A novel and safe protocol for patients with severe comorbidity who undergo haploidentical hematopoietic stem cell transplantation: A single-center prospective study

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ABSTRACT

Background and Objectives: Haploidentical stem cell transplantation (haplo-HSCT) has demonstrated promising results in patients without severe comorbidities. There is also an increasing need for haplo-HSCT in patients with severe comorbidities. However, the high risk of treatment-related mortality (TRM) hindered its extensive application. We aimed to investigate a novel conditioning regimen (Bu/Flu/Cy/ATG) followed by haplo-HSCT in patients with severe comorbidities. **Methods:** This prospective, single-arm clinical trial was performed at Peking University Institute of Hematology, China. Patients were enrolled if they were (1) diagnosed with acute leukemia, myelodysplastic syndrome (MDS), or chronic myelomonocytic leukemia (CMML); (2) patients with no HLA-matched sibling donor or matched unrelated donor available but with a haplo-HSCT donor; (3) patients with hematopoietic cell transplantation comorbidity index (HCT-CI) scores ≥3. The primary endpoint was 2-year TRM. **Results:** From June 2018 to November 2022, a total of 72 patients were enrolled. All patients achieved neutrophil engraftment. The cumulative incidence of grade II–IV acute graft-versus-host disease (aGVHD) at day 100 was 20.8%. The cumulative incidences of cytomegalovirus (CMV) viremia and Epstein–Barr (EB) viremia at day 100 were 72.2% and 31.9%, respectively. The cumulative incidence of 2-year TRM was 25.1%. The cumulative incidence of 2-year relapse was 8.6%. The probabilities of 2-year overall survival and leukemia-free survival were 71.9% and 65.6%, respectively. **Conclusion:** This study suggested that a novel conditioning regimen followed by haploidentical HSCT might be a promising option for patients with severe comorbidities. The study was registered as a clinical trial (NCT03412409).

Key words: conditioning regimen, haploidentical hematopoietic stem cell transplantation, hematopoietic cell transplantation comorbidity index

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective treatment option for hematologic malignancies. When matched sibling donors (MSDs) or unrelated donors (URDs) are not available, haploidentical hematopoietic stem cell transplantation (haplo-HSCT) is a viable and popular option that has been increasingly utilized in recent years. It has been demonstrated that haplo-HSCT can achieve similar or superior clinical outcomes compared to MSD or URD allo-HSCT.[1,2] It is remarkable that most patients who received haplo-HSCT in the early days were young patients or patients without severe comorbidities due to the concern that

patients with comorbidities or older age have a higher risk of treatment-related mortality (TRM) post-hematopoietic stem cell transplantation (HSCT).[3,4] In fact, there is an unmet need for transplantation for this population.

The major concern of this latter population is increased transplant-related toxicity. The ways to address high TRM in these patients include optimizing conditioning regimens, reducing graft-versus-host disease (GVHD), and preventing and treating infections. The current research mainly focuses on improving conditioning regimens. In classical busulfan (Bu) /cyclophosphamide (Cy) conditioning, Cy is considered one of the most significant agents related to regimen-related toxicity.[5] Fludarabine (Flu) has been widely used to reduce regimen-related toxicity by replacing Cy with Flu.[6,7] A study from Peking University demonstrated that in patients with severe comorbidities, a modified Bu/Flu regimen was well tolerated and safe for use with human leukocyte antigen (HLA)-identical sibling transplantation.[8] Sung-Eun Lee *et al.* analyzed patients with old age and/or co-morbidities who received HLA-identical allo-HSCT with Flu/Bu/ total body irradiation (TBI) 400 cGy conditioning regimen. The estimated 2-year rates of overall survival (OS), event-free survival, transplantation-related mortality, and relapse were 66%, 63%, 26%, and 16%,[9] suggesting that this conditioning regimen may be a feasible therapeutic approach for acute myeloid leukemia (AML) with old age and/or co-morbidities. So far, there are no studies aiming at reducing TRM in patients with comorbidities who received haplo-HSCT. In a prospective single-arm phase 2 study conducted by our team, a novel conditioning regimen Bu/Flu/Cy/anti-thymocyte globulin (ATG) followed by haplo-HSCT was safe and feasible in older patients.[10] There is currently no data available on whether this conditioning regimen is safe and will reduce TRM in patients with hematopoietic cell transplantation comorbidity index (HCT-CI) score ≥ 3. In this prospective, single-arm, observational clinical study, we aimed to explore the efficacy and safety of this novel Bu/Cy/Flu/ATG conditioning regimen in patients with comorbidities.

