Outcome of autologous stem cell transplantation in patients with favorable-risk acute myeloid leukemia in first remission

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Abstract

Objective To evaluate the efficacy of autologous hematopoietic stem cell transplantation (auto-HSCT) in patients with favorable-risk acute myeloid leukemia in first remission.

Method Twenty patients who received auto-HSCT at our center between January 2014 and January 2021 were retrospectively reviewed.

Results Until last follow-up, three patients in the cohort were dead due to relapse. The estimated 1-year and 5-year overall survival were 95.00% ± 4.87% and 83.82% ± 8.58%, respectively. The estimated 5-year RFS and CIR (cumulative incidence of relapse) were 85.00% ± 7.98% and 15.00% ±7.98%, respectively.

Conclusion The outcome of auto-HSCT in patients with favorable-risk acute myeloid leukemia in first remission was excellent and auto-HSCT could be an effective treatment for these patients.

Keywords Outcome, Autologous stem cell transplantation, Acute myeloid leukemia, Favorable-risk, Remission

Introduction

According to the ELN risk stratification by genetics, acute myeloid leukemia (AML) can be categorized into favorable-risk, intermediate-risk and adverse-risk groups [1]. For patients in the favorable-risk group, chemotherapy and hematopoietic stem cell transplantation (HSCT) (both auto and allo) are post-remission treatment choice. Consolidation chemotherapy including high dose cytarabine is recommended for favorable-risk AML in first remission by the NCCN (National Comprehensive Cancer Network) guideline [2]. However, a considerable proportion of these patients will experience disease relapse after chemotherapy [3, 4]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) can significantly reduce the relapse rate due to the graft-versus-leukemia (GVL) effect. However, the lack of HLA matched sibling donor and high nonrelapse mortality (NRM) limit its
application. Autologous hematopoietic stem cell transplantation (auto-HSCT) may offer lower transplantation-related mortality (TRM) compared with allogeneic HSCT and lower relapse rate comparing to chemotherapy [5–9]. Therefore, auto-HSCT is a promising treatment for patients with favorable-risk AML as it may improve survival with relatively low TRM. In this study, we aimed to assess the efficacy of autologous HSCT in patients with favorable-risk acute myeloid leukemia in first remission.

Patients and methods

Patients

We retrospectively analyzed the data of 20 consecutive patients with acute myeloid leukemia in first remission who received autologous HSCT at Institute of Hematology, Chinese Academy of Medical Science from January 2014 and January 2021. The patients were categorized as favorable-risk according to the ELN risk stratification by karyotype and/or fluorescence in situ hybridization. Molecular analysis including gene mutation and fusion gene screening was performed by next generation sequencing at diagnosis. Minimal residual disease (MRD) for RUNX1–RUNX1T1, CBFB–MYH11 and NPM1 was determined by real-time quantitative polymerase chain reaction analysis, while for biallelic mutated CEBPA, it was determined by Sanger sequencing.

Cytogenetic and molecular analysis

The cytogenetic analysis was conducted at diagnosis by karyotype and/or fluorescence in situ hybridization. Molecular analysis including gene mutation and fusion gene screening was performed by next generation sequencing at diagnosis. Minimal residual disease (MRD) for RUNX1–RUNX1T1, CBFB–MYH11 and NPM1 was determined by real-time quantitative polymerase chain reaction analysis, while for biallelic mutated CEBPA, it was determined by Sanger sequencing.

Conditioning regime

All patients undergoing auto-HSCT received conditioning based on Bu (busulfan): 0.8 mg/kg q6h×3d or TBI (total body irradiation): 3.3 Gy/d×3d, Flu (fludarabine): 30 mg/m²×3d or Cla (Cladribine): 5 mg/m²×3d, Ara-c (cytarabine): 1-2 g/m²×3d, and 14 patients received Cy (cyclophosphamide): 40 mg/kg×2d in addition.

Transplantation details

Transplantation associated details were shown in Table 1. Seventeen patients received stem cells from donor peripheral blood (PB), 2 patients from PB plus bone marrow (BM), and 1 patient from BM because of poor mobilization of PB stem cells. The median dose of infused MNC and CD34+ cells were 10.90×10⁶/kg (range from 2.33 to 30.55×10⁶/kg) and 3.28×10⁶/kg (range from 1.16 to 3.23×10⁶/kg), respectively.

