The effect of the detection of minimal residual disease for the prognosis and the choice of post-remission therapy of intermediate-risk acute myeloid leukemia without FLT3-ITD, NPM1 and biallelic CEBPA mutations

Wen-shuai Zheng, Ya-lei Hu, Li-xun Guan, Bo Peng, and Shen-yu Wang

Department of Hematology, Hainan Hospital of Chinese PLA General Hospital, Sanya, People’s Republic of China; Department of Hematology, Five Medical Center of Chinese PLA General Hospital, Beijing, People’s Republic of China

ABSTRACT

Background: Intermediate-risk acute myeloid leukemia (IR-AML) without FLT3-ITD, NPM1 and biallelic CEBPA mutations (here referred to as NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML) is a clinically heterogeneous disease. The optimal post-remission therapy (PRT) is unclear for patients with NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML who achieved first complete response (CR1). This study aims to explore clinical and molecular factors that can help determine the prognosis of those patients and their choice of PRT.

Methods: We retrospectively analyzed 28 patients with NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML who received induction chemotherapy and achieved CR1. For PRT, 17 patients received post-remission chemotherapy (PR-CT) and 11 patients received allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Results: For patients with NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML, multivariate analysis indicated that allo-HSCT and negative minimal residual disease (MRDneg) before PRT were favorable prognostic factors of overall survival (OS) (allo-HSCT, P = 0.002; MRDneg, P = 0.018); whereas relapse was an adverse prognostic factor of OS (P = 0.003). Log-rank analysis showed that allo-HSCT significantly improved their OS and RFS compared with PR-CT (OS, P < 0.001; RFS, P = 0.001). Otherwise, allo-HSCT improved the OS and RFS of patients with NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML, whether they obtained MRDneg or MRDpos before PRT (OS: MRDneg, P = 0.036; MRDpos, P = 0.012; RFS: MRDneg, P = 0.047; MRDpos, P = 0.030).

Conclusion: For patients with NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML, MRDneg before PRT and allo-HSCT were favorable prognostic factors of OS. Whether they obtain MRDneg or not, allo-HSCT is the preferred PRT.

Background

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by impaired differentiation and increased proliferation of myeloid progenitor cells [1]. Although most patients with AML receive induction chemotherapy to achieve complete remission (CR), the relapse rate is still high and varies according to the cytogenetic and molecular profiles [1]. Post-remission therapy (PRT) is applied to prevent relapse and usually includes 4–6 cycles of cytarabine, autologous hematopoietic stem cell transplantation (AH SCT), and allogeneic hematopoietic stem cell transplantation (allo-HSCT). In all PRTs, although allo-HSCT offers the strongest antileukemic effect, enhanced nonrelapse mortality (NRM) may compromise the benefit in terms of overall survival (OS). As a result, allo-HSCT is unsuitable for all patients with AML. The intensity and type of PRT is generally tailored according to risk profile. The European Leukemia Network (ELN) proposed three groups of standardized prognostic systems based on cytogenetics, molecular profiling, and clinical data [1]. In general, allo-HSCT is recommended for poor risk and discouraged for good risk AML [1,2]. However, almost half of patients with AML are classified as intermediate-risk AML (IR-AML) determined by karyotype [3]. For these patients, the best PRT is less clear and their prognosis is further determined by specific genetic changes, especially mutation in the nucleophosmin-1 gene (NPM1mut), biallelic mutation in the CCAAT/enhancer binding protein alpha gene (CEBPAdm), and mutation in the FMS-like tyrosine kinase 3 internal tandem duplication gene (FLT3-ITDmut) [4–6].