METHODS

Patient enrollment

This single-arm prospective study was performed at the Peking University People's Hospital, China. The inclusion criteria were as follows: (1) patients diagnosed with acute leukemia, chronic myeloid leukemia, myelodysplastic syndrome (MDS), or chronic myelomonocytic leukemia (CMML); (2) patients with no HLA-MSD or matched URD available but with a haplo-HSCT donor; (3) patients with HCT-CI scores ≥3 but eligible for transplantation after being evaluated by a physician; and (4) patients who signed their informed consent. The exclusion criteria were (1) pregnancy; (2) active infection without control; (3) enrollment in other clinical trials within 1 month; (4) other contradictions to HSCT; and (5) no informed consent. This study was approved by the Ethics Committee of Peking University People's Hospital. All patients provided written informed consent before enrollment. The study was registered as a clinical trial (ClinicalTrials. gov: NCT03412409).

Pretransplant comorbidities assessment

Comorbidities were assessed by a comprehensive review according to the HCT-CI classification.[11] Patients with HCT-CI scores ≥ 3 were selected based on the results of these assessments.

Transplant Regimens

Donor selection and HLA typing were previously described in detail.[12] The preconditioning regimen consisted of cytarabine (2 g/m^2/day, -10 to -9 days), Bu (3.2 mg/kg/day, -8 to -6 days), Flu (30 mg/m^2/day, -6 to -2 days), Cy (1.0 g/m^2/day, -5 to -4 days), semustine (250 mg/m^2, -3 days), and rabbit ATG (2.5 mg/kg, -5 to -2 days; Sanofi, France). All recipients received granulocyte colony-stimulating factor (G-CSF)-mobilized bone marrow and/or peripheral blood-derived stem cells. All patients received cyclosporine A, mycophenolate mofetil, and short-term methotrexate for GVHD prophylaxis.[13-15] Prophylaxis and treatment of cytomegalovirus (CMV) infection after haplo-HSCT were performed as described previously.[16,17] Ganciclovir was administered during conditioning (through day-2) and acyclovir (400 mg twice a day) was given until the discontinuation of all immunosuppressive agents. Due to its launch in China in August 2022, patients receiving haplo-HSCT after August 2022 were treated with letermovir for CMV prophylaxis. Patients also received prophylactic posaconazole to prevent infection by fungi.

Endpoints and definitions

The primary endpoint was the 2-year TRM. The secondary endpoints were regimen-related toxicity, engraftment, acute graft-versus-host disease (aGVHD), CMV reactivation, Epstein-Barr virus (EBV) reactivation, relapse, OS, and leukemia-free survival (LFS). According to the design of this study, regimen-related toxicity, engraftment, aGVHD, CMV reactivation, and EBV reactivation were the safety evaluation indicators.

Myeloid engraftment was defined as the first day of an absolute neutrophil count (ANC) of 0.5 × 10^9/L or more for three consecutive days, and platelet engraftment was defined as the first day of a platelet count of 20 × 10^9/L or more for seven consecutive days without transfusion. aGVHD was graded according to the modified Glucksberg criteria[18] and the National Institutes of Health (NIH)

classification.[19] CMV and EBV viremia were defined as the first of two consecutive detections in which virus DNA reached or exceeded 1000 copies/mL and 500 copies/mL, respectively. Relapse was defined as the reappearance of blasts in the blood, bone marrow (BM, > 5%) or any extramedullary site after complete remission (CR). TRM was defined as death after HSCT without disease progression or relapse. LFS was defined as the time from transplantation to relapse, disease progression, or death, whichever occurred first. OS was defined as the time from transplantation to death from any cause. Regimen-related toxicity was assessed using the Bearman toxicity score.[20]

Statistical analysis

Demographic and clinical characteristics were described and compared using the chi-square and Fisher's exact tests for dichotomous variables. Survival probabilities were estimated by means of the Kaplan-Meier method. The multivariate Cox proportional model and survival analysis were calculated with SPSS software (SPSS 22.0, Chicago, IL, USA). Competing risk analyses were used to calculate the cumulative incidence of engraftment, GVHD, relapse, and TRM using the Gray test.[21] Hazard ratios (HRs) for OS were estimated from univariate and multivariate Cox regression analyses. All of the factors with $P < 0.1$ in the univariate analysis were included in a multivariate regression, and $P < 0.05$ was considered to be statistically significant. All of the reported P values were based on two-sided hypothesis tests. Data analyses were primarily conducted with SPSS software (SPSS Inc., Chicago, IL), and R software (version 2.6.1; http: //www.r-project.org) was used for competing risks analysis. The sample size was calculated according to the assumption that the 2-year TRM for patients with an HCT-CI score of ≥ 3 was approximately 34% on the basis of published data.[3,4] The null hypothesis was a 2-year TRM of 34%, and the alternative hypothesis was a 2-year TRM of 25% with the Bu/Cy/Flu/ATG regimen. The noninferiority margin was set to 0.09. Enrollment of 72 patients would provide 90.08% power to test the null hypothesis with a one-sided significance of 2.5%.

