elderly and secondary AML are less proliferative diseases, partly because they may have either transformed from MDS or experienced an undetected MDS period. Consistently, R. Coleman Lindsley et al reported that one third elderly de novo AML and t-AML patients carried “secondary-type” mutations and showed clinical characteristics indistinguishable from AHD-AML, indicating that a large proportion of elderly de novo AML and t-AML patients may transit through unconscious myelodysplastic disease.

The genetic and molecular heterogeneity of AML have been widely acknowledged and integrated to optimize the prediction of

FIGURE 1 Kaplan-Meier curves for probability of event-free survival and overall survival. A,B, Event-free survival and overall survival for all young, elderly, and secondary acute myeloid leukemia (AML) patients. C,D, Event-free survival and overall survival for young elderly and secondary AML patients treated with intensive therapy. E,F, Event-free survival and overall survival for young, elderly, and secondary AML patients treated with less intensive therapy. G,H Event-free survival and overall survival for patients received intensive therapy, hypomethylation therapy and palliative treatment in elderly and secondary AML group
| Covariate                        | CR           |          | ED           |          | EFS          |          | OS           |          |
|---------------------------------|--------------|----------|--------------|----------|--------------|----------|--------------|----------|
| Total                            |              |          |              |          |              |          |              |          |
| Age (y)                          | 0.945 (0.926-0.963) | <.001    | 1.061 (1.031-1.093) | <.001    | 1.040 (1.029-1.052) | <.001    | 1.042 (1.030-1.055) | <.001    |
| WBC (×10⁹/L)                     | NS           |          | NS           |          | NS           |          | NS           |          |
| Cytogenetics<sup>b</sup>         | 0.328 (0.177-0.607) | <.001    | NS           |          | 3.074 (2.159-4.377) | <.001    | 3.441 (2.371-4.994) | <.001    |
| s-AML vs de novo AML             | NS           |          | NS           |          | NS           |          | NS           |          |
| FLT3-ITD                         | 0.433 (0.224-0.837) | .013     | NS           |          | 1.669 (1.134-2.458) | .009     | 1.957 (1.297-2.955) | .001     |
| KMT2A-PTD                        | 0.330 (0.131-0.830) | .018     | NS           |          | 1.780 (1.000-3.167) | .05      |              |          |
| NRAS                             | NS           |          | 3.010 (1.368-6.620) | .006     | NS           |          | NS           |          |
| BICEBPA                          | 7.004 (1.647-29.782) | .008     | NS           |          | 0.435 (0.274-0.689) | <.001    | 0.333 (0.183-0.606) | <.001    |
| Elderly                          |              |          |              |          |              |          |              |          |
| BM blasts (%)                    | NS           |          | 1.050 (1.016-1.085) | .004     | NS           |          | 1.015 (1.000-1.030) | .051     |
| WBC (×10⁹/L)                     | NS           |          | NS           |          | 1.009 (1.002-1.016) | .01      | 1.008 (1.001-1.016) | .033     |
| Cytogenetics<sup>b</sup>         | NS           |          | NS           |          | 3.370 (1.642-6.916) | .001     | 2.693 (1.241-5.844) | .012     |
| CBFβ-MYH11                       | NS           |          | 49.197 (3.050-793.497) | .006     | 4.171 (1.444-12.048) | .008     | 6.441 (2.097-19.783) | .001     |
| KMT2A-PTD                        | 0.233 (0.055-0.987) | .048     | NS           |          | NS           |          | NS           |          |
| IDH1                             | NS           |          | 6.918 (1.559-30.698) | .011     | NS           |          |              |          |
| Secondary                        |              |          |              |          |              |          |              |          |
| Age (y)                          | 0.927 (0.870-0.987) | .018     | NS           |          | 1.073 (1.020-1.129) | .007     | NS           |          |
| HB (g/L)                         | 1.032 (1.004-1.061) | .027     | NS           |          | NS           |          | NS           |          |
| WBC (×10⁹/L)                     | NS           |          | 1.018 (1.005-1.031) | .006     | 1.014 (1.003-1.026) | .017     |              |          |
| Cytogenetics<sup>b</sup>         | NS           |          | NS           |          | 5.455 (1.621-18.354) | .006     | 5.547 (1.789-17.193) | .003     |
| NRAS                             | NS           |          | 13.125 (1.662-103.673) | .015     | 7.321 (1.700-31.521) | .008     | 4.104 (1.096-15.368) | .036     |

Abbreviation: AML, acute myeloid leukemia; BM, bone marrow; CR, complete remission; ED, early death; EFS, event-free survival; HB, hemoglobin; HR, hazard ratio; OR, odds ratio; OS, overall survival; WBC, white blood cell.

<sup>a</sup>Patients who received HSCT were censored at the time of HSCT.

