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ORIGINAL RESEARCH

Long-Term Results of Busulfan Plus High-Dose Idarubicin as a Conditioning Regimen to Autologous Stem Cell Transplantation Following Cytarabine Consolidation in Young Patients with Favorable or Intermediate-Risk Acute Myeloid Leukemia

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Objective: To evaluate the long-term efficacy and safety of high-dose idarubicin plus busulfan (I-Bu) conditioning followed by autologous stem cell transplantation (ASCT) compared to intermediate- to high-dose cytarabine (Ara-C) consolidation in young acute myeloid leukemia (AML) patients with favorable- or intermediate-risk in first complete remission (CR_1).

Methods: We retrospectively analyzed clinical data from 59 young AML patients (aged ≤ 65 years) with favorable- or intermediate-risk disease who received the I-Bu conditioning regimen followed by ASCT between December 2004 and December 2021 (ASCT group). Clinical outcomes were compared with 57 favorable- and intermediate-risk AML patients treated with intermediate- to high-dose Ara-C consolidation chemotherapy alone (chemotherapy group). Overall survival (OS) and disease-free survival (DFS) were evaluated, and univariate and multivariate analyses were performed to identify prognostic factors associated with OS.

Results: A total of 116 patients were included with a median follow-up of 79.5 months. Median OS was not reached in either group. The ASCT group achieved a significantly higher 2-year OS rate (84.5% vs 59.7%, *P*=0.0018) and sustained a significant OS benefit in the 10-year OS rate (*P*=0.0017). DFS rate also showed superiority in the ASCT group at 2-year (77.7% vs 53.5%, P=0.0037) and maintained this benefit in the 10-year DFS rate (*P*=0.0038). Multivariate Cox regression identified treatment modality as an independent prognostic factor for OS (HR = 3.12, 95% CI: 1.48–6.59, *P*=0.0028). In subgroup analysis, ASCT significantly improved OS (*P*<0.001) and DFS (*P*=0.0014) in favorable-risk patients, whereas no differences were observed in intermediate-risk patients (OS, *P*=0.13; DFS, *P*=0.21).

Conclusion: The I-Bu conditioning regimen followed by ASCT provides durable survival benefits and a favorable safety profile for young, favorable-risk AML patients in CR_1, representing a potential post-remission therapeutic option. Its role in intermediate-risk AML requires further validation.

Keywords: acute myeloid leukemia, autologous hematopoietic stem cell transplantation, High-dose idarubicin

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Introduction

Acute myeloid leukemia (AML) remains at risk of relapse after induction and consolidation therapy.[1] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is currently the only curative approach for leukemia. According to the 2022 European Leukemia Net (ELN) recommendations, consolidation therapy with intermediate-dose cytarabine (Ara-C) retains its status as the standard backbone for chemotherapy-based post-remission consolidation in AML. Notably, the guidelines endorse autologous stem cell transplantation (ASCT) as a viable alternative post-remission strategy for two distinct patient subsets: 1) those with favorable- or intermediate-risk disease who attain a stringent measurable residual disease (MRD)-negative response; and 2) those for whom allo-HSCT is clinically unavailable or contraindicated.[2] Compared with the higher transplant-related mortality and graft-versus-host disease (GVHD) associated with allo-HSCT, ASCT is characterized by a lower transplant-related mortality and the absence of graft rejection and GVHD, thereby allowing patients to achieve a better quality of life. Compared with chemotherapy alone, a randomized controlled trial by Baron et al demonstrated that ASCT improves survival and reduces relapse rates in AML,[3] particularly in favorable- or intermediate-risk patients.[4–6] Since autologous stem cells are derived from the patients' own hematopoietic system, ASCT lacks the graft-versus-leukemia effect, and residual leukemic cells may be present in the graft, resulting in a higher relapse rate compared to allo-HSCT. However, for some patients with favorable- to intermediate-risk AML or those without suitable matched donors, ASCT remains an alternative option for post-remission therapy. The assessment of MRD serves as an important basis for prognostic prediction and treatment response evaluation in AML. With the deepening of related research, MRD has also become a critical factor in guiding post-remission therapeutic strategies.[7] Studies have shown that even in favorable-risk patients with persistent MRD positivity, dynamic monitoring is required and allo-HSCT is recommended. For patients with sustained MRD negativity or those who achieve and maintain MRD negativity after induction and consolidation therapy, there are no significant differences among ASCT, chemotherapy alone, and allo-HSCT in terms of overall survival (OS), disease-free survival (DFS), and cumulative incidence of relapse (CIR).[8]

The conditioning regimen administered prior to ASCT has a certain impact on treatment outcomes in AML patients.[9] The most classic conditioning regimen is busulfan plus cyclophosphamide (BuCy). However, cyclophosphamide-related toxicities, including hepatic toxicity, hemorrhagic cystitis and prolonged immunosuppression, have prompted the exploration of alternative conditioning strategies.[10] More recently, busulfan plus melphalan (BuMel) has shown improved anti-leukemic efficacy and lower relapse rates compared with BuCy in several studies, although increased mucosal toxicity remains a concern.[11] Therefore, optimization of conditioning regimens to achieve a better balance between anti-leukemic activity and toxicity remains an important clinical objective. In 2001, Ferrara et al firstly proposed the use of high-dose idarubicin plus busulfan (I-Bu) as a conditioning regimen prior to ASCT, aiming to further enhance the anti-leukemic effect and reduce the post-transplant relapse rate. Its safety and efficacy have been preliminarily verified.[12–14] In 2014, our center reported 32 patients who underwent ASCT with the I-Bu conditioning regimen, further confirming the efficacy and safety of this regimen.[15]

Apart from the initial proposal by Ferrara et al, long-term follow-up data on ASCT using the I-Bu conditioning regimen are scarce. Moreover, relevant studies have indicated that early post-transplant outcomes cannot reliably predict long-term efficacy.[16] Therefore, the efficacy of this regimen still requires further validation through long-term follow-up. We retrospectively analyzed 59 young (aged $\leq$ 65 years), favorable- to intermediate-risk AML patients who received the I-Bu conditioning regimen followed by ASCT at our hospital between December 2004 and December 2021, including the 32 cases reported in our earlier study. On the basis of our previous work, we expanded the sample size, conducted longer follow-up, and compared the outcomes with those receiving consolidation chemotherapy with intermediate- to high-dose Ara-C, to assess the efficacy and safety of the I-Bu conditioning regimen combined with ASCT versus chemotherapy in this patient population.