RESULTS

Patient characteristics

A total of 72 patients were enrolled in our study, including 40 males and 32 females. The median age was 52 (18-66) years old. The underlying disease included 33 patients of AML, 20 patients of MDS, 16 patients of acute lymphoblastic leukemia (ALL), and 3 patients of CMML. The most common comorbidities among these patients were prior solid malignancy (36.1%) and infection which could be controlled before transplantation (29.2%), followed by moderate pulmonary disease (25.0%), severe pulmonary disease (23.6%), and diabetes (20.8%). The HCT-CI scores of the patients were 3, 4, 5, 6 and 7, with 45 (62.5%), 20 (27.8%), 5 (6.9%), 1 (1.4%) and 1 (1.4%) patients, respectively. The median follow-up time of the survivors was 439 days (ranging from 98 to 1435 days). The baseline clinical characteristics of the patients are shown in Table 1. A detailed list of basic information regarding the age, sex, and HCT-CI scores of all enrolled patients is shown in Supplementary Table 1.

Engraftment, GVHD and infection

All of the patients achieved neutrophil engraftment. The median time of neutrophil engraftment was 13 (10-33) days. However, 3 (4.2%) patients did not achieve platelet engraftment due to a TRM, and another one (1.4%) patients did not achieve platelet engraftment till the last follow-up. The median time of platelet engraftment was 15 (9-163) days.

A total of 26 patients (36.1%) had acute GVHD. The median onset time of aGVHD was 29 (13-269) days after transplantation. The cumulative incidence of grade II-IV aGVHD and grade III-IV aGVHD at day 100 post-HSCT was 20.8% (Figure 1A) and 5.6% (Figure 1B), respectively.

CMV viremia was observed in 54 (75.0%) cases, with a median onset time of 37 (21-146) days post-HSCT. The cumulative incidence of CMV viremia at day 100 post-HSCT was 72.2%, as shown in Figure 1C. Additionally, 24 (33.3%) cases experienced EBV reactivation, with a median onset time of 50 (34-172) days post-HSCT. The cumulative incidence of EBV reactivation at day 100 post-HSCT was 31.9%, as shown in Figure 1D. Among the 24 patients who experienced EBV reactivation, 10 (13.9%) patients presented with EBV post-transplant lymphoproliferative disease (PTLD).

Regimen-related toxicity (RRT)

Within 30 days post transplantation, 86.1% of the patients exhibited varying degrees of RRT). Of these patients, 50% experienced gastrointestinal toxicity, with 33 cases of grade I and 3 cases of grade II. Additionally, 62.5% of patients experienced hepatic toxicity, with 24 cases of grade I and 21 cases of grade II. Cardiac toxicity was observed in 13.9% of patients, with 1 case of grade I, 8 cases of grade II and 1 case of grade III. Some patients experienced grade I renal (16.7%) and stomatitis-related (18.1%) toxicity, while 2.8% of patients developed grade II bladder toxicity. For more detailed information, please refer to Table 2.

Clinical outcomes

The last follow-up was on April 9, 2023. Sixteen of the patients died during this study. The primary cause of death was infection, which accounted for 9 cases, followed

Table 1: The baseline clinical characteristics of the patients with HCT-CI ≥ 3

Characteristics	Parameters
Patient age at HSCT, median (range), yr	52 (18-66)
Patient sex, male/female, *n* (%)	42 (58.3)/30 (41.7)
Disease, *n* (%)	
AML	33 (45.8)
ALL	16 (22.2)
MDS	20 (27.8)
CMML	3 (4.2)
Disease	
AML	
CR1/CR2/ ≥ CR3/NR or relapse	28/2/0/3
ALL	
CR1/CR2/ ≥ CR3/NR or relapse	11/5/0/0
MDS	
Low/int-1/int-2/high	0/6/13/1
CMML	
Low/int-1/int-2/high	1/0/1/1
Disease risk index (low/Intermediate/high)	9/45/18
HCT-CI, *n* (%)	
3	45 (62.5)
4	20 (27.8)
≥5	7 (9.7)
Comorbidity, *n* (%)	
Obesity	0
Pulmonary-morderate	18 (25.0)
Pulmonary-severe	17 (23.6)
Infection	21 (29.2)
Arrhythmia	3 (4.2)
Diabetes	15 (20.8)
Cerebrovascular	8 (11.1)
Hepatic-mild	6 (8.3)
Hepatic-moderate/severe	5 (6.9)
Rheumatologic	1 (1.4)
Peptic ulcer	0
Renal	1 (1.4)
Prior solid malignancy	26 (36.1)
Cardiovascular	4 (5.6)
Heart valve disease	2 (2.8)
Inflamatory bowel disease	0
Depression/anxiety	1 (1.4)
Donor-recipient ABO blood type, *n* (%)	
Match	37 (51.4)
Mismatch	35 (48.6)
Donor sex, male/female, *n* (%)	45 (62.5)/27 (37.5)
Source of stem cell, *n* (%)	
Bone marrow and peripheral blood	22 (30.6)
Peripheral blood	50 (69.4)
Letermovir in CMV prophylaxis	
Yes	9 (12.5)
No	63 (87.5)
DLI or maintenance therapy post-transplant	
DLI	3 (4.1)
Interferon	2 (2.8)
No intervention	67 (93.1)
MNC, 10^8/kg, median (range)	8.79 (5.56-20.18)
CD34, 10^6/kg, median (range)	3.21 (0.83-14.10)