Table 1  Transplantation details and outcomes

| Genetic abnormality | Pre-conditioning | Graft source | MNC cells | CD34+ cells | ANC engraftment | PLT engraftment | Follow-up | Relapse | Death |
|---------------------|------------------|--------------|-----------|-------------|----------------|----------------|-----------|--------|-------|
| t(8;21)(q22;q22.1); RUNX1–RUNX1T1 (N = 3) | Bu + Ara-C | PB | 6.94 | 1.63 | 14 | 154 | 2840 | No | No |
| inv(16)(p13.1;q22); or t(16;16) (p13.1;q22); CBFB–MYH11 (N = 3) | Bu + Flu + Ara-C | PB | 10.5 | 1.95 | 12 | 17 | 2521 | No | No |
| Biallelic mutated CEBPA (N = 5) | Bu + Cy + Cla + Ara-C | PB | 10.9 | 1.64 | 34 | 60 | 1346 | No | No |
| Mutated NPM1 without FLT3-ITD or with FLT3-ITDlow (N = 9) | Bu + Ara-C | PB | 10.44 | 2.13 | 12 | 14 | 2692 | No | No |
| | TBI + Cy + Flu + Ara-C | PB + BM | 4.14 | 2.08 | 43 | 50 | 2545 | No | No |
| | Bu + Cla + Ara-C | PB | 11.41 | 1.52 | 11 | 35 | 345 | No | No |
| | Bu + Cy + Flu + Ara-C | BM | 2.33 | 1.61 | 40 | 60 | 2658 | No | No |
| | Bu + Cy + Cla + Ara-C | PB | 10.63 | 2.43 | 12 | 15 | 1362 | No | No |
| | Bu + Cla + Ara-C | PB | 17.86 | 1.76 | 14 | 28 | 911 | No | No |
| | Bu + Cy + Flu + Ara-C | PB | 30.55 | 2.80 | 12 | 282 | 463 | Yes | Yes |
| | Bu + Cy + Cla + IDA | PB | 8.35 | 1.70 | 13 | 17 | 1821 | No | No |
| | Bu + Cy + Flu + Ara-C | PB | 11.31 | 2.40 | 12 | 16 | 2210 | No | No |
| | Bu + Cla + Ara-C | PB | 8.33 | 2.67 | 11 | 17 | 407 | No | No |
| | Bu + Cy + Flu + Ara-C | PB | 11.56 | 1.16 | 17 | 70 | 2238 | No | No |
| | Bu + Cy + Flu + Ara-C | PB + BM | 17.54 | 2.13 | 15 | 43 | 94 | Yes | Yes |
| | Bu + Cla + Ara-C | PB | 2.88 | 3.23 | 11 | 14 | 408 | Yes | Yes |
| | Bu + Cy + Cla + Ara-C | PB | 20.97 | 2.10 | 16 | 39 | 985 | No | No |
| | Bu + Cy + Cla + Ara-C | PB | 11.38 | 2.50 | 14 | 39 | 1720 | No | No |
Criteria of outcomes
Engraftment was defined as ANC (absolute neutrophil counts) \( \geq 0.5 \times 10^9/L \) for three consecutive days and platelet counts \( \geq 20 \times 10^9/L \) without transfusion for 7 consecutive days.

Overall survival (OS) was defined from HSCT to death of any cause or last follow-up. Relapse free survival (RFS) was calculated as the time from transplantation to relapse or the end of follow-up. Relapse was defined as at least 5% leukemia blasts in a BM smear, or extramedullary leukemia.

Statistical analysis
The data were analyzed by the software GraphPad Prism 8 and IBM SPSS statistics 25. The Kaplan-Meier method was used to estimate the cumulative survival/incidence. The descriptive statistics for continuous variables was used to compare incidence in univariate analysis. The Kaplan-Meier method was used to estimate the cumulative survival/incidence.

Results
Characteristics of patients
The 20 patients were favorable-risk AML categorized by genetics, of which 3 patients were t(8;21)(q22;q22.1); RUNX1-RUNX1T1, 3 patients were inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11, 5 patients were biallelic mutated CEBPA, and 9 patients were normal karyotype with mutated NPM1 without FLT3-ITD. The baseline characteristics of patients in the four groups were listed in Table 2. Median leukocyte counts at diagnosis were \( 26.68 \times 10^9/L \) (range from 1.11 to 190.37 \( \times 10^9/L \)). Three patients were with additional cytogenetic abnormalities, 2 with -Y and 1 with +22. Seven patients had additional molecular abnormality, 3 with FLT3-TKD, 1 with NF1 and RELN mutation, 1 with c-KIT mutation, 1 with TET2 mutation, and 1 with IDH1 mutation. All patients had complete remission after 1 or 2 induction courses of chemotherapy, and received a median of 3.5 (range from 1 to 6) additional consolidation courses of chemotherapy including medium-dose cytarabine before transplantation. MRD was negative for all patients before auto-HSCT.

Engraftment
All patients had ANC engraftment and the median time of engraftment was 13 days (range from 11 to 43 days). For platelet, the median time of engraftment was 33 days (range from 14 to 282 days) and 18 patients (90%) had platelet engraftment in 100 days post transplantation.