Patients and Methods

Patients

Between December 2004 and December 2021, a total of 738 consecutive newly diagnosed AML patients with complete records were retrospectively screened at our center, of whom 422 achieved first complete remission (CR_1). According to the 2022 ELN risk stratification criteria, 298 of these CR_1 patients were classified into the favorable- or intermediate-risk group.

To construct a rigorous comparative cohort between ASCT and consolidation chemotherapy, we applied explicit exclusion criteria to this eligible population: patients who subsequently received allo-HSCT as post-remission therapy during CR_1 were excluded. Furthermore, in clinical practice, patients receiving ASCT are generally younger and have better functional status. To minimize confounding by indication and ensure baseline comparability, we systematically excluded patients older than 65 years and those unfit for intensive therapy (Eastern Cooperative Oncology Group performance status score > 2). Ultimately, 116 AML patients in CR_1 were retrospectively included in this study. Among them, 59 patients received the addition of ASCT (with the I-Bu conditioning regimen) at the end of consolidation (ASCT group), and 57 patients stopped therapy after consolidation alone (chemotherapy group) (Figure 1). To address potential temporal allocation bias arising from the long study period, we analyzed the distribution of diagnosis years between the treatment cohorts. As detailed in Supplementary Table S1, patients diagnosed before 2011 more frequently opted for the ASCT regimen. The treatment strategy (ASCT, consolidation chemotherapy, or allo-HSCT) was jointly determined by physician evaluation and patient preference after thorough clinical consultation. This decision was primarily influenced by the availability of HLA-matched donors, socioeconomic factors, and individual patient willingness.

The diagnostic criteria for AML were based on the 2022 World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia. Complete remission (CR) was defined by the following criteria: (1) <5% blasts in bone marrow; (2) no blasts in peripheral blood; (3) no extramedullary disease; (4) neutrophil count $\geq 1.0\times10^9$/L; platelet count $\geq 100\times10^9$/L.

According to the French–American–British (FAB) classification system, the distribution of FAB subtypes among all patients was as follows: M0 in 1 case (0.8%), M1 in 13 cases (11.2%), M2 in 71 cases (61.2%), M4 in 9 cases (7.7%), M4Eo in 3 cases (2.6%), M5 in 14 cases (12.1%), and M6 in 3 cases (2.6%). Two cases could not be classified due to insufficient data. Genetic risk stratification was performed based on the 2022 ELN guidelines: 64 patients were classified

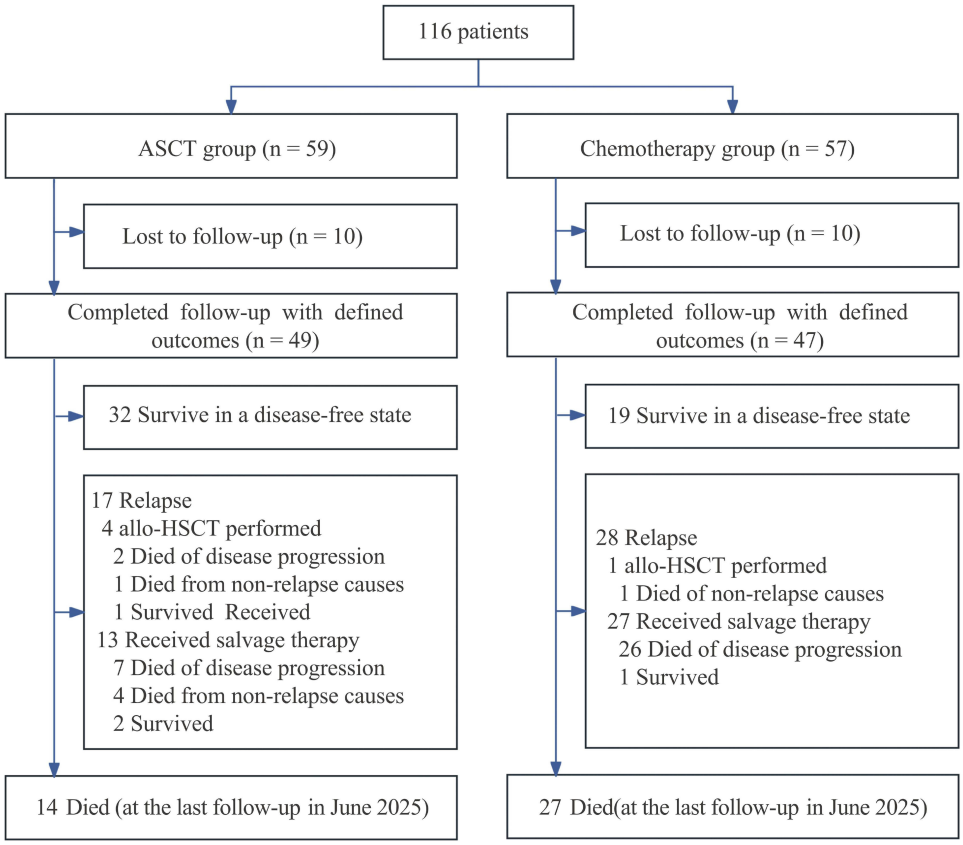

Figure 1 Grouping and follow-up outcomes for 116 patients.

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Table 1 Baseline Clinical Characteristics of the 116 AML Patients

Clinical Characteristics	ASCT Group (n=59)	Chemotherapy Group (n=57)	*P*
Age [years, median (range)]	36(14–62)	42(14–57)	<0.01
Gender [n (%)]			0.681
Male	28(47.5)	29(50.9)	
Female	31(52.5)	28(49.1)	
Type of AML (FAB)			0.436
M_0	1	0	
M_1	5	8	
M_2	35	36	
M_4	7	5	
M_5	10	4	
M_6	1	2	
Unclassifiable	0	2	
ELN risk stratification [n (%)]			0.316
Favorable [n (%)]	30(50.8)	34(59.6)	
CBF	19(32.2)	20(35.1)	
$NPM1^+/FLT3\text{-}ITD^-$	10(16.9)	1(1.8)	
$CEBPA^{bZIP\text{-}inf}$	2(3.4)	12(21.1)	
Intermediate [n (%)]	23(40.0)	23(40.4)	
$FLT3\text{-}ITD^+/NPM1^-$	1(1.7)	4(7.0)	
Cytogenetic karyotype			0.146
Normal	29	29	
Abnormal	24	27	
Cytogenetics and molecular mutations			
T(8;21)	13	16	0.449
inv(16) or t(16;16)	6	4	0.558
NPM1 mutation	10	5	0.219
CEBPA mutation	8	17	0.058
WBC [$\times 10^9$/L, median (range)]	12.17(1.2–484.6)	15.5(0.9–274)	0.235
HGB [$\times 10^9$/L, median (range)]	83.5(49–148)	87(46–129)	0.412
PLT [$\times 10^9$/L, median (range)]	35(4–272)	27(2–95)	0.168
LDH [$\times 10^9$/L, median (range)]	312(120–2020)	434(144–3226)	0.257

as favorable risk, 46 as intermediate risk. A total of 7 patients lacked cytogenetic metaphases at initial diagnosis. Among them, 1 patient was successfully classified into the favorable-risk group due to the presence of a CEBPA bZIP in-frame mutation. The remaining 6 patients lacked both cytogenetic and molecular marker data, and thus could not be categorized (unclassifiable). Among these, 29 patients had t(8;21), 10 had inv(16) or t(16;16), and 15 carried NPM1 mutations (Table 1).