(To be continued)

(Continued)

HSCT: hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: Acute myeloid leukemia; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia; HCT-CI: hematopoietic cell transplantation comorbidity index; MNC: mononuclear cells; CMV: cytomegalovirus; DLI: donor lymphocyte infusion.

by transplant-related thrombotic microangiopathy with 4 cases. There was also 1 case each of relapse, cerebral hemorrhage, and myocardial infarction. The cumulative incidence of 30-day, 100-day, 1-year and 2-year TRM was 0%, 4.2%, 21.4% and 25.1%, respectively (Figure 2A). The cumulative incidence of 2-year relapse was 8.6%, as depicted in Figure 2B. The probabilities of 2-year OS and LFS were 71.9% and 65.6%, respectively, as shown in Figure 2C-D. The main clinical outcome was then analyzed according to disease type. The 2-year TRM of acute leukemia and non-acute leukemia (MDS or CMML) were 21.6% and 34.7% (P = 0.093), and the 2-year cumulative incidence of relapse (CIR) were 10.3% and 4.5% (P = 0.438), respectively. The 2-year OS was 75.2% and 64.3%, respectively (P = 0.133). The 2-year LFS was 67.1% and 60.5%, respectively (P = 0.251; Figure 3A-D).

Univariate analysis, including age, sex, HCT-CI score, underlying diseases (acute leukemia or nonacute leukemia), disease risk index, donor sex, ABO blood type, source of stem cells (bone marrow plus peripheral blood *vs.* peripheral blood), and grafts (mononuclear cell count and $CD34^+$ cell count), was performed for all patients. The results of the univariate analysis showed that no factors were associated with TRM, LFS, OS, or CIR.

DISCUSSION

For the first time in a prospective study, we have shown that the modified Bu/Cy/Flu/ATG reduced-toxicity