Deaths and survival
The median follow up of the patients was 1362 days (range from 94 to 2840 days). Of all the patients, three patients received cytokine induced killer (CIK) cell infusion after transplantation, three patients received
interleukin-2 therapy and one patient received azacitidine treatment for maintaining therapy. Until the last follow up, three patients died and they all died of relapse. Time to relapse from HSCT was 94 days, 184 days and 315 days, respectively. The relapsed patients did not receive maintaining therapy after transplantation. Median OS for the nonrelapse patients were 1821 days (range from 345 to 2840 days). The estimated 1-year and 5-year OS were 95.00% ± 4.87% and 83.82% ± 8.58%, respectively. The estimated 5-year RFS and CIR (cumulative incidence of relapse) were 85.00% ± 7.98% and 15.00% ± 7.98%, respectively (Fig. 1).

Discussion
AML is a kind of heterogeneous diseases and currently stratified by karyotype and molecular characteristics. Patients with t(8;21)(q22;q22.1); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11, biallelic mutated CEBPA or mutated NPM1 without FLT3-ITD or with FLT3-ITD low were thought to be favorable-risk with good prognosis [1]. Although these patients can achieve complete remission easily after induction chemotherapy, high relapse rate was observed for patients receiving consolidation chemotherapy alone [3]. Allo-HSCT can reduce relapse significantly, but it is a little aggressive regarding favorable-risk AML in first remission and usually not considered due to high nonrelapse mortality. The role of auto-HSCT for AML is controversial since it lacks GVL effect which may be associated with increased relapse risk [10–14]. Given this context, we aimed to evaluate the efficacy of auto-HSCT for these patients.

Several previous studies [4, 15] has focused on auto-HSCT in patients with core binding factor (CBF) AML, including t(8;21)(q22;q22.1); RUNX1-RUNX1T1, inv(16)(p13.1q22) and t(16;16)(p13.1;q22); CBFB-MYH11, which accounts for 10–15% of all AML patients [16–18]. The estimated 5-year OS and CIR for these patients were 84–89% and 16–17.5%, respectively. Other studies [5, 7] evaluated auto-HSCT for patients with favorable-risk AML also showed good efficacy. Moreover, comparing to allo-HSCT, the efficacy was identical. A recent study comparing the efficacy of auto-HSCT and haplo-HSCT (haploidentical HSCT) for favorable-risk AML patients found that there was no significant difference in 3-year OS between the two groups (88.3%±5.2% vs. 93.1%±4.7%, P=0.318) [8]. Another study from the EBMT (European Cooperative Group for Blood and Marrow Transplantation) also showed similar outcomes after auto-HSCT or allo-HSCT in first remission of AML carrying inversion 16 or t(8;21) [18].

In the current study, we retrospectively analyzed the data of 20 patients with favorable-risk AML who underwent auto-HSCT in first remission and identified excellent efficacy. With a median follow up of 1362 days (range from 94 to 2840 days), 17 (85.00%) patients survived without relapse. The estimated 1-year and 5-year OS were 95.00% ± 4.87% and 83.82% ± 8.58%, respectively, which corresponded well with other studies. The estimated 5-year RFS and CIR were also similar to previous studies [4, 7, 8, 15]. MRD status before auto-HSCT was
suggested as an independent prognostic factor for both OS and RFS [7, 8]. Three patients experienced relapse (all in one-year) and responded poorly to subsequent chemotherapy and then died unfortunately. This result was consistent with previous study [15], indicating that relapse was the leading cause of death for auto-HSCT and should be paid more attention with may be more frequent MRD assessments. Moreover, in our study, the three relapsed patients had relatively older age (56 years old (range from 33 to 59 years old)) vs. 34 years old (range from 16 to 56 years old), \( P = 0.053 \) and higher leukocyte counts [56.87 * 10^9/L] (range from 26.25 to 124.00 * 10^9/L) vs. 25.97 * 10^9/L (range from 1.11 to 190.37 * 10^9/L), \( P = 0.348 \) at diagnosis comparing to other patients. These two factors (especially old age) were prognostic factors for auto-HSCT identified by many studies [5, 19–21] and may be associated with relapse, but pending further confirmation.

In conclusion, auto-HSCT could achieve excellent outcome with low relapse rate for young favorable-risk AML patients in first remission with MRD negativity. The present study provided evidence in clinical application of auto-HSCT for these patients. However, due to the retrospective origin and small sample size, future prospective, large-scaled clinical trials are needed to investigate and confirm the efficacy and more efforts should be made to furtherly reduce relapse.

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Authors‘ contributions

SZF conceived and designed the study, JC analysed the data and drafted the manuscript. SZF secured financing of the study. LL, RZM, AMP, DLY, XC, JLW, YH, DLY, RLZ, WHZ, QLM, ELJ and MZH contributed to the review and editing. All authors read and approved the final manuscript. All authors read and approved the final manuscript.

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Data Availability

The data and materials can be obtained from the first author and corresponding author.

Competing interests

The authors declare that they have no competing interests.

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