In general, NPM1mut / FLT3-ITDmutneg or CEBPAdm provides a good prognosis for IR-AML, whereas IR-AML with FLT3-ITDmut has a poor prognosis [7–9]. For the subgroup of patients with IR-AML negative for NPM1mut, CEBPAdm, and FLT3-ITDmut (here referred to as NPM1mut-neg/CEBPAdm-neg/FLT3-ITDneg AML), the

KEYWORDS

Allogeneic hematopoietic stem cell transplantation; Post-remission therapy; Acute myeloid leukemia; Intermediate-risk; Minimal residual disease; CEBPA; FLT3-ITD; NPM1
risk–benefit ratio of allo-HSCT is poorly defined. Schlenk et al. reported that the benefit of transplantation is limited for NPM1mut-negCEBPAdm-negFLT3-ITDneg AML [7]. However, other retrospective studies reported a favorable OS after allo-HSCT for NPM1mut-negCEBPAdm-negFLT3-ITDneg AML, and the survival is even similar to those of good risk group classified according to ENL criteria [10,11].

This study aims to explore additional clinical and molecular factors that can contribute to the prognosis of patients with NPM1mut-negCEBPAdm-negFLT3-ITDneg AML, and to assess the value of allo-HSCT in these patients.

Materials and methods

Patients

The study selected 122 newly diagnosed patients with AML who underwent therapy at Hainan Hospital of Chinese PLA General Hospital from July 2012 to March 2019. The last follow-up time was March 2020. All patients’ risk and prognosis groups were classified according to ENL criteria [1].

Treatment protocols

Induction chemotherapy consisted of idarubicin 10 mg/m²/d for 3 days in combination with cytarabine 100–200 mg/m²/d for 7 days (IA); daunorubicin 60 mg/m²/d for 3 days in combination with cytarabine 100–200 mg/m²/d for 7 days (DA); mitoxantrone 10–12 mg/m²/d for 3 days in combination with cytarabine 100–200 mg/m²/d for 7 days (MA); or descitabine 20 mg/m²/d for 5 days in combination with aclacinomycin 10 mg/d for 1–5 days, cytarabine 10 mg/m²/12 h for 1–5 days, and G-CSF 5 µg/kg/d for 0–14 days (D-CAG). Patients who achieved partial remission (PR) were re-induced with the original scheme, whereas those who demonstrated no remission (NR) were induced with other schemes. Patients who achieved CR continued to receive 4–6 courses of consolidation chemotherapy with Ara-C (2–3 g/m²; every 12 h; doses 1, 3, and 5) or proceeded to allo-HSCT. The choice of PRT depended on donor, individual wishes, finances, physical conditions, and genetic changes. Finally, a total of 11 patients underwent allo-HSCT, of which 5 and 6 underwent haploidentical HSCT and matched sibling HSCT, respectively. The transplantation scheme has been previously explained [12,13].

MRD, cytogenetics, and molecular analysis

The minimal residual disease (MRD) study was performed on bone marrow samples from patients who achieved CR. Collection and analysis were performed on a FACS Aria II flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA), which detected the immunophenotype of bone marrow cells through 14- color immunomarker. Monoclonal antibody combinations used in all of the cases were as follows: CD34-FITC/CD13-PE/CD117-PerCP/CD33-APC/HLA-DR-APC-CY7/CD45-V500 and CD38/CD7/CD56. The karyotype analysis of bone marrow samples was performed by g-banding method at initial diagnosis. Common fusion genes were detected by Prism 7500 real-time PCR. Target-region PCR enrichment and high-throughput parallel sequencing of gene mutations related to hematological malignancies were performed under the Ion Torrent sequencing platform. The average sequencing depth was 2000x, and the sensitivity was 1%. In total, 34 related gene mutations of AML/MDS/MPN were detected.

Endpoints and definitions

The endpoints include OS, which was measured from the date of diagnosis to death or the last follow-up time; relapse-free survival (RFS), which was measured from the date of CR1 to the first relapse, death or the last follow-up time; and cumulative incidence of relapse (CIR), which is defined as the ratio of the number of patients who have relapsed to the original total patients. Hematological CR was defined as less than 5% marrow blasts, no extramedullary disease, an absolute neutrophil count (ANC) of >1.0 × 10⁹/L, a platelet count of >100 × 10⁹/L, and independence from red cell transfusions. Relapse was defined as a recurrence of ≥5% bone marrow blasts, reappearance of blasts in the blood, or the development of extramedullary disease infiltrates at any site. Negative MRD before PRT (MRDneg) was defined as <10⁻³ blasts (≤0.1%) in bone marrow samples. Positive MRD before PRT (MRDpos) was defined as ≥10⁻³ blasts (≥0.1%) in bone marrow samples. IR-AML without NPM1mut, CEBPAdm and FLT3-ITDmut was defined as NPM1mut-negCEBPAdrnegFLT3-ITDneg AML.