Treatment Procedures

All the patients received standard IA induction therapy, consisting of idarubicin 12 mg/m^2 administered once daily by intravenous infusion on days 1–3, combined with Ara-C 100 mg/m^2 administered once daily by intravenous infusion on day 1–7. Consolidation therapy mainly consisted of intermediate- to high-dose cytarabine (2–3 g/m^2, twice daily by intravenous infusion on day 1–3). Specifically, the administered dosages were comparable between the two cohorts: in the ASCT group, 56 patients received 2 g/m^2 and 3 received 3 g/m^2; similarly, in the chemotherapy group, 54 received 2 g/m^2 and 3 received 3 g/m^2 (P = 1.000).

The ASCT group received 3–4 cycles of consolidation therapy with intermediate- or high-dose Ara-C regimen. After mobilization and collection of sufficient peripheral hematopoietic stem cells, ASCT was performed. The conditioning regimen prior to transplantation was I-Bu, consisting of idarubicin 20 mg/m^2/day administered as a 24-hour intravenous

infusion on day –13 to –11, combined with busulfan 0.8 mg/kg administered intravenously every 6 hours or 1 mg/kg administered orally every 6 hours on day –5 to –2. Phenytoin was given concomitantly for seizure prophylaxis. In the chemotherapy group, consolidation therapy also mainly consisted of intermediate- to high-dose Ara-C, with 3–4 courses administered. Therefore, the comparison in this study is essentially between the addition of ASCT at the end of consolidation versus stopping therapy after consolidation alone.

End Points

OS was defined as the time from the diagnosis of AML to death or last follow-up. DFS was defined as the time from the first complete remission after chemotherapy to disease progression, death, or last follow-up. The median follow-up time for the 116 patients was 79.5 months (range, 2~204 months), with the last follow-up date of June 2025. All data were obtained through medical record review and telephone follow-up.

Statistical Analysis

Statistical analysis was conducted using R version 4.3.3. The Kaplan-Meier method was used to describe OS and DFS, and comparisons were made using the Log rank test. Quantitative data were compared between groups using the rank-sum test, while qualitative data were compared using Fisher's exact test. Univariate and multivariate analyses were conducted using the Cox proportional hazards regression model. A two-sided test was applied, and $P<0.05$ was considered statistically significant.

Results

Patients

Among the 116 AML patients, the median age was 38.5 years (range, 14~61 years), including 59 females (50.9%) and 57 males (49.1%). The median follow-up for all the patients was 79.5 months (range, 2~204 months). The median durations of follow-up for the ASCT group and the chemotherapy group were 101 months (range, 7~204 months) and 43 months (range, 2~175 months), respectively. The median OS was not reached in either group.

Efficacy

After a median follow-up of 101 months for the ASCT group, the median OS was not reached. The median interval from diagnosis to ASCT was 6 months (range, 3~18 months). At the last follow-up in June 2025, among the 49 evaluable patients in the ASCT group, 35 were confirmed alive (Figure 1). Specifically, 32 patients remained in continuous CR. A total of 17 patients experienced relapse, with a median time to relapse of 6 months (range, 1~63 months) after transplantation. As shown in Figure 2F, the 2-year cumulative incidence of relapse was 23%, and the 10-year cumulative incidence was 26.7%. Among the 17 relapsed patients in the ASCT group, 3 achieved long-term survival. One patient achieved a second remission after receiving the CAG regimen, and subsequently underwent allo-HSCT. Another patient achieved remission again with salvage therapy of D-IA regimen (Decitabine, Daunorubicin and Ara-C) followed by consolidation treatment. A total of 4 relapsed patients eventually underwent allo-HSCT, of whom only 1 achieved long-term DFS. Nine patients died from disease relapse (15.3%), and 5 patients died from non-relapse causes. No early deaths (defined as death within 90 days after transplantation) were observed in the ASCT group.

In the ASCT group, 51 patients diagnosed after January 2010 had complete MRD data by multiparametric flow cytometry available. Only 6 patients (11.8%) were MRD-positive (>0.1%) before ASCT, while the remaining patients were negative. Among patients in CR_1 at the time of ASCT, no significant difference in outcomes was observed between MRD-positive and MRD-negative subgroups (P=0.56). A total of 49 patients had multiparametric flow cytology MRD data available at a median of 32 days after ASCT, all of whom were MRD-negative. Regarding the long-term clinical outcomes of these 6 patients with baseline MRD positivity: three maintained sustained continuous CR and were still alive at last follow-up. The other three patients experienced disease relapse. Among these three relapsed patients, one achieved long-term survival after salvage re-induction chemotherapy followed by allo-HSCT, one died of disease progression, and the last one died from non-relapse causes.

