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Original Article

A novel reduced toxicity conditioning regimen for older myelodysplastic neoplasms patients undergoing haploidentical stem cell transplantation: a prospective cohort study

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Abstract: A novel reduced-toxicity conditioning (RTC) regimen of busulfan, fludarabine, cyclophosphamide, and antithymocyte globulin (Bu/Flu/Cy/ATG) followed by haploidentical hematopoietic stem cell transplantation (haplo-HSCT) in older patients with hematologic malignancies has been reported and the results was encouraging. However, the safety and efficacy of this regimen was unknown in older myelodysplastic neoplasms (MDS) patients. From January 2018 to December 2021, 68 consecutive older patients (aged over 50) using the RTC regimen for T-cell replete haplo-HSCT (RTC group) at our center were eligible, 68 patients aged under 50 using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen (Bu/Cy/ATG) (Bu/Cy/ATG group) were randomly selected from 223 MDS patients during the same period in a 1:1 ratio matched-pair analysis for patient sex, World Health Organization (WHO) category, international prognostic scoring system (IPSS) risk group, time from diagnosis to HSCT, chemotherapy in advanced, response after chemotherapy, donor sex, infused mononuclear cells and the CD34-positive cell count. The transplant outcomes were also compared between the RTC group and the matched sibling donor (MSD) haploidentical stem cell transplantation (HSCT) with the busulfan and cyclophosphamide (Bu/Cy) conditioning regimen. The cumulative incidences of grade II-IV acute graft versus host disease (aGVHD) in the RTC group were significantly lower than that in the Bu/Cy/ATG group. The 3-year cumulative incidences of treatment related mortality (TRM) in the two groups were 12.3% versus 14.7% (P=0.613). The cumulative incidences of relapse, disease-free survival (DFS) and overall survival (OS) were comparable between the two groups. The outcomes were better in RTC group than those patients received MSD transplant, with lower incidence of TRM, and higher OS and DFS. The advantages were still significant when comparing patients receiving children donors HSCT in RTC group with MSD transplant in survival and TRM. Children donor with the RTC regimen could be a better choice than the MSD HSCT with Bu/Cy regimen for the elderly MDS patients. The encouraging results suggest that the RTC regimen followed by haplo-HSCT is a potentially promising method for older MDS patients. The trail number of the prospective study is "NCT03412409" and the trial URL is "https://clinicaltrials.gov/study/NCT03412409?term=NCT03412409&rank=1".

Keywords: Myelodysplastic neoplasms, reduced-toxicity conditioning, haploidentical stem cell transplantation, children donor, Bu/Cy regimen

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment approach for patients with myelodysplastic neoplasms (MDS) [1-5]. Prevalence of MDS increases with age. MDS was reported to be more currently diagnosed in older patients, especially patients aged over 60 [6].

Over the past decades, advances in haplo-HSCT, including improvement of conditioning

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regimens, stronger prophylaxis, and therapy for organ complications, have allowed for the use of transplant in many older patients [7]. However, allo-HSCT was previously performed in relatively younger patients since the risk of treatment related mortality (TRM) in older patients who received myeloablative conditioning regimen transplant procedures was relatively higher. Using data from the European Society for Blood and Marrow Transplantation (EBMT) registry, age ≥50 years was identified as independent predictors for post-transplant survival [8]. Previous research results from our center have shown that among patients with MDS undergoing haplo-HSCT, those aged over 50 have significantly higher TRM than those aged under 50, and age over 50 is an independent risk factor for TRM [9]. Previous studies have used age ≥50 years as the age range for older patients with MDS [10-12]. If reduced-intensity conditioning regimens are adopted, we will be encountered with the dilemma of an increase in the recurrence rate despite of a decrease in TRM. Therefore, there is an unmet need for appropriate conditioning regimen in allo-HSCT for older patients. Our center has reported satisfactory results of a novel reduced-toxicity conditioning (RTC) regimen of busulfan, fludarabine, cyclophosphamide, and antithymocyte globulin (Bu/Flu/Cy/ATG) followed by haplo-HSCT in older patients over 55 years old in the setting of various hematologic malignancies [13]. The previous encouraging results suggested that haplo-HSCT with the novel RTC regimen might be a potentially promising option for older patients with MDS. Matched sibling donors (MSDs) are only available for less than one-quarter of older patients, haploidentical donors have been proved to be good alternative donors for those without MSDs [14, 15]. Furthermore, there is evidence that younger haploidentical donors may be superior to older MSDs for older patients [9, 16-20]. Therefore, haplo-HSCT for older patients is a promising option when MSD or unrelated donor (URD) is unavailable.

We extensively analyzed the prognosis of older MDS patients who received the haplo-HSCT with the RTC regimen and compared it with younger MDS patients aged under 50 years old who received the traditional busulfan and cyclophosphamide (Bu/Cy) plus ATG condition regimen (the Bu/Cy/ATG group) and also with the older patients who received MSD hematopoietic stem cell transplantation (HSCT) (MSD group) to evaluate the safety and efficacy of this conditioning regimen in older MDS patients.

Materials and methods

Patients

Consecutive enrolment began in January 2018 and extended to December 2021. A total of 68 consecutive patients with MDS who used the RTC regimen (RTC group) as described below for T-cell-replete haplo-HSCT at our center were eligible, and we randomly selected control subjects from 223 MDS patients during the same period in a 1:1 ratio matched-pair analysis (matching for patient sex, World Health Organization (WHO) category, international prognostic scoring system (IPSS) risk group, time from diagnosis to HSCT, chemotherapy in advanced, response after chemotherapy, donor sex, infused mononuclear cells and the CD34-positive cell count). Finally, 68 matched control subjects using modified Bu/Cy plus ATG regimen (Bu/Cy/ATG group) were chosen for the analyses. Data from 21 consecutive MDS patients were previously reported [13] and these cases are further followed in this study. The ethics committee of the Peking University People's Hospital approved the study protocol. Informed consent was obtained according to the Declaration of Helsinki.

Conditioning regimens, donor selection, mobilization, supportive care, and GVHD prophylaxis

The novel Bu/Flu/Cy/ATG regimen consisted of the following agents: cytarabine (2 g/m^2/day, injected i.v.) on days-10 and -9; busulfan (9.6 mg/kg, injected i.v. in 12 doses) on days-8, -7 and -6; fludarabine (30 mg/m^2/day, injected i.v.) from day-6 to day-2; cyclophosphamide (1000 mg/m^2/day, injected i.v.) on days-5 and -4; semustine (250 mg/m^2 20, orally) on day-3 and ATG (10 mg/kg, rabbit, SangStat (Lyon, France)) on days-5, -4, -3 and -2. And the study of the novel conditioning regimen was registered as a prospective, single-arm phase 2 clinical trial (ClinicalTrials.gov: NCT03412409).

The donor selection rule was based on previous literature [21]. Patients were eligible for haploidentical HSCT if an MSD or URD was unavail-

able. All recipients received granulocyte colony-stimulating factor-mobilized peripheral blood with or without bone marrow-derived stem cells. All patients received cyclosporine (CsA), mycophenolate mofetil (MMF) and short-term methotrexate (MTX) for graft-vs-host disease (GVHD) prophylaxis as previously described [22-24]. The dosage of CsA was 2.5 mg/kg per day, i.v., from day 9 before transplantation until bowel function returned to normal. Then, the patient was switched to oral CsA. MMF was administered orally, at 0.5 g every 12 h, from day 9 before transplantation until hematopoietic recovery after transplantation. The dosage of MTX was 15 mg/m^2, administered i.v. on day 1, and 10 mg/m^2 on days 3, 6, and 11 after transplantation. Prophylaxis and treatment of Cytomegalovirus (CMV) infection after allo-HSCT were performed as described previously [25, 26]. Ganciclovir was administered during conditioning (through day-2) and acyclovir (400 mg twice a day) was given until the discontinuation of all immunosuppressive agents. Patients also received prophylactic drugs to prevent infection by fungi. CMV and Epstein-Barr virus (EBV) were monitored twice per week via real-time PCR. Hematopoietic chimerism was evaluated by fluorescence in situ hybridization (FISH) (for sex-mismatched pairs), or the short tandem repeat technique [18]. The hematopoietic cell transplantation-comorbidity index (HCT-CI) score was evaluated according to the literature.