Statistical analysis

SPSS 20.0 was used for statistical analysis. Firstly, the normality test was conducted for all continuous variables, and mean ± standard deviation (SD) was used to describe the variables that followed normal distribution. Variables that don’t conform to normal distribution were described by median and quartile. Comparisons of patient characteristics between two groups were performed by independent-samples T test, Mann–Whitney U test, Chi-square or Fisher’s exact test. CRI was calculated by Kaplan-Meier method. Survival analysis was carried out by Kaplan-Meier method, and the difference between groups was compared by log-rank method. The factors affecting relapse was analyzed by Logistic analysis. The factors with P < 0.05 were entered into Cox regression model for multiple-factor analysis. Hazard
ratios were presented with 95% confidence intervals (95% CI). A P value of <0.05 was considered to be statistically significant.

Results

Patients’ characteristics

According to karyotype, 64 patients were classified as intermediate-risk group (52.5%), 30 patients were classified as high-risk group (24.5%), and 28 patients were classified as low-risk group (23.0%). Among intermediate-risk group, 28 patients with NPM1mut-negCEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML (43.8%) who obtained CR within 2 course were further analyzed. We retrospectively analyzed their clinical features at diagnosis, including peripheral blood, white blood cell count (WBC), blast percentages in bone marrow and frequencies of known recurrent genetic mutations. No significant differences were found between PR-CT and allo-HSCT groups in terms of gender, WBC, bone marrow blasts and MRD\textsuperscript{pos} or MRD\textsuperscript{neg}. A lower percentage of one courses to CR, higher relapse rate and higher age were observed in the PR-CT group (P = 0.040, P = 0.042, P = 0.007, respectively) (Table 1).

Analysis of risk factors of OS, RFS, and relapse in patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML

To assess the prognostic factors of patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML about OS, PFS, and relapse, we applied univariate and multivariate analysis in age (≥50 vs. <50 years), sex (male vs. female), WBC (≥100 vs. <100 × 10\textsuperscript{9}/L), blast (≥50% vs. <50%), courses to CR (>1 vs. 1 courses), MRD (positive vs. negative), treatment (PR-CT vs. allo-HSCT), and common genetic mutations (NRAS and C-Kit; mutated vs. wild). In patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML, univariate analysis indicated that that relapse was an adverse factor of OS (P = 0.001), whereas allo-HSCT and MRD\textsuperscript{neg} were favorable factors (P < 0.001, P = 0.043, respectively). allo-HSCT and MRD\textsuperscript{neg} were favorable factors of PFS (P = 0.001, P = 0.030, respectively). No factors affected relapse. Multivariate analysis showed that allo-HSCT and MRD\textsuperscript{neg} were independent favorable factors of OS (P = 0.002, P = 0.018, respectively), whereas relapse was independent adverse factor (P = 0.003). Allo-HSCT was independent favorable factor of RFS (P = 0.011) (Table 2).

Survival analysis in patients with IR-AML and NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML

For patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML, 11 patients (39.3%) received allo-HSCT, and 17 patients (60.7%) received PR-CT. Compared with PR-CT, allo-HSCT markedly improved the OS and RFS (OS, P < 0.001, Figure 1(a); RFS, P = 0.001, Figure 1(b)), and reduced the CR (P = 0.011, Figure 1(c)).

MRD analysis

In our study, multivariate analysis showed that MRD\textsuperscript{neg} was an independent favorable factor of OS in patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML. Thus, we further performed a subgroup analysis. For patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML, allo-HSCT also improved the OS and RFS of patients who obtained MRD\textsuperscript{pos} or MRD\textsuperscript{neg} compared with PR-CT (OS, P = 0.012, P = 0.036, respectively, Figure 2(a); RFS, P = 0.030, P = 0.047, respectively, Figure 2(b)).