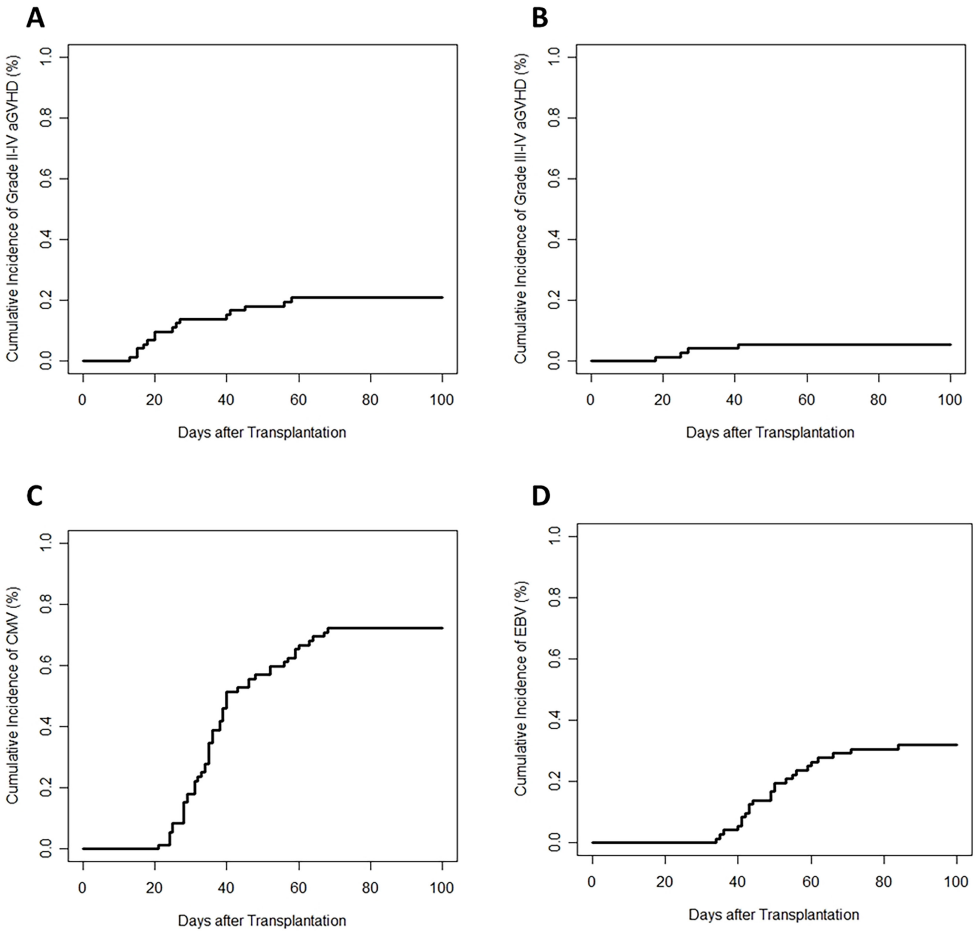

Figure 1: GVHD and virus infection. (A) The cumulative incidence of grade II-IV aGVHD at day 100 post-HSCT. (B) The cumulative incidence of grade III-IV aGVHD at day 100 post-HSCT. (C) The cumulative incidence of CMV viremia at day 100 post-HSCT. (D) The cumulative incidence of EBV reactivation at day 100 post-HSCT. aGVHD: acute graft-versus-host disease; GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; CMV: cytomegalovirus; EBV: Epstein-Barr virus.

conditioning regimen followed by haplo-HSCT is a viable option for patients with high HCI-CI scores. This novel protocol resulted in acceptable TRM rates, along with successful engraftment, GVHD, relapse and survival outcomes. These findings show that haplo-HSCT holds great promise as a potential treatment option for patients with HCT-CI score ≥ 3. Previous studies concerning haplo-HSCT following reduced intensity conditioning have indicated OS rates ranging from 44% to 56%, disease-free survival (DFS) rates between 34% and 44%, incidence of relapse rates from 45% to 57.8%, and non-relapse mortality (NRM) rates ranging from 5.0% to 23%.[22-25] Pan *et al.* investigated the safety and efficacy of the reduced-intensive conditioning (RIC) regimen (Bu2Flu or Bu3Flu) ATG-based haplo-HSCT in older or unfit patients. The 2-year OS and 2-year DFS in whole cohort were 67.7% and 61.4% respectively. The 2-year cumulative incidence rates of relapse and NRM rates in whole cohort were 27.5% and 11.6% respectively.[26] The aforementioned studies reported suboptimal survival outcomes in comparison to our research findings.

It is widely recognized that a high HCT-CI score is indicative of a greater risk of complications with organ function. In this study, we observed that no patients died within the first 30 days post-transplantation, and there was an absence of regimen-related toxic death events. In this cohort, although 83% of patients experienced early toxicity related to transplantation within 30 days, grade I RRT made up 70.3% of cases, and grade III RRT was only reported in one case. In addition, the cumulative incidence of 30-day and 100-day TRM was relatively low, demonstrating that the early toxicity of the modified Bu/Cy/Flu/ATG regimen was manageable. However, it was remarkable that the TRM between day 100 and 1 year increased substantially, infection was the main cause of increased TRM.

Chang *et al.* reported that unmanipulated haplo-HSCT patients with HCT-CI scores of ≥ 3 who received Bu/Cy/ATG conditioning regimen exhibited a high probability