Statistical analyses

Matched-pair analysis was performed to reduce or eliminate confounding effects, and a 1:1 ratio matched-pair analysis was implemented. Matching was done on the logit of the propensity score using calipers with width equal to 0.05 of the standard deviation of the logit of the estimated propensity score. Groups were compared with the χ^2 statistic for categorical variables and the Mann-Whitney test or Student's t test for continuous variables. Competing risk model was used to calculate cumulative incidences, with relapse treated as a competing event for TRM and with death from any cause as a competing risk for engraftment, graft versus host disease (GVHD), and relapse [27-29]. The Kaplan-Meier curves were used to estimate disease-free survival (DFS) and overall survival (OS). All reported *P* values were based on 2-sided tests. Alpha was set at 0.05. The cumulative incidence was calculated with R statistical software, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Both the RTC group and Bu/Cy/ATG group included 68 patients. The median age of patients was 59 (50-71) and 35.5 (7-50) in the RTC and the Bu/Cy/ATG group, respectively. Patient sex, WHO category, IPSS risk group, time from diagnosis to HSCT, chemotherapy in advanced, response after chemotherapy, donor sex, mononuclear cells and the CD34-positive cell count between the two groups were comparable. The HCT-CI score of RTC group was significantly higher than that of Bu/Cy/ATG group (P<0.001). The characteristics of the patients are displayed in **Table 1**.

Hematopoietic recovery

The cumulative incidences of 30-day myeloid recovery were 100% and 98.5% (P=0.496) in the RTC group and the Bu/Cy/ATG group, respectively. Patients achieved myeloid recovery at a median of 13 (9-21) days and 13 (9-23) in two groups (P=0.435). The median time of platelet recovery in the RTC and the Bu/Cy/ATG group were 13.5 (8-70) days and 14.5 (8-86) days (P=0.566), with 90-day cumulative incidence of platelet recovery of 94.1% and 88.2%, respectively (P=0.227).

Regimen-related toxicity

All patients tolerated the conditioning regimen. The incidences of grade 1-4 regimen-related toxicity were 75% and 69.1% in RTC and Bu/Cy/ATG group, respectively (P=0.445). The incidences of grade 3-4 regimen-related toxicity were 20.6% and 20.5% in RTC and Bu/Cy/ATG group, respectively (P=0.834). Renal dysfunction was more common in the RTC group (17.6% versus 2.9%; P=0.005). However, there was no severe renal dysfunction grade 3 or 4 in both groups. The incidences of grade 1-4 mucositis were 33.8% and 26.5% in RTC and Bu/Cy/ATG group, respectively (P=0.350). The incidences of grade 3-4 mucositis were 1.5% and 7.4% in RTC and Bu/Cy/ATG group, respec-

Table 1. Patient characteristics

Characteristics	RTC group n=68	Bu/Cy/ATG group n=68	*P*-value
Age years, median (range)	59 (50-71)	35.5 (7-50)	<0.001
Gender, n (%)			0.282
Male	57 (83.8%)	52 (76.5%)	
Female	11 (16.2%)	16 (23.5%)	
WHO category, n (%)			0.272
MDS-LB/MDS-h	5 (7.4%)	8 (11.8%)	
MDS-IB1	21 (30.9%)	26 (38.2%)	
MDS-IB2	34 (50.0%)	26 (38.2%)	
AML-MR	8 (11.8%)	8 (11.8%)	
IPSS risk group, n (%)			0.263
Intermediate-1	14 (20.6%)	7 (10.3%)	
Intermediate-2	36 (52.9%)	41 (60.3%)	
High	18 (26.5%)	20 (29.4%)	
Time from diagnosis to HSCT, months; Median (range, months)	5 (0.5-158)	6 (1-132)	0.345
Chemotherapy in advanced, n (%)			0.078
No	37 (54.4%)	47 (69.1%)	
Yes	31 (45.6%)	21 (30.9%)	
Bone marrow blasts before haplo-HSCT, n (%)			0.120
≤5%	14 (20.6%)	22 (32.4%)	
>5%	54 (79.4%)	46 (67.6%)	
Donor sex, n (%)			0.151
Male	40 (58.8%)	48 (70.6%)	
Female	28 (41.2%)	20 (29.4%)	
Donor-patient relation, n (%)			<0.001
Father donor		23 (33.8%)	
Mother donor		5 (7.4%)	
Sibling donor	7 (10.3%)	11 (16.2%)	
Children donor	61 (89.7%)	26 (38.2%)	
Other		3 (4.4%)	
HCT-CI			<0.001
0	18 (26.5%)	49 (72.0%)	
1-2	39 (57.3%)	18 (26.5%)	
≥3	11 (16.2%)	1 (1.5%)	
Median MNCs, × 10^8/kg (range)	8.83 (4.05-14.47)	9.24 (2.99-25.16)	0.107
Median $CD34^+$ cell, × 10^6/kg (range)	3.19 (0.62-13.28)	2.69 (0.64-11.75)	0.413

AML-MR, acute myeloid leukemia myelodysplasia-related; Bu/Cy/ATG group, patients using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen; haplo-HSCT, haploidentical hematopoietic stem cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; HSCT, hematopoietic stem cell transplantation; IPSS, international prognostic scoring system; MDS-h, MDS hypoplastic; MDS-IB1, MDS with increased blasts-1; MDS-IB2, MDS with increased blasts-2; MDS-LB, MDS with low blasts; MNC, mononuclear cell; RTC group, patients using the reduced-toxicity conditioning regimen; WHO, World Health Organization.

tively (P=0.208). Other toxicities affecting the heart and digestive tract were observed to the same extent in both groups (**Table 2**). No veno-occlusive disease of the liver was observed in both groups, and there was no regimen-related death in both groups.

Acute GVHD

The cumulative incidences of 100-day grade II-IV acute graft versus host disease (aGVHD) in the RTC group was significantly lower than that in the Bu/Cy/ATG group [13.2% (95% CI=10.5%-

Table 2. Regimen-related toxicity

Variable	RTC group n=68	Bu/Cy/ATG group n=68	*P*-value
Organ dysfunction or mucositis grade 1-4	51 (75%)	47 (69.1%)	0.445
Organ dysfunction or mucositis grade 3-4	14 (20.6%)	15 (20.5%)	0.834
Heart			0.983
None	67 (98.5%)	67 (98.5%)	
Grade 1	1 (1.5%)	0	
Grade 2	0	1 (1.5%)	
Grade 3	0	0	
Grade 4	0	0	
Renal			0.005
None	56 (82.4%)	66 (97.1%)	
Grade 1	11 (16.2%)	2 (2.9%)	
Grade 2	1 (1.5%)	0	
Grade 3	0	0	
Grade 4	0	0	
Liver			0.139
None	41 (60.3%)	34 (50%)	
Grade 1	19 (27.9%)	18 (26.5%)	
Grade 2	2 (2.9%)	7 (10.3%)	
Grade 3	6 (8.8%)	9 (13.2%)	
Grade 4	0	0	
Mucositis			0.389
None	45 (66.2%)	50 (73.5%)	
Grade 1	16 (23.5%)	13 (19.1%)	
Grade 2	6 (8.8%)	0	
Grade 3	1 (1.5%)	3 (4.4%)	
Grade 4	0	2 (2.9%)	
Diarrhea			0.301
None	52 (76.5%)	57 (83.8%)	
Grade 1	7 (10.3%)	1 (14.7%)	
Grade 2	2 (2.9%)	8 (11.8%)	
Grade 3	7 (10.3%)	2 (2.9%)	
Grade 4	0	0	

Bu/Cy/ATG group, patients using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen; RTC group, patients using the reduced-toxicity conditioning regimen.