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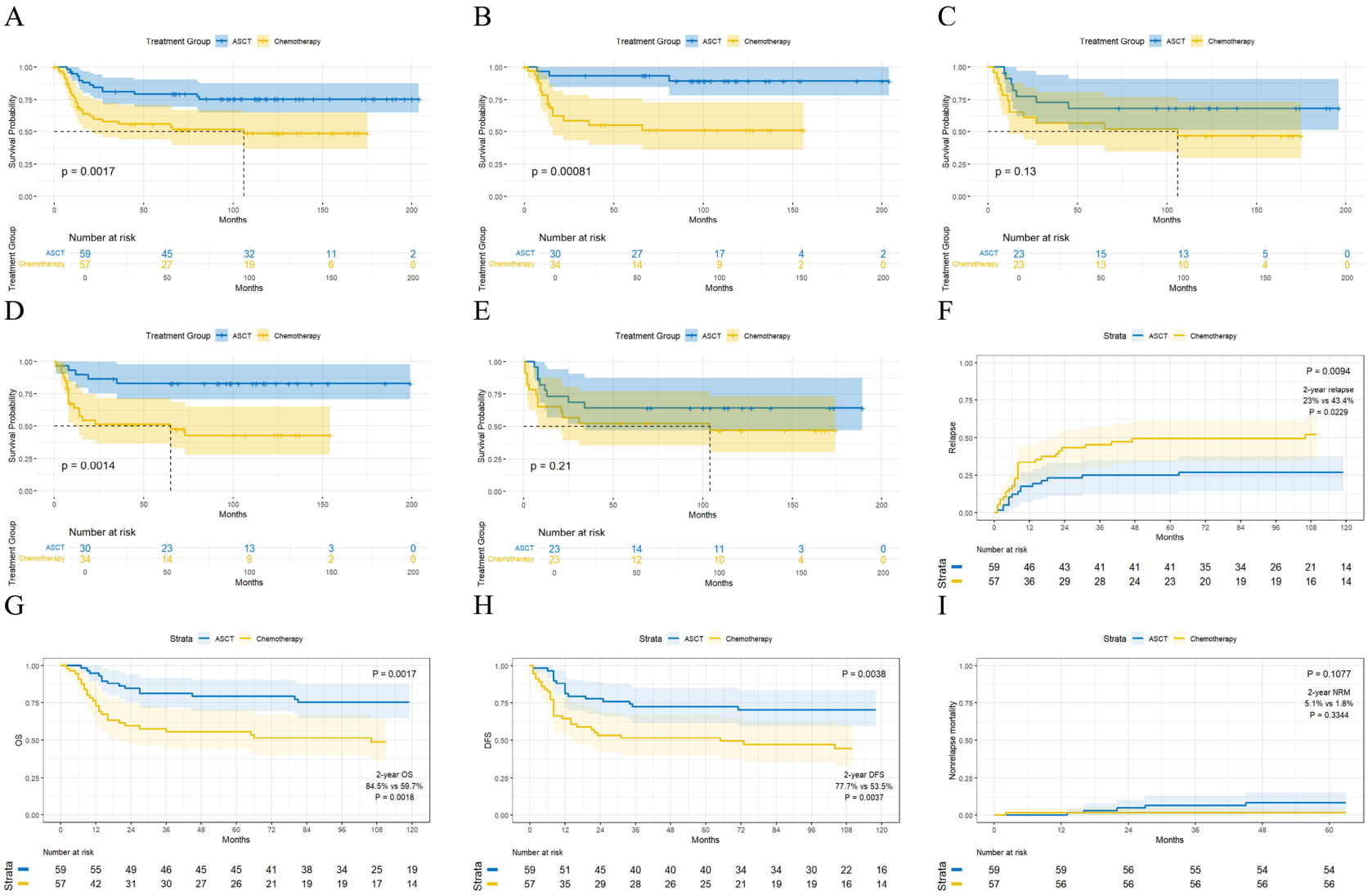

Figure 2 (A): OS in ASCT vs chemotherapy group. (**B**): OS in favorable-risk patients (ASCT vs chemotherapy). (**C**): OS in intermediate-risk patients (ASCT vs chemotherapy group). (**D**): DFS in favorable-risk patients (ASCT vs chemotherapy). (**E**): DFS in intermediate-risk patients (ASCT vs chemotherapy). (**F**): Relapse rates in ASCT vs chemotherapy groups. (**G**): OS rates in ASCT vs chemotherapy groups. (**H**): DFS in ASCT vs chemotherapy groups. (**I**): NRM in ASCT vs chemotherapy groups.

Furthermore, we specifically analyzed the pre-transplant MRD status of patients harboring CBF abnormalities or NPM1 mutations in the ASCT cohort. Among the 19 patients with CBF abnormalities, 4 lacked pre-ASCT MRD data, 4 were MRD-positive, and 11 were MRD-negative (including 1 patient with both a CBF abnormality and an NPM1 mutation). Among the 10 patients with NPM1 mutations, 1 was MRD-positive and 9 were MRD-negative prior to ASCT. Notably, out of the 6 total pre-ASCT MRD-positive patients in our cohort, 5 harbored defining genetic abnormalities (4 with CBF translocations/inversions and 1 with an NPM1 mutation). All of these patients successfully achieved MRD negativity after receiving the I-Bu conditioned ASCT.

After a median follow-up of 43 months, the median OS was not reached in the chemotherapy group. At the last follow-up in June 2025, the 2-, 5-, and 10-year OS rates were 59.7%, 55.8%, and 48.7%, respectively, while the corresponding DFS rates were 53.5%, 51.7%, and 44.5%. After excluding 10 patients lost to follow-up, 19 patients remained alive in continuous remission (Figure 1). A total of 28 patients experienced disease relapse, with a median time from CR_1 to relapse of 8 months (range: 1~106 months). Among the 28 relapsed patients, only 1 survived. This patient achieved remission after receiving re-induction chemotherapy with the IA regimen and continued consolidation treatment with medium-dose cytarabine combined with venetoclax. Among the relapsed patients, 1 eventually underwent allo-HSCT but later died due to septic shock. The other 26 patients died due to relapse (45.6%). As shown in Figure 2F, the cumulative incidence of relapse in chemotherapy group was 43.4% at 2 years and 52.2% at 10 years. The ASCT group demonstrated a sustained advantage in relapse control over time, with significantly lower relapse rates at both 2 years (23.0% vs 43.4%, P=0.0229) and 10 years (26.7% vs 52.2%, P=0.0094) compared to the chemotherapy group, with both differences being statistically significant.

Kaplan–Meier survival analysis showed that OS in the ASCT group was significantly better than that in the chemotherapy group (P=0.0017) (Figure 2A). The 2-year OS rates in ASCT and chemotherapy group were 84.5% and 59.7%, respectively (Figure 2G), with a statistically significant difference (P=0.0018). The 10-year OS rates in long-term follow-up also showed significant separation between the two groups (75.4% vs 48.7%, P=0.0017), suggesting that ASCT could provide durable survival benefit. During a median follow-up of 79.5 months, the ASCT group demonstrated a consistent advantage in DFS across both short- and long-term follow-up periods. The 2-year and 10-year DFS rates showed significant differences compared to the chemotherapy group, both statistically significant. The 2-year DFS rate in the ASCT group was 77.7%, significantly higher than the 53.5% in the chemotherapy group (P=0.0037; Figure 2H). After follow-up extended to 10 years, the ASCT group maintained its DFS advantage, with the difference persisting and remaining statistically significant compared to the chemotherapy group (P=0.0038). The 2-year non-relapse mortality (NRM) rate was not significantly different between the two groups (5.1% vs 1.8%, P=0.3344), and no significant difference was observed in long-term follow-up either (P=0.1077; Figure 2I).