Table 1. The characteristics of patients with NPM1\textsuperscript{mut-neg}CEBPA\textsuperscript{dm-neg}FLT3-ITD\textsuperscript{neg} AML.

| Patients | Total | allo-HSCT | PR-CT | P |
|----------|-------|-----------|-------|---|
| Number of patients, n | 28 | 11 | 17 | 0.823 |
| Sex, n | | | | 0.269 |
| Male | 16 | 6 | 10 | 0.556 |
| Female | 12 | 5 | 7 | 0.556 |
| Age, years: median + quartile | 53.00 + 28.50 | 39.00 + 27.00 | 59.00 + 25.00 | 0.007 |
| WBC, ×10\textsuperscript{9}/L: median + quartile | 6.00 + 41.18 | 7.00 + 29.34 | 4.19 + 55.09 | 0.007 |
| Blast in BM;%; mean ± SD | 54.85 ± 23.36 | 55.82 ± 16.42 | 54.22 ± 27.41 | 0.864 |
| Courses to CR, n | | | | 0.004 |
| 1 | 16 | 9 | 7 | 0.040 |
| >1 | 12 | 2 | 10 | 0.042 |
| MRD before PRT, n | | | | 0.042 |
| MRD\textsuperscript{neg} | 12 | 6 | 6 | 0.269 |
| MRD\textsuperscript{pos} | 16 | 5 | 11 | 0.042 |
| Relapse | | | | 0.042 |
| Yes | 13 | 4 | 13 | 0.360 |
| No | 15 | 7 | 4 | 0.671 |
| Mutations, n | | | | 0.360 |
| NRAS\textsuperscript{mut} | 3 | 2 | 0 | 0.671 |
| C-Kit\textsuperscript{mut} | 5 | 2 | 3 | 0.360 |

allo-HSCT: allogeneic hematopoietic stem cell transplantation; PR-CT: post-remission chemotherapy; SD: standard deviation; WBC: white blood cell count; CR: complete remission; MRD\textsuperscript{pos}: negative minimal residual disease before PRT; MRD\textsuperscript{neg}: positive minimal residual disease before PRT; NRAS\textsuperscript{mut}: NRAS mutation; C-Kit\textsuperscript{mut}: C-Kit mutation.
Discussion

PRT in patients with AML includes continuing chemotherapy and AH SCT or allo-HSCT. In all PRT, although allo-HSCT has the strongest anti-leukemia effect, the benefits of OS is compromised by recurrent NRM, which limits its further application [14]. For patients with AML in CR1, the indication for allo-HSCT is usually based on genetic risk factors. In general, patients with good cytogenetics receive PRCT as preferred PRT, because the probability of obtaining a second CR is very high and the subsequent outcome upon proceeding to allo-HSCT in second CR is favorable [15–17]. Allo-HSCT is considered to be the preferred PRT for patients with poor cytogenetics [2]. However, for patients with IR-AML determined by karyotype, the best choice of PRT is not clear [18,19].