16.0%) vs. 29.5% (95% CI=24.5%-34.6%), P=0.018] (**Figure 1A**). The cumulative incidences of 100-day grade III-IV aGVHD were comparable in the two groups [4.4% (95% CI=3.4%-5.4%) vs. 7.4% (95% CI=5.8%-9.0%), P=0.461] (**Figure 1B**).

Chronic GVHD

The cumulative incidences of 3-year chronic graft versus host disease (cGVHD) in the RTC group and the Bu/Cy/ATG group were comparable [36.2% (95% CI=30.3%-42.0%) vs. 40.4% (95% CI=34.4%-46.4%), P=0.592] (**Figure 1C**). The cumulative incidences of 3-year moderate to severe cGVHD in the RTC group and the Bu/Cy/ATG group were comparable [17.0% (95% CI=12.9%-21.1%) vs. 21.1% (95% CI=16.5%-25.6%), P=0.482] (**Figure 1D**).

CMV and EBV infection

The cumulative incidences of 1-year CMV infection in the RTC group and the Bu/Cy/ATG group

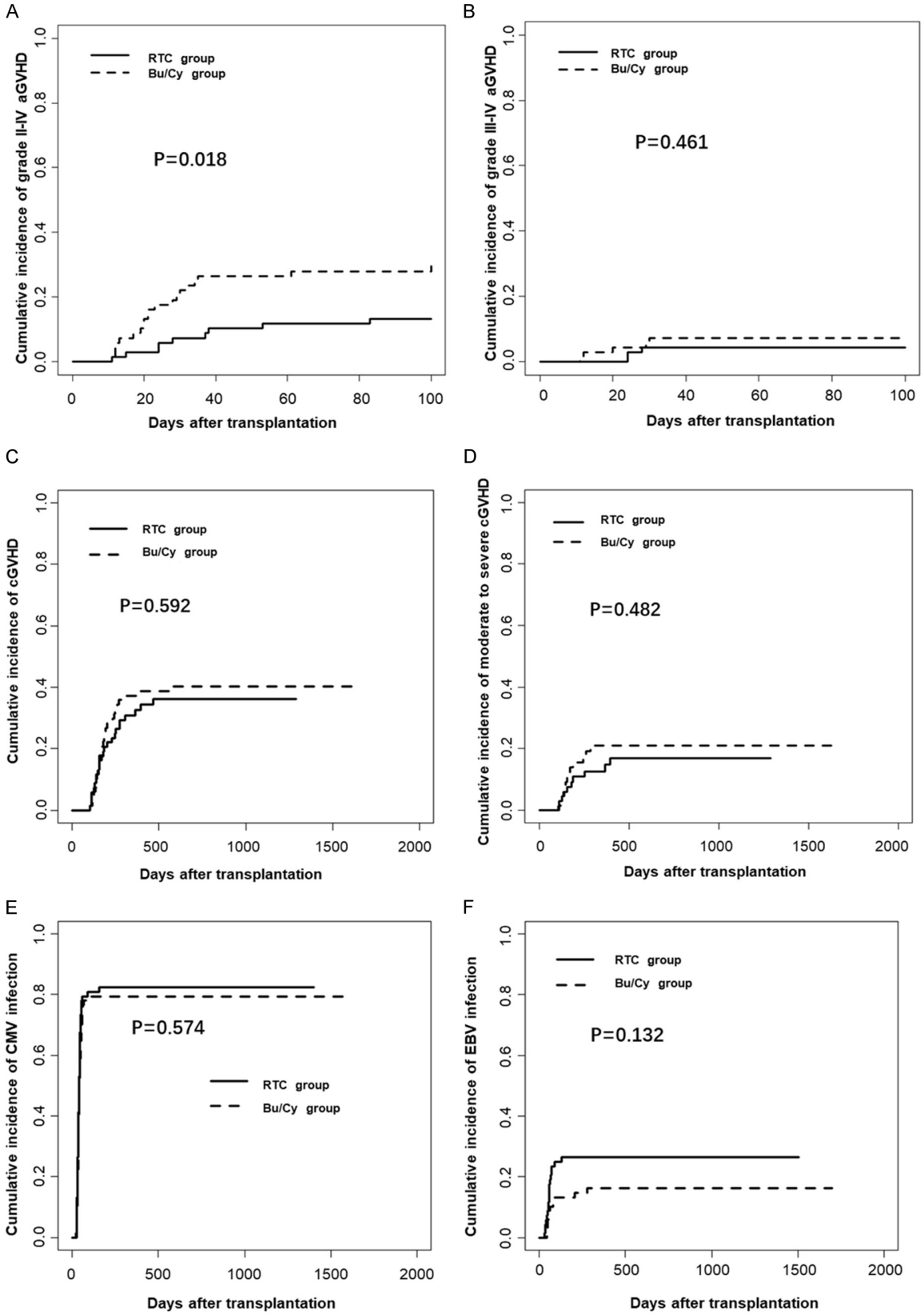

Figure 1. The cumulative incidences of grade II-IV acute graft-versus-host disease (aGVHD) (A), and grade III-IV aGVHD (B) in the reduced-toxicity conditioning (RTC) group and the busulfan and cyclophosphamide (Bu/Cy) group. The cumulative incidences of chronic graft-versus-host disease (cGVHD) (C), and moderate to severe cGVHD (D) in the RTC group and the Bu/Cy group. The cumulative incidences of cytomegalovirus (CMV) infection (E), and Epstein-Barr virus (EBV) infection (F) in the RTC group and the Bu/Cy group.