According to 2022 ELN risk stratification criteria, compared with the chemotherapy group, OS (P<0.001) and DFS (P=0.0014) were significantly prolonged in favorable-risk AML patients undergoing ASCT (OS: not reached vs 29 months; DFS: not reached vs 19.5 months; Figure 2B,D). For intermediate-risk patients, the ASCT group showed a trend toward superior DFS and OS compared with the chemotherapy group, suggesting potentially better survival outcomes. However, differences in OS (P=0.13) and DFS (P=0.21) between the two groups did not reach statistical significance (Figure 2C,E).

We included age, sex, WBC count, hemoglobin at initial diagnosis, ELN risk stratification, core-binding factor (CBF; CBF vs non-CBF), and treatment modality (ASCT vs chemotherapy) in univariate analysis of all 116 patients. The forest plot (Figure 3) showed that age <39 years (median age), WBC count, hemoglobin, sex, CBF status (CBF vs non-CBF), and ELN risk stratification were not statistically significant. Notably, treatment modality had a significant impact on OS: patients receiving chemotherapy alone had a significantly higher risk of death compared with those receiving ASCT with the I-Bu conditioning regimen (HR=3.27, 95% CI: 1.58–6.77, P=0.0014). Multivariate Cox regression analysis (Figure 4) further demonstrated that treatment modality was an independent prognostic factor for OS, with ASCT conferring superior survival compared with chemotherapy (HR=3.12, 95% CI: 1.48–6.59, P=0.0028).

Subsequently, we conducted subgroup analyses within the ASCT group (n=59). Age, sex, ELN risk stratification, CBF status, WBC count, hemoglobin at diagnosis, and time from CR to ASCT were included in univariate analysis (Figure 5). Age was identified as an important predictor of prognosis, with younger patients showing better outcomes

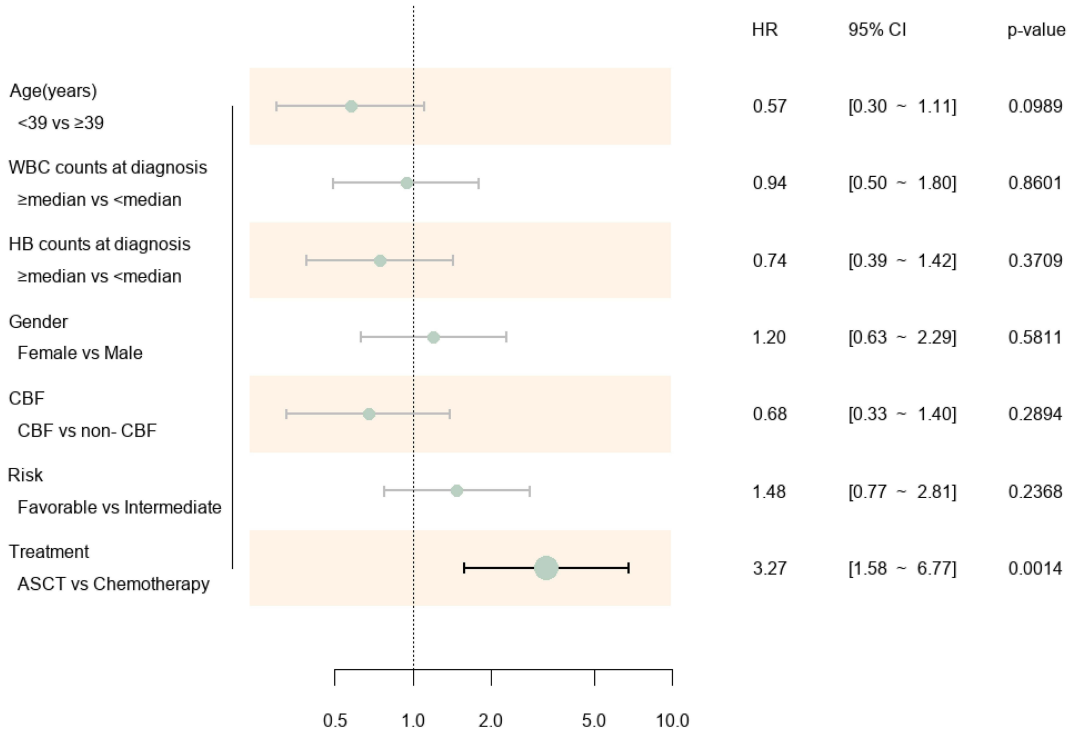

Figure 3 Univariate analysis of OS in 116 patients.

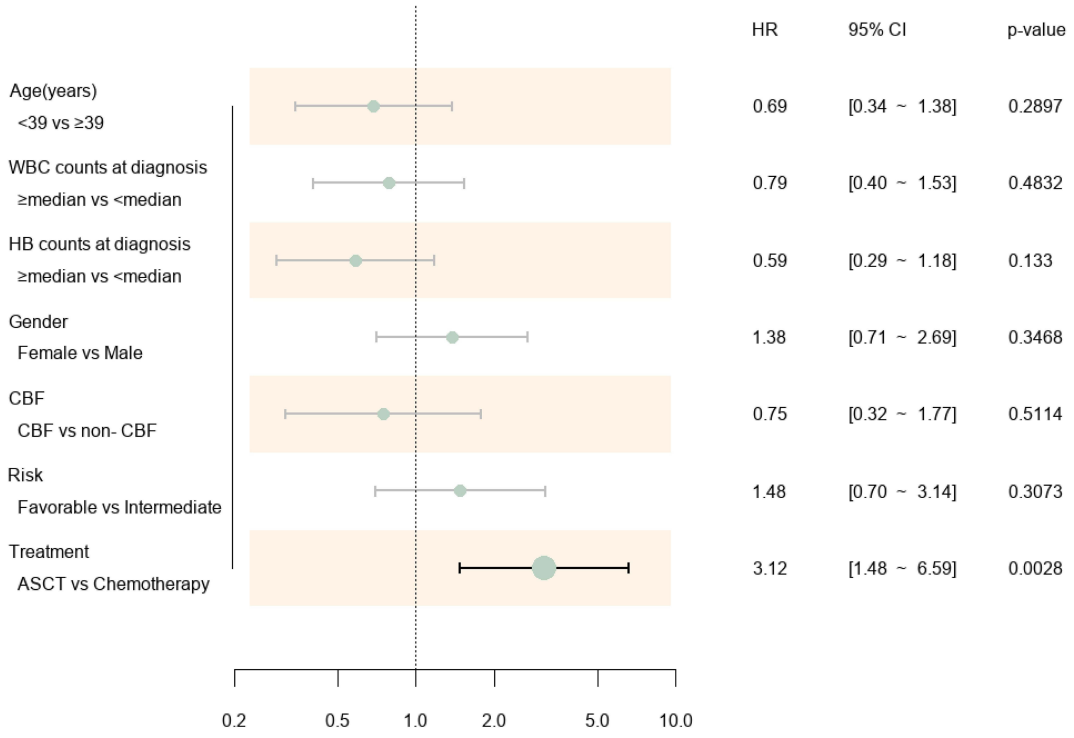

Figure 4 Multivariate analysis of OS in 116 patients.