<sup>b</sup>Unfavorable vs others.
clinical outcomes for AML patients. Previous studies demonstrated that FLT3-ITD, TP53, RUNX1, ASXL1 aberrations, and KMT2A rearrangements are associated with adverse prognosis, while patients with biCEBPA mutations, RUNX1-RUNXT1T1, and CBFβ-MYH11 seem to have a relatively good outcome.\(^{10,16-22}\) However, our knowledge concerning distribution and prognostic significance of gene alterations in e/s-AML patients remains scarce. Our study indicated that elderly and secondary patients carried more molecular events such as KMT2A-AF9 and DNMT3A mutations and less favorable ones including RUNX1-RUNXT1T1, CBFβ-MYH11, and biallelic CEBePA. Furthermore, genetic aberrations including NRAS, DNMT3A, IDH1 mutations, and CBFβ-MYH11 conveyed prognostic information independently in e-AML or s-AML patients. However, some significant genetic alterations such as TP53, TET2, ASXL1, and RUNX1 mutations were not routinely tested in our center and accordingly not available in this retrospective study. Tsai et al\(^{22}\) reported that the e-AML harbored more mutations concerning PTPN11, NPM1, RUNX1, ASXL1, TET2, DNMT3A, and TP53 genes, but had less WT1 mutations. In addition, DNMT3A and TP53 mutations were independent adverse prognostic factors for elderly patients. Other studies\(^{10,23-25}\) showed epigenetic modifier genes (EMGs) including DNMT3A, ASXL1, and TET2 were more frequent in e-AML patients, which was thought to be associated with age-related clonal hematopoiesis and inferior survival. S-AML patients were reported to carry less NPM1 mutations and FLT3-ITD.\(^{26,27}\) Besides, patients with AML secondary to MDS and CMMML carried more ASXL1 and TP53 mutations.\(^{27}\) Currently, a prospective study including more molecular events is performed in our center, which will provide more integrated results concerning the distribution and prognostic significance of molecular alterations in e/s-AML patients.

Consistent with previous studies,\(^{3,6,24-28}\) we observed that both e-AML and s-AML were associated with lower CR rate and a short duration of EFS and OS. Although some new therapeutic agents were applied to these high-risk AML patients, the treatment of e/s-AML remains a challenge, and there is no consensus on this controversial issue. Some studies indicated that because of remarkable improvement in supportive care, intensive therapy leads to a better survival without increasing early death rate in e/s-AML patients.\(^{3,6,29,30}\) Canadian Consensus Guidelines recommended that patients under the age of 80 should be treated with intensive therapy, except for those with major comorbidities or adverse risk cytogenetics who are not candidates for HSCT.\(^{31}\) However, other studies including MD Anderson reported that patients receiving less intensive therapy such as hypomethylation drugs had superior prognosis compared with those receiving intensive induction.\(^{28,32,33}\) Our study showed that e/s-AML patients treated with intensive therapy had a higher CR rate and tended to have a lower frequency of positive MRD. More importantly, a tendency of a longer EFS and OS was observed in intensively treated patients compared with those who received hypomethylation therapy or palliative treatment. These results may partially be because patients receiving intensive therapy have better performance status and fewer comorbidities, and our prospective study will provide more convincing evidence.

Recently, a study reported that CPX-351 could improve the response rates and survival of patients aged 60 to 75 with s-AML compared with standard 3 + 7 treatment.\(^{34}\) The Food and Drug Administration (FDA) approved glasdegib and venetoclax for the treatment of patients over 75 years old, or young patients who have comorbidities that are not suitable for intensive induction chemotherapy.\(^{35,36}\) We expect that the frontline use of these new drugs may improve the outcomes of e/s-AML individuals, which need to be compared with traditional intensive therapy in prospective research.

In summary, the incidence of e/s-AML is increasing and will be more common in the future, which merits our attention. Both elderly and secondary AML presented with distinct clinical, cytogenetic, and molecular features, whose prognosis remains dismal compared with young de novo patients, with a significant shorter EFS and OS. Intensive therapy could improve the prognosis of e/s-AML patients to a certain degree and should be recommended for patients as long as the conditions are appropriate. HSCT could abrogate the adverse prognostic impact of s-AML and should be considered for the treatment of fit s-AML patients. More importantly, prospective clinical trials with new drugs are warranted in this special group of patients.

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**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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**REFERENCES**

1. Dores GM, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. Blood. 2012;119(1):34-43.
2. Lazarevic V, Horstedt AS, Johansson B, et al. Incidence and prognostic significance of karyotypic subgroups in older patients with acute myeloid leukemia: the Swedish population-based experience. Blood Cancer J. 2014;4(2):e188.
3. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: the Swedish population-based experience. Blood. 2009;113(18):4179-4187.
4. Granfeldt Ostgard LS, Medeiros BC, Sengelov H, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. J Clin Oncol Off J Am Soc Clin Oncol. 2015;33(31):3641-3649.
5. Xu XQ, Wang JM, Gao L, et al. Characteristics of acute myeloid leukemia with myelodysplasia-related changes: a retrospective analysis in a cohort of Chinese patients. Am J Hematol. 2014;89(9):874-881.
6. Hulegardh E, Nilsson C, Lazarevic V, et al. Characterization and prognostic features of secondary acute myeloid leukemia in a population-based setting: a report from the Swedish Acute Leukemia Registry. Am J Hematol. 2015;90(3):208-214.

7. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med. 2016; 374(23):2209-2221.

8. Ley TJ, Miller C, Ding L, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368(22):2059-2074.

9. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults; 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-447.

10. Shen Y, Zhu YM, Fan X, et al. Gene mutation patterns and their prognostic impact in a cohort of 1185 patients with acute myeloid leuke mia. Blood. 2011;118(20):5593-5603.

11. Weng XQ, Shen Y, Sheng Y, et al. Prognostic significance of monitoring leukemia-associated immunophenotypes by eight-color flow cytometry in adult B-acute lymphoblastic leukemia. Blood Cancer J. 2013; 3(8):e133.

12. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in acute myeloid leukemia. J Clin Oncol Off J Am Soc Clin Oncol. 2003;21(24):4642-4649.

13. Miranda-Filho A, Pineros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study. The Lancet Haematology. 2018;5(1):e14-e24.

14. Morton LM, Dores GM, Tucker MA, et al. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood. 2013;121(15):2996-3004.

15. Lindsay RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood. 2015;125(9):1367-1376.

16. Taskesen E, Bullinger L, Corbacigolu A, et al. Prognostic impact, concurrent genetic mutations, and gene expression features of AML with CEBPA mutations in a cohort of 1182 cytogenetically normal AML patients: further evidence for CEBPA double mutant AML as a distinctive disease entity. Blood. 2011;117(8):2469-2475.

17. Fröhling S, Schlenk RF, Breittruck J, et al. Prognostic significance of activating FLT3 mutations in younger adults (≤ 16 years) to acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. Blood. 2002;100(3):4372-4380.

18. Stengel A, Kern W, Waferlach T, Meggendorfer M, Fasan A, Haferlach C. The impact of TP53 mutations and TP53 deletions on survival varies between AML, ALL, MDS and CLL: an analysis of 3307 cases. Leukemia. 2017;31(3):705-711.

19. Tang JL, Hou HA, Chen CY, et al. AML1/RUNX1 mutations in 470 adult patients with de novo acute myeloid leukemia: prognostic implication and interaction with other gene alterations. Blood. 2009; 114(26):5352-5361.

20. Metzeler KH, Becker H, Maharry K, et al. ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN Favorable genetic category. Blood. 2011; 118(26):6920-6929.

21. Muñoz L, Nomdedéu JF, Villamor N, et al. Acute myeloid leukemia with MLL rearrangements: clinicobiological features, prognostic impact and value of flow cytometry in the detection of residual leukemic cells. Leukemia. 2003;17(1):76-82.

22. Tsai CH, Hou HA, Tang JL, et al. Genetic alterations and their clinical implications in older patients with acute myeloid leukemia. Leukemia. 2016;30(7):1485-1492.

23. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014; 371(26):2488-2498.

24. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006;107(9):3481-3485.

25. Park SH, Chi HS, Cho YU, Jang S, Park CJ. Evaluation of prognostic factors in patients with therapy-related acute myeloid leukemia. Blood Research. 2013;48(0):185-192.

26. Kayser S, Dohner K, Krauter J, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011;117(7):2137-2145.

27. Fernandez-Mercado M, Yip BH, Pellagatti A, et al. Mutation patterns of 16 genes in primary and secondary acute myeloid leukemia (AML) with normal cytogenetics. PLoS ONE. 2012;7(8):e42334.

28. Boddou PC, Kantarjian HM, Ravandi F, et al. Characteristics and outcomes of older patients with secondary acute myeloid leukemia according to treatment approach. Cancer. 2017;122(16):3050-3060.

29. Sorror ML, Storer BE, Elsayw M, et al. Impact of comorbidities at diagnosis of acute myeloid leukemia on one-year mortality. Blood. 2015; 126:532-532.

30. Othus M, Kantarjian H, Petersdorf S, et al. Declining rates of treatment-related mortality in patients with newly diagnosed AML given ‘intense’ induction regimens: a report from SWOG and MD Anderson. Leukemia. 2014;28(2):289-292.

31. Brandwein JM, Zhu N, Kumar R, et al. Treatment of older patients with acute myeloid leukemia (AML) revised Canadian consensus guidelines. American Journal of Blood Research. 2017;7(4):30-40.

32. Quintás-Cardama A, Ravandi F, Liu-Dumlao T, et al. Epigenetic therapy is associated with similar survival compared with intensive chemotherapy in older patients with newly diagnosed acute myeloid leukemia. Blood. 2012;120(24):4840-4845.

33. Kantarjian H, Ravandi F, O’Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood. 2010;116(22):4422-4429.

34. Kim M, Williams S. Daunorubicin and cytarabine liposome in newly diagnosed therapy-related acute myeloid leukemia (AML) or AML with myelodysplasia-related changes. Ann Pharmacother. 2018;52(8):792-800.

35. DiNardo CD, Prat K, Pullarkat V, et al. Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. Blood. 2019;133(17):17.

36. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2019;33(2):379-389.

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