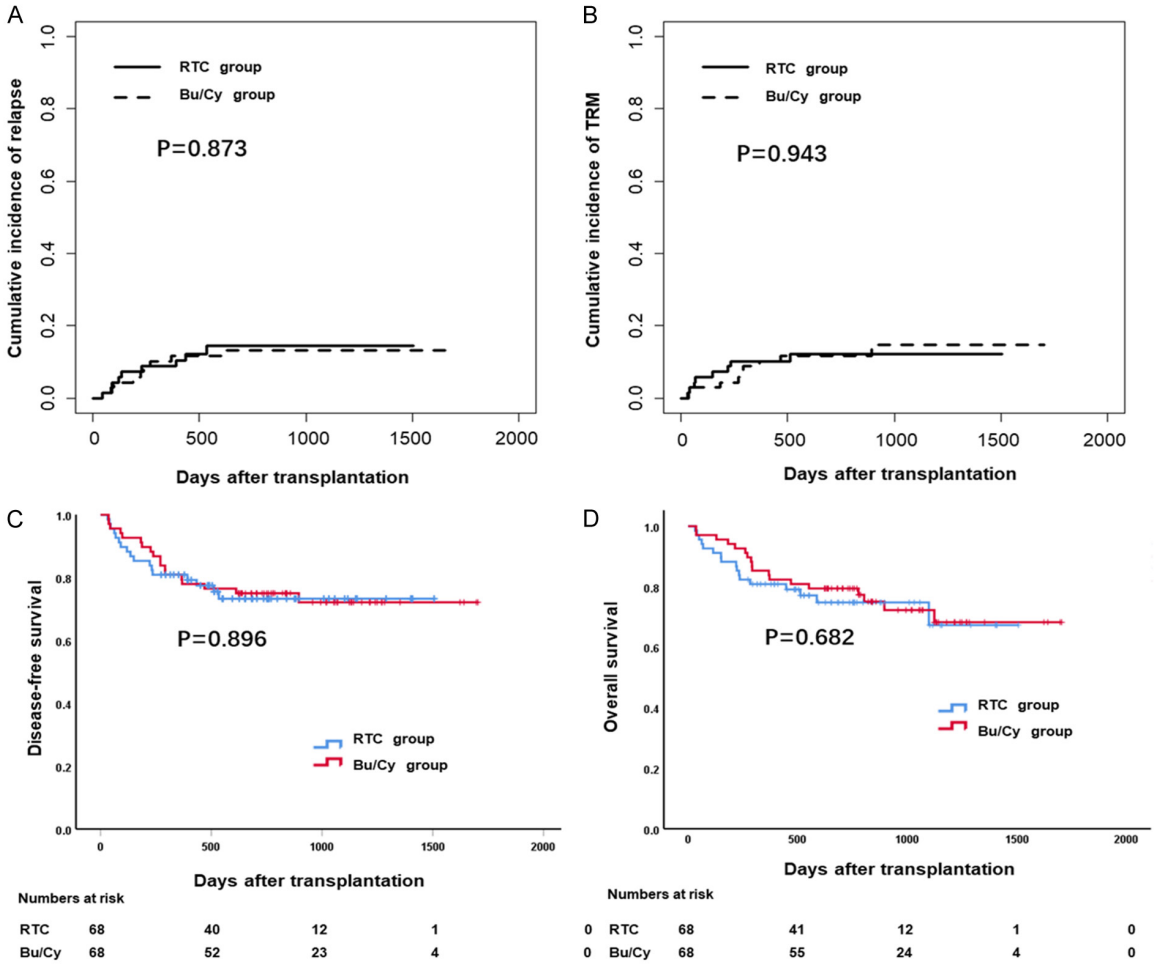

Figure 2. The cumulative incidences of relapse (A), and treatment related mortality (TRM) (B) in the RTC group and the Bu/Cy group. The probability of disease-free survival (C), and overall survival (D) in the RTC group and the Bu/Cy group.

were comparable [82.4% (95% CI=78.7%-86.0%) vs. 80.6% (95% CI=76.6%-84.6%), P=0.574] (**Figure 1E**). The cumulative incidences of 1-year EBV infection in the RTC group and the Bu/Cy group were comparable [26.5% (95% CI=21.8%-31.2%) vs. 16.2% (95% CI=12.9%-19.5%), P=0.132] (**Figure 1F**).

Relapse and TRM

Patients in the RTC group and the Bu/Cy group had similar risks of relapse. The 3-year cumulative incidences of relapse in the two groups were 14.5% (95% CI=11.1%-17.8%) versus 13.2% (95% CI=9.9%-16.6%) (P=0.873) (**Figure 2A**). Patients in the RTC group and the Bu/Cy/ATG group had similar risks of TRM. The 3-year cumulative incidences of TRM in the two groups were 12.3% (95% CI=9.5%-15.1%) versus 14.7% (95% CI=11.0%-18.3%) (P=0.943) (**Figure 2B**).

DFS and OS

The DFS were comparable in both the RTC group and the Bu/Cy/ATG group. The 3-year DFS were 73.3% (95% CI=63.0%-85.2%) versus 72.1% (95% CI=61.6%-84.4%) (0.896) (**Figure 2C**). The OS were also comparable between the RTC group and the Bu/Cy/ATG group. The 3-year OS were 74.8% (95% CI=64.6%-86.6%) versus 72.3% (95% CI=61.5%-85.0%), respectively (P=0.682) (**Figure 2D**).

RTC group vs. MSD group

The MSD group included 32 patients. The median age of patients was 59 (55-67). Patient

Table 3. The clinical outcomes of RTC and MSD groups

Outcomes	RTC group n=68	MSD group n=32	*P*-value
Cumulative incidences of 30-day myeloid recovery	100%	100%	1.000
Cumulative incidences of 90-day platelet recovery	94.1%	84.4%	0.225
Median time of myeloid recovery	13 (9-21)	14 (9-21)	0.004
Median time of platelet recovery	13.5 (8-70)	16 (8-70)	0.094
Cumulative incidences of 100-day grade II-IV aGVHD	13.2% (95% CI=10.5%-16.0%)	21.9% (95% CI=12.9%-30.8%)	0.321
Cumulative incidences of 100-day grade III-IV aGVHD	4.4% (95% CI=3.4%-5.4%)	9.4% (95% CI=4.9%-13.8%)	0.350
Cumulative incidences of 3-year cGVHD	36.2% (95% CI=30.3%-42.0%)	37.9% (95% CI=27.8%-48.0%)	0.806
Cumulative incidences of 3-year moderate to severe cGVHD	17.0% (95% CI=12.9%-21.1%)	17.8% (95% CI=8.9%-26.7%)	0.964
Cumulative incidences of TRM	12.3% (95% CI=9.5%-15.1%)	37.3% (95% CI=22.9%-51.7%)	0.018
Cumulative incidences of relapse	14.5% (95% CI=11.1%-17.8%)	12.5% (95% CI=6.7%-18.3%)	0.891
3-year DFS	73.3% (95% CI=63.0%-85.2%)	50.2% (95% CI=31.8%-68.6%)	0.055
3-year OS	74.8% (95% CI=64.6%-86.6%)	54.1% (95% CI=36.1%-72.1%)	0.073

aGVHD, acute graft versus host disease; Bu/Cy/ATG group, patients using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen; cGVHD, chronic graft versus host disease; DFS, disease-free survival; MSD, matched sibling donor; OS, overall survival; RTC, reduced-toxicity conditioning; RTC group, patients using the reduced-toxicity conditioning regimen; TRM, treatment related mortality.

sex, WHO category, IPSS risk group, interval from diagnosis to HSCT, chemotherapy in advanced, response after chemotherapy, donor sex, HCT-CI score between the RTC group and MSD group were comparable. The patient characteristics are displayed in Supplementary Table 1.

The cumulative incidences of 30-day myeloid recovery and 90-day platelet recovery were 100% and 84.4% in the MSD group. The median time of myeloid and platelet recovery were 14 (9-21) days and 16 (8-70) days, respectively. The myeloid recovery time of MSD group was significantly longer than that of RTC group (P=0.004). The cumulative incidences of 100-day grade II-IV and grade III-IV aGVHD in the MSD group were 21.9% (95% CI=12.9%-30.8%) and 9.4% (95% CI=4.9%-13.8%), respectively (Supplementary Figure 1). The cumulative incidences of 3-year cGVHD and moderate to severe cGVHD in MSD group were 37.9% (95% CI=27.8%-48.0%) and 17.8% (95% CI=8.9%-26.7%), respectively (Supplementary Figure 2). The incidences of GVHD were comparable to those of the RTC group. The 3-year cumulative incidence of TRM in MSD group were 37.3% (95% CI=22.9%-51.7%), which was significantly higher than that of RTC group 14.5% (95% CI=11.1%-17.8%) (P=0.018) (Supplementary Figure 3A). The 3-year cumulative incidence of relapse in MSD group was 12.5% (95% CI=6.7%-18.3%) (Supplementary Figure 3B), which was comparable with the RTC group. The 3-year DFS and OS were 50.2% (95% CI=31.8%-68.6%) and 54.1% (95% CI=36.1%-72.1%), respectively, which was significantly lower than that of RTC group (Supplementary Figure 4). The clinical outcomes of RTC and MSD group were displayed in **Table 3**.

RTC children donor group vs. MSD group

In RTC group, patients received HSCT with children donors (the RTC children donor group) included 61 patients. Patient sex, WHO category, IPSS risk group, interval from diagnosis to HSCT, chemotherapy in advanced, response after chemotherapy, donor sex, HCT-CI score between the RTC children donor group and MSD group were comparable. The patient characteristics are displayed in Supplementary Table 2.