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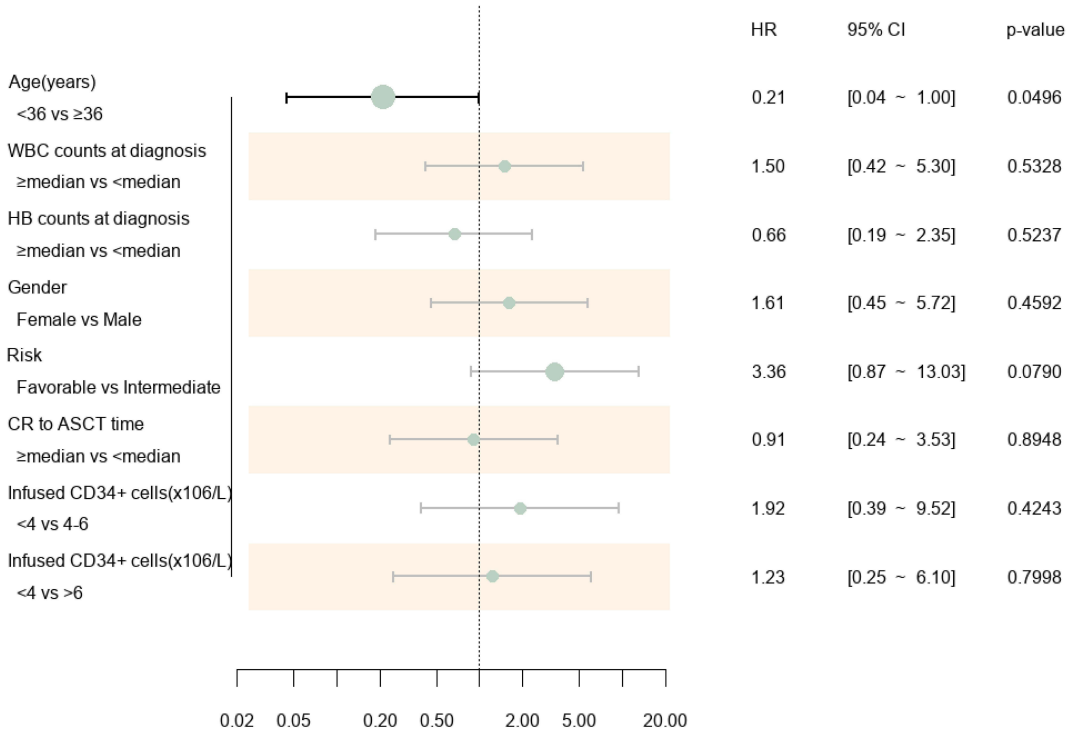

Figure 5 Univariate analysis of OS in the ASCT group.

(HR=0.21, 95% CI: 0.04–1.00, *P*=0.0496). After incorporating all aforementioned factors into a multivariate Cox analysis and adjusting for potential confounders, age emerged as an independent significant factor influencing recurrence, DFS, and OS in the ASCT group. Using the median age of ASCT patients (36 years) as a cutoff, patients aged <36 years demonstrated a significantly reduced risk of recurrence (HR=0.16, 95% CI: 0.04–0.71, *P*=0.016), with significantly prolonged DFS (HR=0.12, 95% CI: 0.03–0.56, *P*=0.007) and OS (HR=0.08, 95% CI: 0.01–0.53, *P*=0.0089) (Figure 6 and Table 2). Concurrently, risk stratification emerged as an independent significant factor influencing OS in the ASCT cohort. Compared with favorable-risk patients, intermediate-risk patients exhibited a markedly elevated risk of death (HR=7.78, 95% CI: 1.53–39.48, *P*=0.013), further confirming that favorable-risk patients derive greater benefit in the ASCT group. In the intermediate-risk patients among the ASCT subgroup, seven patients died. Among these, two died from relapse, one died from septic shock during re-induction therapy after relapse, and four patients died from causes unrelated to the disease. Factors such as gender, WBC count, hemoglobin at diagnosis, time from CR to ASCT, and $CD34^+$ cell infusion dose had no significant impact on relapse, DFS, or OS in the ASCT group (*P*>0.05).

Adverse Events

All the patients in the ASCT group achieved successful hematopoietic reconstitution after transplantation. The median time to sustained recovery of neutrophils $\geq 0.5\times10^9$/L and platelets $\geq 20\times10^9$/L were 11 days (range, 9~13) and 13 days (range, 12~16), respectively. All patients in the ASCT group experienced severe myelosuppression and hematologic toxicity (Table 3). A total of 47 patients (79.7%) developed fever after ASCT, including 27 cases of grade 1, 15 cases of grade 2, and only 4 cases of grade 3–4. Causes of fever included fever of unknown origin (3.4%), respiratory tract infection (11.9%), gastrointestinal infection (10.2%), urinary tract infection (1.7%), bacterial sepsis (6.8%), and fungal sepsis (6.8%). Oral mucositis, nausea/vomiting, and diarrhea were also common, with incidences of 44.1%, 28.8%, and 18.6%, respectively. These were all grade 1–3 and improved after anti-infective and symptomatic treatment. Importantly, no severe (grade 3–4) cardiovascular adverse events were observed either during the ASCT procedure or throughout the entire long-term follow-up period.