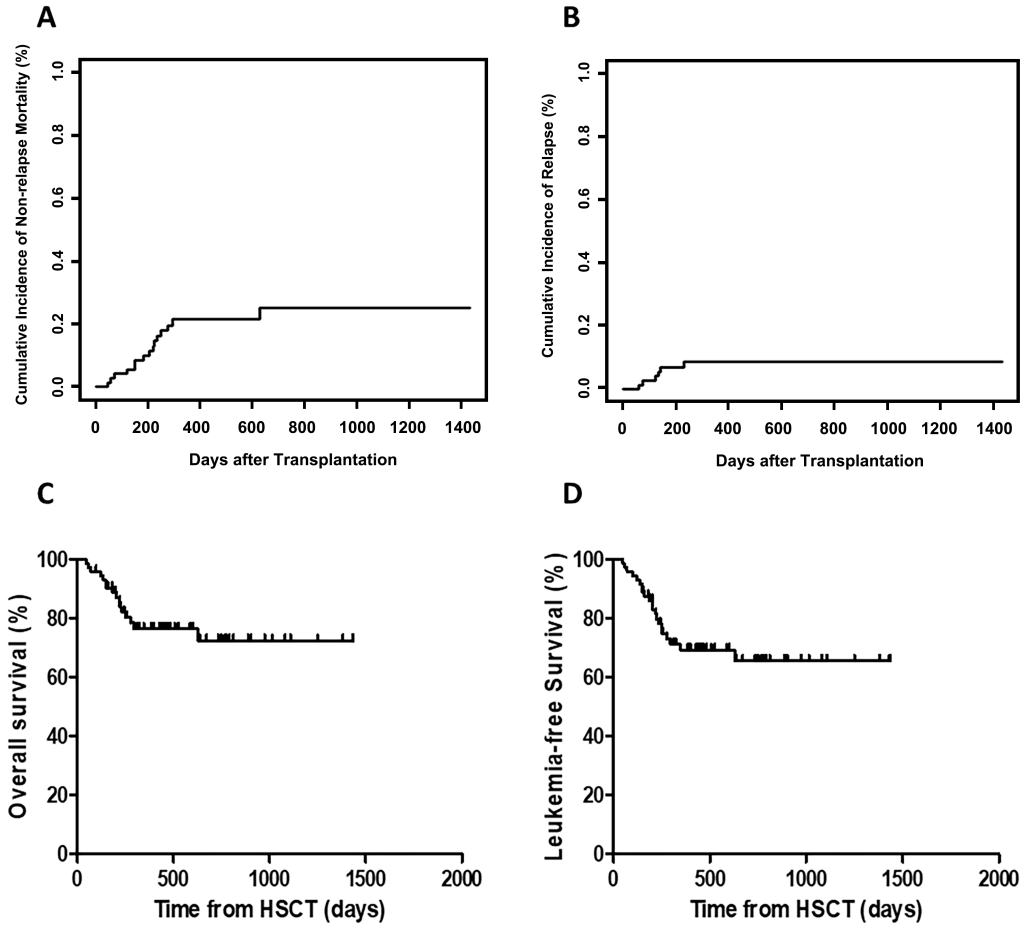

Figure 2: Outcomes. (A) The cumulative incidence of 2-year TRM. (B) The cumulative incidence of 2-year relapse. (C) The probabilities of 2-year overall survival. (D) The probabilities of 2-year LFS. LFS: leukemia-free survival; OS: overall survival; HSCT: hematopoietic stem cell transplantation; TRM: treatment-related mortality.

of NRM (33.1%).[4] Mo *et al.* confirmed that the 2-year cumulative incidence of NRM in patients with HCT-CI scores of ≥ 3 who received haplo-HSCT of Bu/Cy/ATG regimen was 34.3%.[3] In this study, we observed that this reduced-toxicity conditioning could reduce the 2-year cumulative incidence of NRM to 25.6%, indicating that this novel protocol was promising for patients with HCT-CI scores ≥ 3.

The use of Flu might play an important role. Liu *et al.* performed an open-label, randomized phase III trial to compare the outcomes of the Bu/Flu regimen with those of the Bu/Cy regimen for AML in haplo-HSCT. Grade 3 RRT was reported for 0 of 191 patients following the Bu/Flu regimen and 9 (4.7%) of 190 patients following the Bu/Cy regimen ($P = 0.002$), while the 1-year TRM was 7.2% and 14.1% ($P = 0.041$), respectively, indicating that the Bu/Flu regimen has a lower TRM and RRT for patients with AML undergoing haplo-HSCT compared with the Bu/Cy regimen.[27] In another study from the same team, the incidences of total and III-IV RRT were 94.4% and 81.5% ($P = 0.038$) and 16.7% and 0.0% ($P = 0.002$), respectively, in the Bu/Cy and Bu/Flu groups. The 5-year TRM rates were 18.8 ± 6.9% and 9.9 ± 6.3% ($P = 0.104$), suggesting that the use of Bu/Flu was associated with reduced RRT without a significant impact on NRM for AML patients in CR1 undergoing allo-HSCT.[28] Wang JM *et al.* reported that the incidences of diarrhea and severe oral mucositis within the first 30 days post-transplantation were lower in the Bu/Flu/cytarabine group [28.57% *vs.* 65.45%, $P < 0.001$; 51.79% *vs.* 70.91%, $P = 0.039$)] than in the Bu/Cy group, and both regimens achieved a similar TRM rate.[29]

We have attempted the complete replacement of Cy by Flu; however, primary engraftment failure with this modified regimen seemed to be higher than that with the Bu/Cy/ATG regimen in elderly patients or in patients with severe comorbidities who underwent haplo-HSCT. Sun *et al.* reported that the cumulative incidence of primary engraftment failure was higher in the Bu-Flu group than in the Bu-Cy group (17.6% *vs.* 3.0%, $P = 0.04$).[30] This suggests that fludarabine may not be sufficient to replace Cy. Under