The cumulative incidences of 30-day myeloid recovery, 90-day platelet recovery, 100-day grade II-IV aGVHD, 100-day grade III-IV aGVHD, 3-year cGVHD, 3-year moderate to severe cGVHD in the RTC children donor group and the MSD group were comparable (Supplementary Figures 5, 6). The 3-year cumulative incidence of TRM in RTC children donor group were 10.5% (95% CI=7.9%-13.1%), which was significantly lower than that of MSD group (P=0.009) (Supplementary Figure 7A). The 3-year cumulative incidence of relapse in RTC children donor group was 12.7% (95% CI=9.6%-15.8%) (Supplementary Figure 7B), which was comparable with the MSD group. The 3-year DFS and OS in RTC children donor group were 76.8% (95% CI=65.5%-88.3%) and 79.3%

Table 4. The clinical outcomes of RTC children donor and MSD groups

Outcomes	RTC children donor group n=61	MSD group n=32	*P*-value
Cumulative incidences of 30-day myeloid recovery	100%	100%	1.000
Cumulative incidences of 90-day platelet recovery	95.1%	84.4%	0.174
Median time of myeloid recovery	13 (9-21)	14 (9-21)	0.004
Median time of platelet recovery	13 (8-70)	16 (8-70)	0.066
Cumulative incidences of 100-day grade II-IV aGVHD	13.1% (95% CI=10.2%-16.0%)	21.9% (95% CI=12.9%-30.8%)	0.328
Cumulative incidences of 100-day grade III-IV aGVHD	4.9% (95% CI=3.7%-6.1%)	9.4% (95% CI=4.9%-13.8%)	0.431
Cumulative incidences of 3-year cGVHD	37.9% (95% CI=31.5%-44.3%)	37.9% (95% CI=27.8%-48.0%)	1.000
Cumulative incidences of 3-year moderate to severe cGVHD	17.2% (95% CI=12.7%-21.7%)	17.8% (95% CI=8.9%-26.7%)	0.931
Cumulative incidences of TRM	10.5% (95% CI=7.9%-13.1%)	37.3% (95% CI=22.9%-51.7%)	0.009
Cumulative incidences of relapse	12.7% (95% CI=9.6%-15.8%)	12.5% (95% CI=6.7%-18.3%)	0.923
3-year DFS	76.8% (95% CI=65.5%-88.3%)	50.2% (95% CI=31.8%-68.6%)	0.021
3-year OS	79.3% (95% CI=68.7%-89.9%)	54.1% (95% CI=36.1%-72.1%)	0.023

aGVHD, acute graft versus host disease; Bu/Cy/ATG group, patients using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen; cGVHD, chronic graft versus host disease; DFS, disease-free survival; MSD, matched sibling donor; OS, overall survival; RTC, reduced-toxicity conditioning; RTC group, patients using the reduced-toxicity conditioning regimen; TRM, treatment related mortality.

(95% CI=68.7%-89.9%), respectively, which were significantly higher than that of MSD group (Supplementary Figure 8). The clinical outcomes of RTC children donor and MSD group were displayed in **Table 4**.

Discussion

Previous studies have shown that in MDS patients undergoing haplo-HSCT, aged over 50 is an independent risk factor for platelet engraftment failure, TRM, and OS [9, 14]. Therefore, we define patients aged over 50 as older MDS patients. In the present study, we demonstrated that the novel RTC conditioning regimen of Bu/Flu/Cy/ATG followed by haplo-HSCT was a feasible option in older patients aged over 50 with MDS, with the similar outcomes as compared with the younger patients with Bu/Cy/ATG conditioning regimen. And the clinical results was superior to those transplanted from MSDs, especially from children donors.

Based on previous findings and our experience [25, 30-32], a reduced dose of Cy (2 g/m^2) may be a balanced dose in combination with BU/Flu/ATG for haplo-HSCT for hematological malignancies, with good engraftment and safety profiles. Our center pioneered the novel MAC regimen with the aim of reducing toxicity in older patients who received T cell-replete haplo-HSCT, which was reported in a prospective single-arm phase II study. In our study, we further explored the application of this novel protocol and focused on MDS, and we compared the transplant results with the younger patients received the traditional conditioning Bu/Cy/ATG haplo-HSCT.

Engraftment is a major concern in haplo-HSCT in situation with a conditioning regimen. In the present study, prompt and sustained achievement of neutrophil engraftment was documented in 100% patients in RTC group. Both the cumulative incidence and median time of platelet engraftment were also similar between the RTC and the Bu/Cy/ATG groups.

As for the tolerance, it is another important factor in the choice of conditioning regimen [33]. The RTC conditioning regimen consisting of lower doses of Cy and fludarabine. Fludarabine has been widely used to reduce regimen-related toxicity in previous studies was also used in most reports using haplo-SCT in older patients [30, 32, 34, 35]. In our study, the rates of early toxicities of the RTC regimen were similar to the Bu/Cy/ATG group expect for the renal toxicity, however, there was no difference in grade 3 and 4 renal toxicity. Furthermore, TRM in the RTC group was as low as that of the Bu/Cy/ATG group. The RTC regimen as a preparative regimen showed good tolerance in T cell-replete haplo-HSCT in older cases with MDS. Importantly, the tolerability of the conditioning regimen should not compromise powerful antitumor activity in patients undergoing transplant with MDS.

In previous research, it was reported that selected older leukemia patients aged over 50

years old with low HCT-CI scores (0-2) and good performance status could safely undergo haplo-HSCT [36]. In our study, the HCT-CI scores of the older patients (RTC group) was significantly higher than the younger patients (Bu/Cy group). The advanced age often correlates with an increased HCT-CI score, as the older patients have higher incidences of coronary heart diseases, diabetes, heart or liver or kidney dysfunctions, or other comorbidities. It was noteworthy that despite the significantly higher HCT-CI scores and the older age in RTC group, the 3-year cumulative incidence of TRM of the RTC group was comparable to that of the Bu/Cy group (12.3% versus 14.7%, P=0.613).

Except the relapse of MDS, GVHD and infections remained two main causes of death after allo-HSCT. Interestingly, we observed a lower incidence of grade II-IV aGVHD in the RTC group although the patient age has been shown to be a risk factor for GVHD [37, 38]. Chae et al. once reported that the incidence of aGVHD were lower in Bu/Flu regimen compared with BuCy regimen [39]. Whether the lower rate of aGVHD was relative to the conditioning regimen needed to be proved in larger cohort in future. As for the fludarabine, it has both antineoplastic and immunosuppressive activity. Some studies suggested that the conditioning regimens containing fludarabine were associated with higher incidence of opportunistic infections such as EBV after HSCT because of the immunosuppressive effect of fludarabine [40-44]. In our study, we observed that the incidences of CMV and EBV infections were similar between the RTC and Bu/Cy/ATG groups.

MSD is traditionally convinced as the best choice for allo-HSCT, but it is difficult for older patients since matched siblings would be expected to be similar age and often unavailable or ineligible. However, in our present study, we found that in the RTC conditioning regimen background, the older MDS patients received haplo-HSCT could achieve significantly better transplant outcomes than those received sibling-matched HSCT, with a lower incidence of TRM, and then a significantly higher DFS and OS. Besides, the cumulative incidences of acute or chronic GVHD, and relapse were comparable in the two groups. It follows that the RTC regimen had a very prominent advantage in safety for older MDS patients, while also not increasing the risk of recurrence, and could achieve satisfactory transplant outcomes. Furthermore, when we concentrated on the 61 patients received children-donors haplo-HSCT in the RTC group, who occupied the majority of the patients of RTC group, the significant advantages over MSD HSCT still existed. The result was consistent with the conclusion that children donors are better than older sibling donors in several present studies reported in acute leukemia [21, 24, 45]. This conclusion needs to be further confirmed with researches of a larger sample size.