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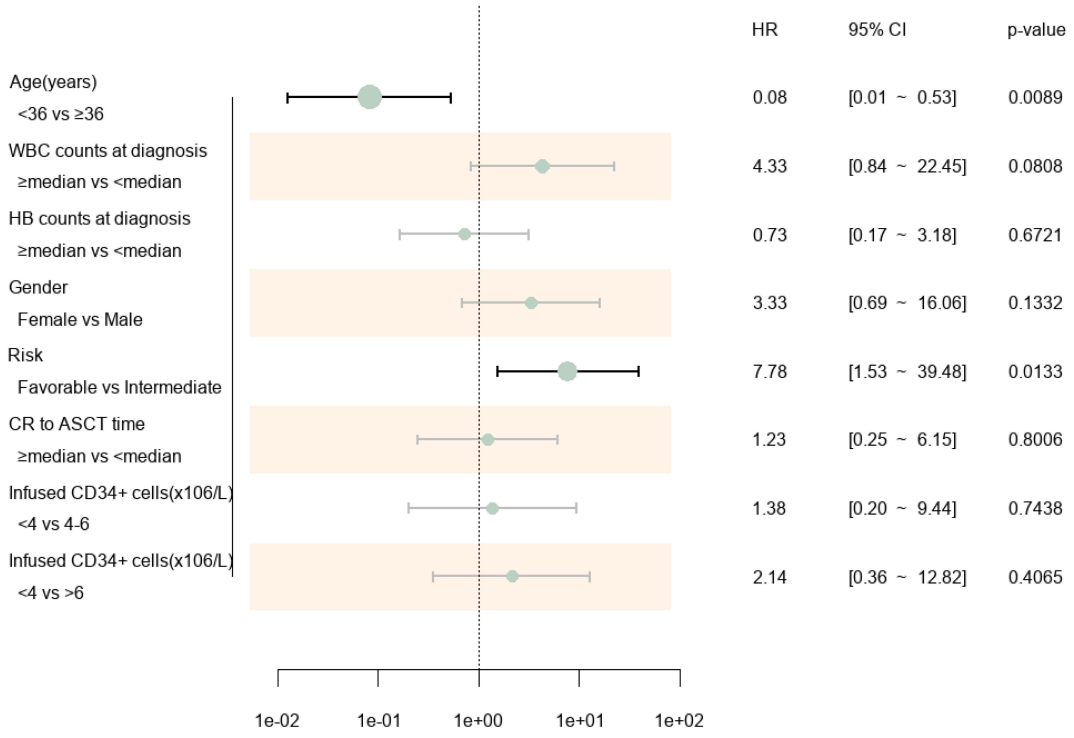

Figure 6 Multivariate analysis of OS in the ASCT group.

In the chemotherapy group, the main adverse events during consolidation chemotherapy were fever of varying degrees due to neutropenia, nausea/vomiting, rash, and diarrhea. Similarly, no severe non-hematologic adverse events were observed. Furthermore, no severe neurological toxicities, including cytarabine-induced cerebellar toxicity in either cohort or busulfan-related seizures in the ASCT cohort, were observed.

Discussion

The efficacy of ASCT may be influenced by various factors, including conditioning regimen, age, cytogenetics, and molecular biology.[17] In the I-Bu regimen, high-dose idarubicin was used instead of cyclophosphamide, which significantly enhanced anti-leukemic activity, reduced relapse rates, and alleviated immunosuppression. This regimen was designed and first reported by Ferrara et al.[14] Overall, our long-term results demonstrated that I-Bu conditioned ASCT provided significantly superior OS and DFS compared to consolidation chemotherapy alone for patients in CR_1, while maintaining a comparable NRM and a manageable safety profile.

In this study, after a median follow-up of 79.5 months (range, 2~204 months), the median OS was not reached in either ASCT group or chemotherapy-only group. The 2-year OS and DFS rates were significantly higher in the ASCT group than in the chemotherapy group. With longer follow-up, OS and DFS in the ASCT group remained significantly superior to those in the chemotherapy group, indicating a sustained anti-leukemic effect of ASCT. Multiple retrospective cohorts, including large registry studies from the GITMO group[18] and Israeli centers,[4] have consistently demonstrated favorable long-term survival and acceptable non-relapse mortality with ASCT in CR_1 compared with chemotherapy. Prospective evidence further supports its role, as the GIMEMA AML1310 MRD-directed trial showed that ASCT retains significant benefit in MRD-negative favorable- and intermediate-risk AML patients.[19] The 6-year update of this trial confirmed long-term advantages of employing a risk-adapted, MRD-driven strategy to guide post-remission treatment decisions.[20] The low cumulative incidence of relapse observed in our study (from 23.0% at 2 years to 26.7% at 10 years) further supports the potent anti-leukemic efficacy of high-dose idarubicin in the conditioning regimen.[21] This rate compares favorably to historical data from large European registry series. For instance, Czerw et al reported a relapse incidence ranging from 40% to 45% for AML patients autografted in CR_1. Similarly, in a large EBMT analysis

Table 2 Risk Factors for Relapse and Survival in the ASCT Group

	Relapse			DFS			OS		
	Univariate	Multivariate		Univariate	Multivariate		Univariate	Multivariate	
	p	HR (95% CI)	p	p	HR (95% CI)	p	p	HR (95% CI)	p
Age (years) <36 vs ≥36	0.058	0.16 (0.04–0.71)	0.016	0.033	0.12 (0.03–0.56)	0.007	0.049	0.08 (0.01–0.53)	0.009
WBC count at diagnosis ≥median vs <median	0.530	3.18 (0.81–12.50)	0.098	0.742	2.92 (0.75–11.33)	0.121	0.533	4.33 (0.84–22.45)	0.081
HB count at diagnosis ≥median vs <median	0.514	1.49 (0.40–5.47)	0.552	0.769	1.08 (0.30–3.88)	0.905	0.524	0.73 (0.17–3.18)	0.683
Gender Female vs Male	0.872	1.89 (0.52–6.85)	0.336	0.665	2.05 (0.58–7.22)	0.264	0.460	3.33 (0.69–16.06)	0.131
Risk Favorable vs Intermediate	0.233	2.94 (0.82–10.54)	0.098	0.146	3.83 (1.06–13.78)	0.040	0.079	7.78 (1.53–39.48)	0.013
CR to ASCT time ≥median vs <median	0.854	1.31 (0.36–4.68)	0.682	0.589	1.67 (0.49–5.67)	0.409	0.895	1.23 (0.25–6.15)	0.804
Infused CD34+ cells ($\times 10^6$/kg) <4 vs 4-6	0.684	1.10 (0.20–6.01)	0.910	0.722	1.02 (0.18–5.81)	0.983	0.424	1.38 (0.20–9.44)	0.742
Infused CD34+ cells ($\times 10^6$/kg) <4 vs >6	0.835	0.98 (0.20–4.72)	0.977	0.742	1.01 (0.21–4.86)	0.985	0.800	2.14 (0.36–12.82)	0.413

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Table 3 Adverse Events in the ASCT Group and Chemotherapy Groups

Adverse events	ASCT Patients (%)	Chemotherapy Patients (%)
Grade 3–4 myelosuppression	59(100)	57(100)
Fever (unknown origin)	2(3.4)	7(12.3)
Fever (documented infection)	45(76.3)	45(78.9)
Pulmonary	7(11.9)	20(35.1)
Gastrointestinal	6(10.2)	4(7.0)
Hepatic	1(1.7)	0(0.0)
Oral	4(6.8)	5(8.8)
Urinary tract	1(1.7)	0(0.0)
Skin and soft tissue infection	1(1.7)	2(3.5)
Sepsis	4(6.8)	7(12.3)
Fungal infection	4(6.8)	8(14.0)
Nausea/vomiting	17(28.8)	12(21.1)
Rash	8(13.6)	8(14.0)
Oral mucositis	26(44.1)	3(5.3)
Diarrhea	11(18.6)	5(8.8)
Bleeding	6(10.2)	11(19.3)

evaluating preparative regimens, the 3-year relapse incidence was 48.7% overall, and 39.5% specifically for patients receiving busulfan combined with melphalan.