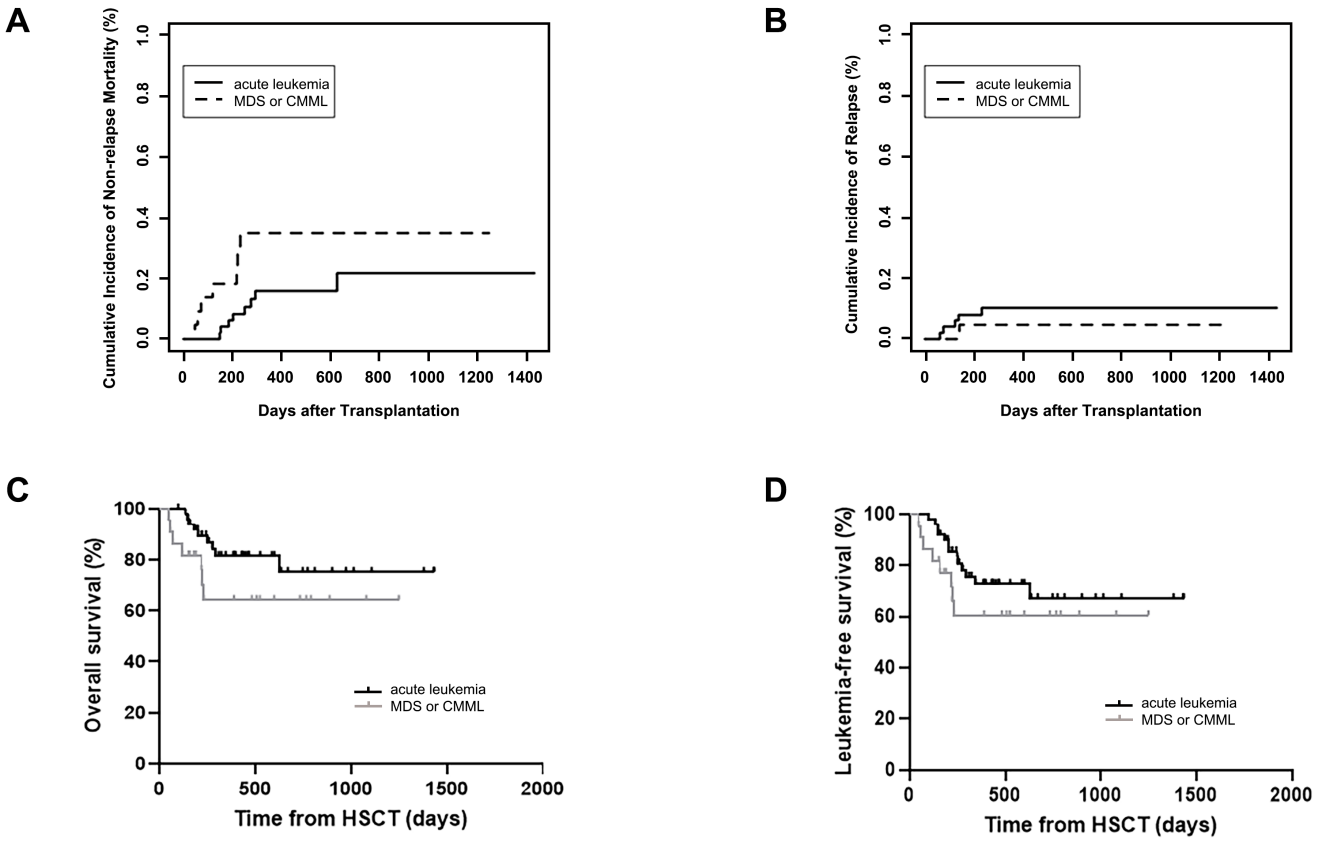

Figure 3. Outcomes of disease subtype. (A) The cumulative incidence of 2-year TRM. (B) The cumulative incidence of 2-year relapse. (C) The probabilities of 2-year overall survival. (D) The probabilities of 2-year LFS. TRM: treatment-related mortality; HSCT: hematopoietic stem cell transplantation; LFS: leukemia-free survival; MDS: myelodysplastic syndrome; CMML: chronic myelomonocytic leukemia.

this condition, a novel regimen with a combination of reduced doses of Cy and fludarabine has been introduced. Our previous study demonstrated that this modified Bu/Cy/Flu/ATG regimen did not affect engraftment and may be an option for older patients who undergo haplo-HSCT.[10] However, the above literature focused on patients over 55 years old who underwent the Bu/Flu/Cy/ATG conditioning regimen during haploidentical transplantation. In our current study, we found that all of the patients achieved neutrophil engraftment, suggesting that this novel regimen consisting of low doses of Cy and fludarabine has an excellent engraftment profile.