Therefore, out study showed that age alone seemed to be not a contraindication with current novel RTC conditioning regimen. Children donor with the RTC regimen could be a better choice than the MSD HSCT with Bu/Cy regimen for the older MDS patients. The encouraging results suggest that the RTC regimen followed by haplo-HSCT is a potentially promising method for older MDS patients.

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Disclosure of conflict of interest

None.

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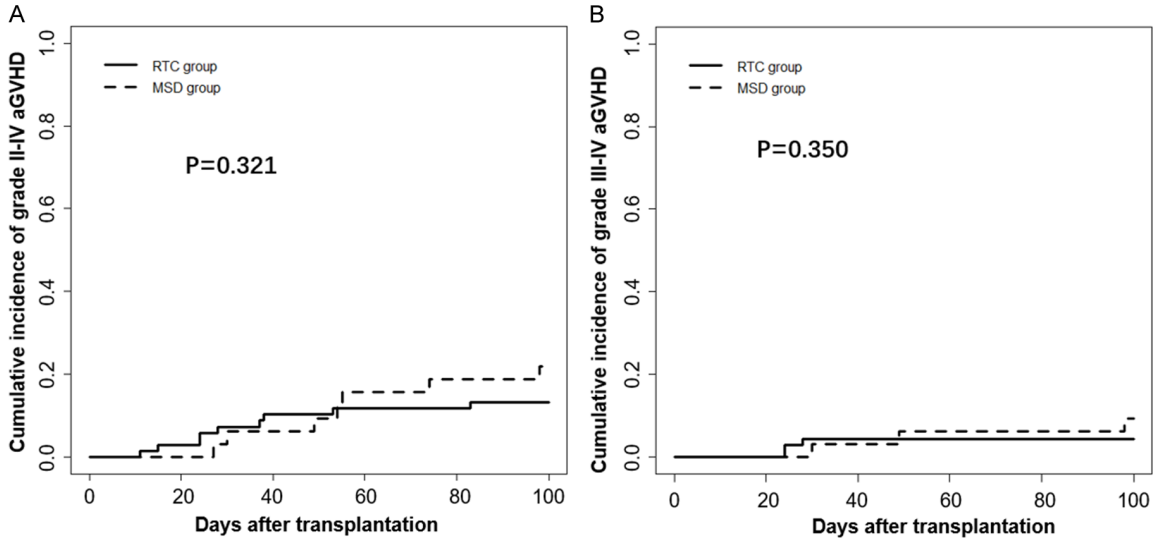
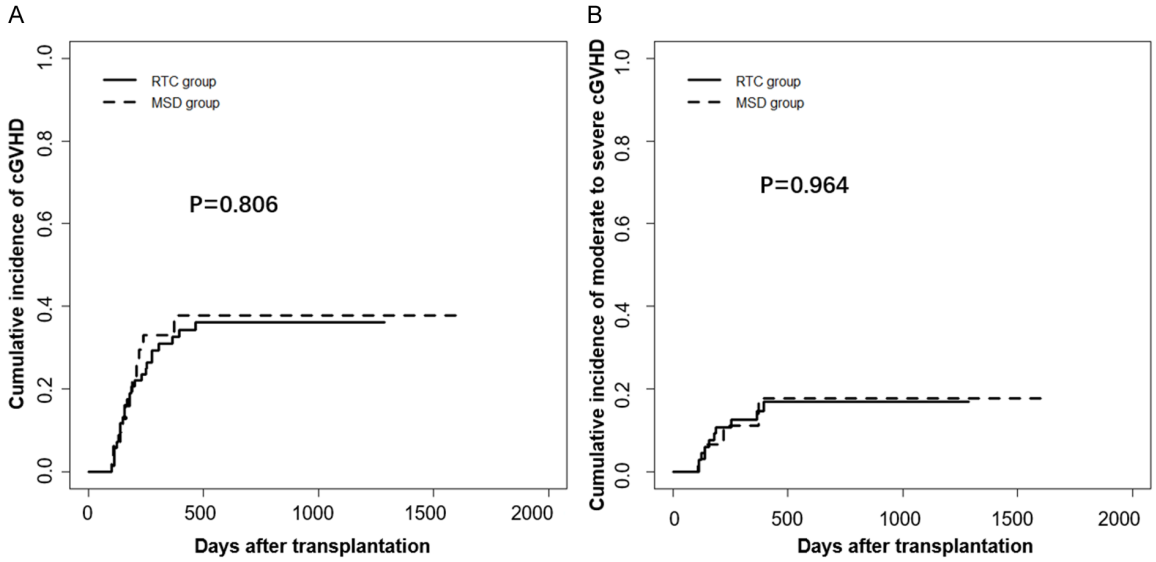
Supplementary Table 1. Patient characteristics of RTC and MSD group

Characteristics	RTC group n=68	MSD group n=32	*P*-value
Age years, median (range)	59 (50-71)	59 (55-67)	0.804
Gender, n (%)			0.163
Male	57 (83.8%)	23 (71.9%)	
Female	11 (16.2%)	9 (28.1%)	
WHO category, n (%)			0.239
MDS-LB/MDS-h	5 (7.4%)	1 (3.1%)	
MDS-IB1	21 (30.9%)	9 (28.1%)	
MDS-IB2	34 (50.0%)	15 (46.9%)	
AML-MR	8 (11.8%)	7 (21.9%)	
IPSS risk group, n (%)			0.130
Intermediate-1	14 (20.6%)	4 (12.5%)	
Intermediate-2	36 (52.9%)	15 (46.9%)	
High	18 (26.5%)	13 (40.6%)	
Time from diagnosis to HSCT, months; Median (range, months)	5 (0.5-158)	6 (1-72)	0.235
Chemotherapy in advanced, n (%)			0.863
No	37 (54.4%)	18 (56.3%)	
Yes	31 (45.6%)	14 (43.8%)	
Bone marrow blasts before haplo-HSCT, n (%)			0.830
≤5%	14 (20.6%)	6 (18.8%)	
>5%	54 (79.4%)	26 (81.3%)	
Donor sex, n (%)			0.061
Male	40 (58.8%)	17 (53.1%)	
Female	28 (41.2%)	25 (46.9%)	
Donor-patient relation, n (%)			<0.001
Father donor			
Mother donor			
Sibling donor	7 (10.3%)	32 (100%)	
Children donor	61 (89.7%)		
Other			
HCT-CI			0.150
0	18 (26.5%)	14 (43.8%)	
1-2	39 (57.3%)	12 (37.5%)	
≥3	11 (16.2%)	6 (18.7%)	
Median MNCs, × 10^8/kg (range)	8.83 (4.05-14.47)	7.50 (5.28-17.19)	0.018
Median $CD34^+$ cell, × 10^6/kg (range)	3.19 (0.62-13.28)	2.08 (0.62-5.30)	0.003