Multivariate analysis for the entire cohort (n=116) identified ASCT with the I-Bu regimen as the sole independent predictor of improved OS. Forest plot analysis of the 59 patients in the ASCT group suggested that the efficacy of ASCT may be influenced by age and risk stratification. In our ASCT cohort, multivariate analysis identified younger age as a favorable independent prognostic factor for both relapse reduction and survival. This is highly consistent with large-scale EBMT registry data, which demonstrated that younger AML patients undergoing ASCT in CR_1 achieve significantly superior overall survival, leukemia-free survival, and lower non-relapse mortality. This suggests that age should be a critical consideration when selecting candidates for ASCT.[22] Despite the relatively small sample size, no significant difference in flow cytometry–based MRD status was observed among patients in CR_1 prior to ASCT in this study, which may be due to the enhanced anti-leukemic effect of ASCT partially offsetting the adverse impact of MRD positivity. All 6 patients who were MRD-positive before ASCT became MRD-negative at a median of 32 days after ASCT. This further supports its feasibility as a consolidation therapy.

Compared with chemotherapy alone, ASCT improved OS and DFS in favorable-risk patients. However, in intermediate-risk AML patients, no statistically significant differences were observed between ASCT and chemotherapy in terms of OS or DFS. Currently, the optimal treatment strategy for intermediate-risk AML patients after achieving CR_1 remains controversial. By contrast to favorable-risk disease, intermediate-risk AML exhibits pronounced biological heterogeneity, encompassing a broader spectrum of cytogenetic and molecular abnormalities. In our study, the lack of a significant survival benefit in the intermediate-risk subgroup likely reflects this inherent biological complexity. Molecular characterization during the study period was primarily based on conventional cytogenetic analysis and limited Sanger sequencing methods, rather than comprehensive next-generation sequencing panels. Consequently, the exact role of I-Bu conditioned ASCT in this specific population cannot be definitively established from our current data. Future prospective, multicenter studies incorporating comprehensive genomic annotations are required to precisely define the optimal post-remission strategy for molecularly defined intermediate-risk AML.

Gorin et al[11] demonstrated that replacing cyclophosphamide with melphalan (BuMel) significantly improved survival in high-risk patients. While BuMel maintained an acceptable NRM of approximately 5%, its toxicity profile was noted to be primarily characterized by mucositis. Although idarubicin is associated with known cardiotoxicity, no severe (Grade 3–4) cardiac adverse events were observed during ASCT or throughout the subsequent follow-up period. Similarly, no busulfan-related neurotoxicity, such as seizures, occurred, owing to effective prophylaxis. This demonstrates that high-

dose idarubicin can enhance anti-leukemic efficacy while maintaining a favorable safety profile. In our study, oral mucositis was a frequent adverse event, occurring in 44.1% of the patients. However, it is crucial to note that this mucosal toxicity was confined to grades 1–3 and was effectively managed with standard supportive and anti-infective care, without any grade 4 occurrences. Furthermore, the 2-year NRM in our I-Bu cohort was 5.1%, which aligns closely with the established safety profiles of BuCy (5.2%) and BuMel (5–7.3%) reported in the aforementioned studies. Therefore, the additional clinical value of the I-Bu regimen lies in its capacity to deliver profound, long-term disease control for favorable- and intermediate-risk AML patients while maintaining a predictable and manageable mucosal toxicity profile.

This study was a single-center retrospective analysis with a relatively small sample size, and potential selection and confounding biases cannot be excluded, as patients experiencing severe toxicities during initial consolidation were naturally ineligible for subsequent ASCT. Although the earlier diagnosis dates of the ASCT cohort introduce potential era bias, standard cytarabine consolidation remained unchanged during this period. While this difference in diagnosis periods cannot be entirely excluded as a confounding factor, given that the chemotherapy cohort received more modern supportive care yet still demonstrated inferior survival, the observed survival advantage in the ASCT group is unlikely to be fully explained by era differences alone. In addition, since all patients in our study were young, the safety of this regimen in elderly AML patients still needs to be validated. Due to the small sample size and the lack of next generation sequencing data, the relationship between specific molecular characteristics and prognosis was not analyzed in the ASCT cohort. Prospective randomized controlled trials are warranted to validate these findings.

Despite these limitations, our results provide long-term follow-up evidence for the prognostic value of I-Bu conditioned ASCT in AML patients, which warrants further validation in future multicenter prospective studies. While the I-Bu conditioning regimen followed by ASCT offers a robust and durable consolidation strategy for favorable- and intermediate-risk patients, we acknowledge that it does not address the unmet clinical needs of patients with poor-risk AML. For this high-risk population, ASCT is generally insufficient, and novel therapeutic modalities—such as targeted therapies, advanced cellular immunotherapies, or early allo-HSCT—remain urgently required. Furthermore, the development of novel targeted agents—such as venetoclax-based regimens,[23] along with IDH,[24] menin,[25] and FLT3 inhibitors[26,27]—has significantly improved the remission rates and survival outcomes for AML patients harboring specific genetic mutations. Consequently, the clinical value of ASCT during CR_1 for this specific patient subset requires careful re-evaluation. Moving forward, the decision to proceed with ASCT should be highly individualized, comprehensively integrating the inherent disease biology, dynamic MRD levels, patient age, and overall performance status. Ultimately, the definitive role of ASCT in the current era of targeted therapy remains to be further validated through prospective clinical studies.

Conclusion

The I-Bu conditioning regimen combined with ASCT is safe for post-remission treatment in young favorable- to intermediate-risk AML patients and might provide superior survival benefits compared with intermediate- to high-dose Ara-C consolidation. These findings may serve as a reference for clinical practice.

Data-Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics Approval and Consent to Participate

Approval was obtained from the Institutional Review Board of Nanjing Medical University, with the approval number 2026-SR-060. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. This was a retrospective clinical study, and informed consent was waived on account of anonymized patient data.

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Disclosure

No potential conflict of interest was reported by the authors.

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