Prevention and treatment of relapse is an important issue in HSCT.[31] Another concern is that reduced organ damage by the Bu/Flu regimen might cause a lower anti-leukemic effect or a higher relapse rate than the Bu/Cy regimen. In the present study, it was noted that the relapse rate of this novel regimen did not seem to increase compared to our historical cohort,[3] suggesting that this novel conditioning regimen not only reduced toxicity but also had a graft-versus-leukemia (GVL) effect. In the present study, we also confirmed that the incidence of aGVHD was comparable in older patients with the same modified Bu/Cy/Flu/ATG conditioning regimen[10] or even lower in patients whose HCT-CI scores ≥ 3 with standard Bu/Cy/ATG conditioning regimen.[3] The cumulative incidence of CMV viremia at day 100 post-HSCT was 72.2%, but this result was in a pre-detemovir prophylaxis era. In today's era of widespread use of letmovir, the incidence of CMV viremia may decrease. We found that the incidence of EBV reactivation and PTLD was high by using this modified Bu/Cy/Flu/ATG regimen. Anderlini *et al.* observed that EBV reactivation and viremia in 35% of severe aplastic anemia patients underwent allo-HSCT with Flu, Cy and ATG from a matched related or URD.[32] Gao *et al.* demonstrated that a fludarabine-containing conditioning regimen was one of the risk factors for PTLD after haplo-HSCT.[33] So further exploration of the mechanism and how to prevent EBV infection may be a way to take this conditioning regimen further.

It is important to note that this study has several limitations. Firstly, it was found that the main comorbidities of patients with high HCT-CI scores were pulmonary disease, infection, and a prior solid tumor in this

Table 2: RRTs within 30 days post-HSCT

Index	*n* (%)
Numbers of organs involved	
None	10 (13.9)
One organ	26 (36.1)
Two organs	22 (30.5)
Three organs	9 (12.5)
Four organs	3 (4.2)
Five organs	2 (2.8)
Frequency of involvement in each organ	
Gastrointestinal toxicity	36 (50.0)
Grade I	33 (45.8)
Grade II	3 (4.2)
Hepatic toxicity	45 (62.5)
Grade I	24 (33.3)
Grade II	21 (29.2)
Cardiac toxicity	10 (13.9)
Grade I	1 (1.4)
Grade II	8 (11.1)
Grade III	1 (1.4)
Renal toxicity	12 (16.7)
Grade I	12 (16.7)
Stomatitis toxicity	13 (18.1)
Grade I	13 (18.1)
Bladder toxicity	2 (2.8)
Grade II	2 (2.8)

HSCT: hematopoietic stem cell transplantation; RRTs: regimen-related toxicities.

study. Additional studies are necessary to confirm the comorbidities of crucial organs, such as cardiac disease and renal dysfunction. Secondly, since the sample size was relatively small, the results need to be interpreted with caution. Additionally, since this was a single-arm clinical trial, a comparison with the standard myeloablative conditioning cohort could not be made. Thus, the baseline characteristics of cases may be biased when comparisons are made with historical control cohorts. In the future, multicenter, randomized controlled trials should be conducted to further verify the safety and efficacy of this novel regimen.

Overall, this novel conditioning regimen is a viable choice for patients whose HCT-CI scores ≥ 3. It has a low risk of TRM and leads to successful engraftment with favorable outcomes in terms of GVHD, relapse, and OS. However, multicenter randomized controlled head to head comparative trials should be conducted in the future to validate the results.

Supplementary Information

Supplementary materials are only available at the official site of the journal (www.intern-med.com).

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None.

Author Contributions

Wei Sun Writing—Original draft, Yu-Qian Sun Writing—Review and Editing, Xiao-Dong Mo Data curation, Rui Ma Data curation, Yun He Data curation, Yuan-Yuan Zhang Data curation, Yu-Hong Chen Data curation, Feng-Rong Wang Data curation, Huan Chen Data curation, Yao Chen Data curation, Chen-Hua Yan Data curation, Wei Han Data curation, Lan-Ping Xu Data curation, Yu Wang Data curation, Xiao-Hui Zhang Data curation, Kai-Yan Liu Data curation, Xiao-Jun Huang Writing—Review and Editing, Supervision, Project administration, and Funding acquisition.

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Ethical Approval

This study was approved by the Ethics Committee of Peking University People's Hospital. Patient Consent Statement (ClinicalTrials. gov: NCT03412409).

Informed Consent

Not applicable.

Conflict of Interest

The authors declared no potential conflicts of interest.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

All data is included in the manuscript.

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