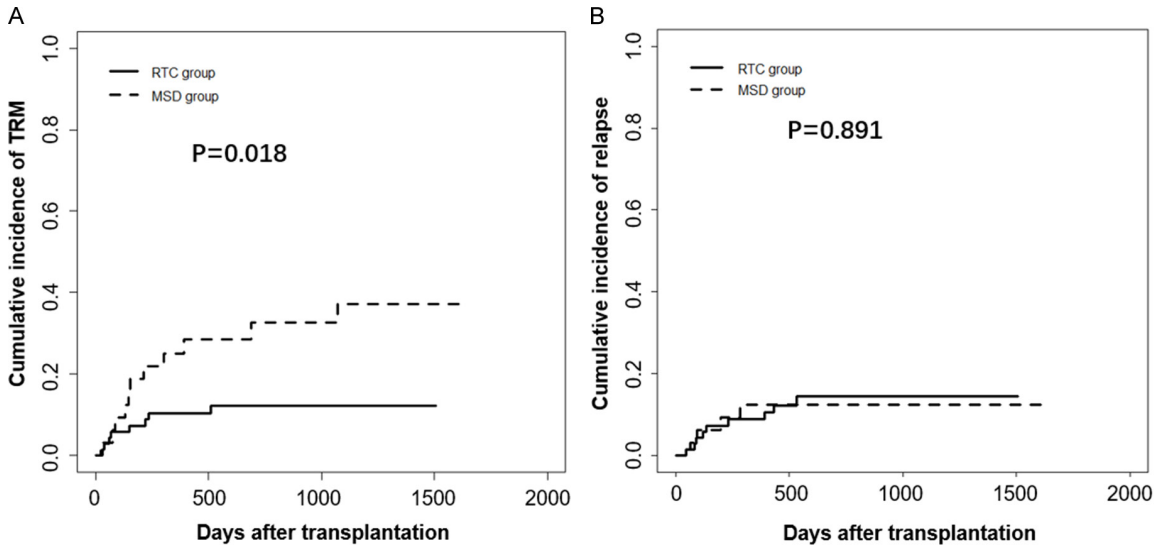
AML-MR, acute myeloid leukemia myelodysplasia-related; Bu/Cy/ATG group, patients using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen; haplo-HSCT, haploidentical hematopoietic stem cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; HSCT, hematopoietic stem cell transplantation; IPSS, international prognostic scoring system; MDS-h, MDS hypoplastic; MDS-IB1, MDS with increased blasts-1; MDS-IB2, MDS with increased blasts-2; MDS-LB, MDS with low blasts; MNC, mononuclear cell; RTC group, patients using the reduced-toxicity conditioning regimen; WHO, World Health Organization.



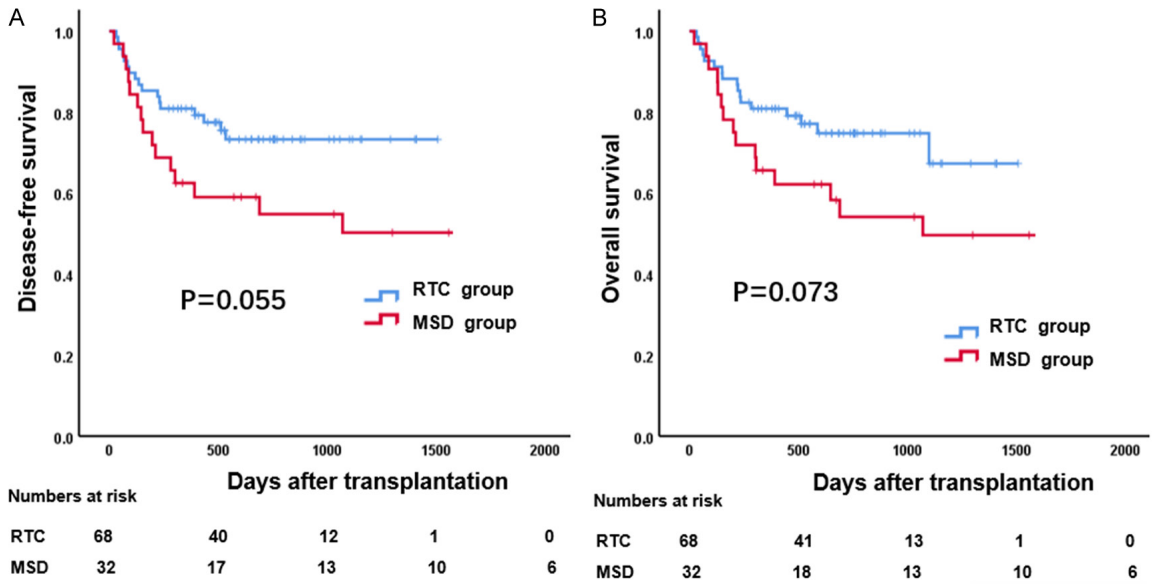
Supplementary Figure 1. The cumulative incidences of grade II-IV acute graft-versus-host disease (aGVHD) (A), and grade III-IV aGVHD (B) in the reduced-toxicity conditioning (RTC) group and the matched sibling donor (MSD) group.



Supplementary Figure 2. The cumulative incidences of chronic graft-versus-host disease (A), and moderate to severe chronic graft-versus-host disease (B) in the RTC group and the MSD group.



Supplementary Figure 3. The cumulative incidences of treatment related mortality (TRM) (A), and relapse (B) in the RTC group and the MSD group.

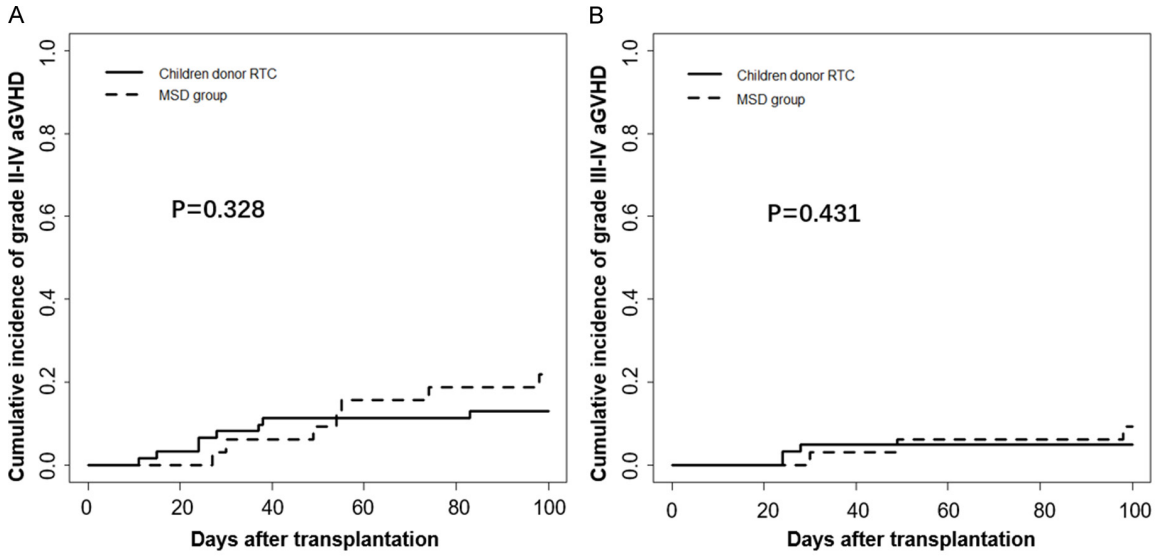


Supplementary Figure 4. The probability of disease-free survival (A), and overall survival (B) in the RTC group and the MSD group.

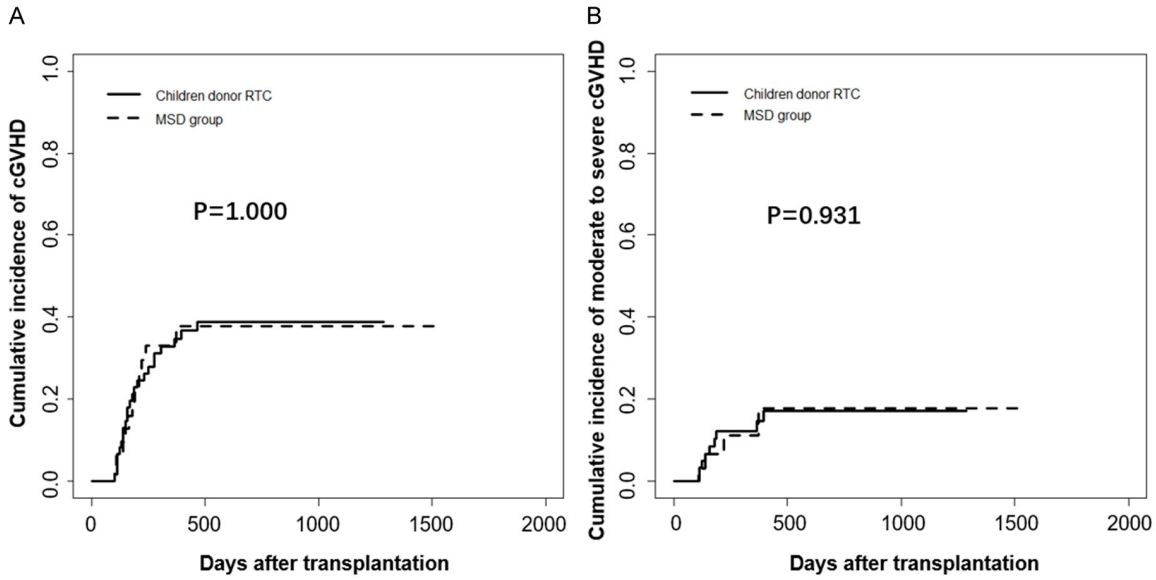
Supplementary Table 2. Patient characteristics of RTC children donor group and MSD group