With the development of second-generation sequencing technology, the role of molecular genetics in prognostic assessment has been increasingly emphasized in the past decade to improve prognostic stratification, especially for IR-AML [20]. For example, IR-AML with FLT3-ITDmut has poor prognosis in terms of increasing the risk of relapse and death. Compared with PR-CT, allo-HSCT reduces the risk of relapse and improves RFS and OS in this group [9]. IR-AML with NPM1mut/FLT3-ITDmut-neg or CEBPA dm-neg usually has good prognosis, high CR rate, and high survival rate [7,8]. In this group, procedure-related mortality after allo-HSCT offsets disease benefits. The standard treatment for this group is induction chemotherapy followed by three or four high-dose cytarabine consolidation cycles [7,21]. A remaining issue is the poorly defined risk–benefit ratio of allo-HSCT in patients with NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML. Data comparing the outcomes of allo-HSCT and PR-CT for NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML are few and unclear. Schlenk et al. reported that the benefit of transplantation is limited for NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML [7]. Heidrich et al. demonstrated that patients with NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML can achieve longer RFS from matched sibling allo-HSCT compared with PR-CT [11]. Ying Zhang et al. indicated a 5-year OS close to 59% for NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML patients in allo-HSCT group, whereas 33% in PR-CT (P = 0.024) [22]. In our study, multivariate analysis showed that allo-HSCT was an independent good prognostic factor (P = 0.002) and improved the OS and RFS compared with PR-CT (OS, P < 0.001, Figure 1(a); RFS, P = 0.001, Figure 1(b)) in patients with NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML. We believe that the improvement in survival is mainly due to the lower risk of relapse after allo-HSCT, whereas the CIR of patients treated with allo-HSCT is better than that with PR-CT (P = 0.011, Figure 1(c)). Thus, for patients with NPM1 mut-neg CEBPA dm-neg FLT3-ITD neg AML, allo-HSCT is also a preferred PRT over PR-
Although the patients treated by allo-HSCT was younger and had a lower percentage of one courses to CR, multivariate analysis showed that the age and courses to CR weren’t independent prognostic factors for patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML. So the effect of age and courses to CR on the reliability of the result were little.

The recent studies showed that combining MRD with treatment-related prognosis will contribute to favorable clinical outcomes. For example, Ying Zhang et al. demonstrated that allo-HSCT and MRD$^{\text{neg}}$ were independent favorable prognostic factors of OS and RFS in patients with IR-AML [22]. Ravandi et al. confirmed that MRD$^{\text{pos}}$ was an independent adverse prognostic factor of OS and RFS in patients with AML [23]. Our results are similar to the previous studies. In our study, besides allo-HSCT, multivariate analysis showed that MRD$^{\text{neg}}$ is also an independently favorable prognostic factor of OS in patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML ($P = 0.018$).

Based on the above results, we assumed that patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML who obtained MRD$^{\text{neg}}$ may not need allo-HSCT. The sub-group analysis showed that, although MRD$^{\text{neg}}$ was a predictor for better OS in patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML, allo-HSCT also improved their OS and RFS compared with PR-CT (OS, $P = 0.036$ Figure 2(a); RFS, $P = 0.047$ Figure 2(b)). Similar to patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML who obtained MRD$^{\text{neg}}$, allo-HSCT also improved the OS and RFS of patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML who obtained MRD$^{\text{pos}}$ compared with PR-CT (OS, $P = 0.012$ Figure 2(a); RFS, $P = 0.030$, Figure 2(b)). Thus, we suggest that whether or not patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML obtained MRD$^{\text{neg}}$, allo-HSCT is a preferred PRT over PR-CT.

Our work has some limitations. First, this work was a retrospective study that resulted in a lack of molecular profiling data in a proportion of patients. Second, our study involved few patients. Therefore, caution should be taken when interpreting our data given that this work was a single-center, retrospective study with a small number of heterogeneous patients.

Figure 1. The comparison of allo-HSCT versus PR-CT in patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML. (a) OS, (b) RFS, (c) CIR.

Figure 2. The comparison of allo-HSCT versus PR-CT in patients with NPM1$^{\text{mut-neg}}$CEBPA$^{\text{dim-neg}}$FLT3-ITD$^{\text{neg}}$ AML who obtained MRD$^{\text{neg}}$ or MRD$^{\text{pos}}$. (a) OS, (b) RFS.
In summary, for patients with NPM1mut-negCEBPAdm-neg FLT3-ITDneg AML, MRDneg and allo-HSCT were favorable prognostic factors and relapse was risk prognostic factor of OS. Our results found that allo-HSCT is a preferred PRT for patients with NPM1mut-negCEBPAdm-negFLT3-ITDneg AML over PR-CT, even if these patients obtained MRDneg.

**Ethics approval and consent to participate**

The ethics committee waived the need for informed consent for this retrospective study because of the absence of impact on the management of patients.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Data availability statement**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**ORCID**

Wen-shuai Zheng [http://orcid.org/0000-0002-4489-5526](http://orcid.org/0000-0002-4489-5526)

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