Characteristics	RTC children donor group n=61	MSD group n=32	*P*-value
Age years, median (range)	59 (50-71)	59 (55-67)	0.964
Gender, n (%)			0.121
Male	52 (85.2%)	23 (71.9%)	
Female	9 (14.8%)	9 (28.1%)	
WHO category, n (%)			0.207
MDS-LB/MDS-h	5 (8.2%)	1 (3.1%)	
MDS-IB1	19 (31.1%)	9 (28.1%)	
MDS-IB2	30 (49.2%)	15 (46.9%)	
AML-MR	7 (11.5%)	7 (21.9%)	
IPSS risk group, n (%)			0.144
Intermediate-1	12 (19.7%)	4 (12.5%)	
Intermediate-2	33 (54.1%)	15 (46.9%)	
High	16 (26.2%)	13 (40.6%)	
Time from diagnosis to HSCT, months; Median (range, months)	5 (0.5-158)	6 (1-72)	0.259
Chemotherapy in advanced, n (%)			0.962
No	34 (55.7%)	18 (56.3%)	
Yes	27 (44.3%)	14 (43.8%)	
Bone marrow blasts before haplo-HSCT, n (%)			0.932
≤5%	11 (18.0%)	6 (18.8%)	
>5%	50 (82.0%)	26 (81.3%)	
Donor sex, n (%)			0.174
Male	33 (54.1%)	17 (53.1%)	
Female	28 (45.9%)	25 (46.9%)	
HCT-CI			0.286
0	18 (29.5%)	14 (43.8%)	
1-2	33 (54.1%)	12 (37.5%)	
≥3	10 (16.4%)	6 (18.7%)	
Median MNCs, × 10^8/kg (range)	8.85 (4.05-14.47)	7.50 (5.28-17.19)	0.018
Median $CD34^+$ cell, × 10^6/kg (range)	3.24 (0.81-13.28)	2.08 (0.62-5.30)	0.001

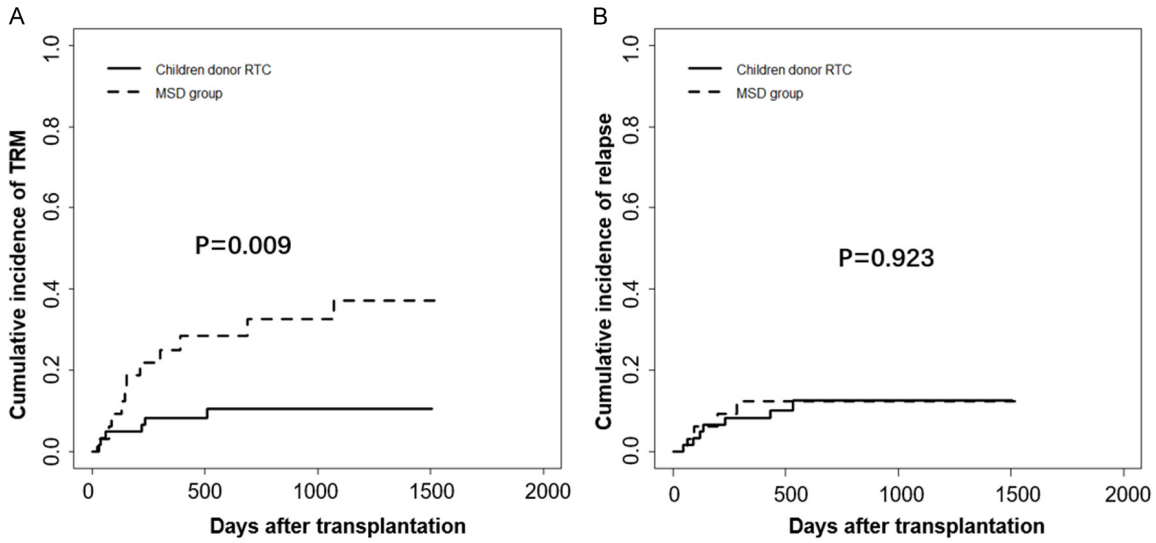
AML-MR, acute myeloid leukemia myelodysplasia-related; Bu/Cy/ATG group, patients using modified busulfan, cyclophosphamide plus antithymocyte globulin regimen; haplo-HSCT, haploidentical hematopoietic stem cell transplantation; HCT-CI, hematopoietic cell transplantation-comorbidity index; HSCT, hematopoietic stem cell transplantation; IPSS, international prognostic scoring system; MDS-h, MDS hypoplastic; MDS-IB1, MDS with increased blasts-1; MDS-IB2, MDS with increased blasts-2; MDS-LB, MDS with low blasts; MNC, mononuclear cell; RTC group, patients using the reduced-toxicity conditioning regimen; WHO, World Health Organization.



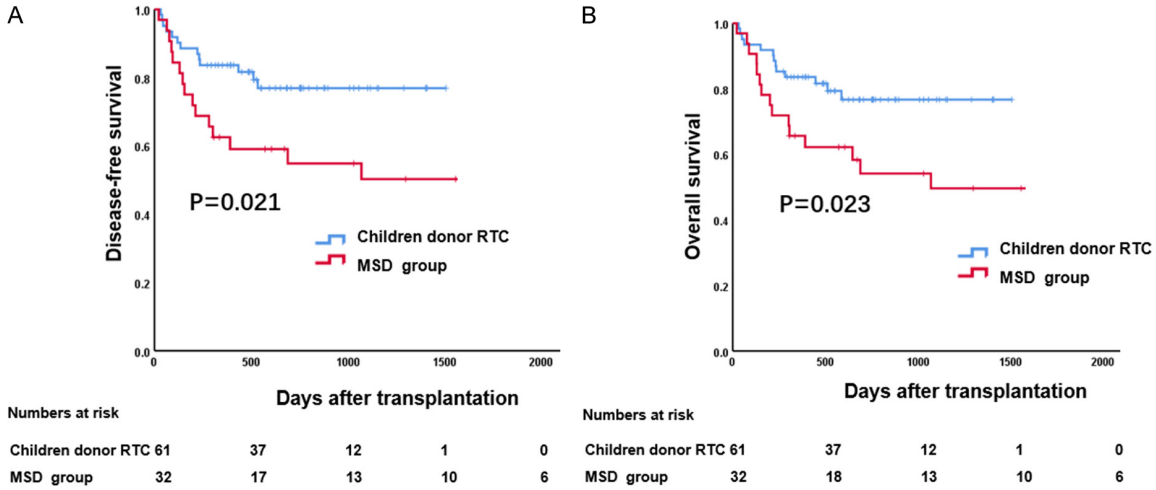
Supplementary Figure 5. The cumulative incidences of grade II-IV aGVHD (A), and grade III-IV aGVHD (B) in the RTC children donor group and the MSD group.



Supplementary Figure 6. The cumulative incidences of chronic graft-versus-host disease (cGVHD) (A), and moderate to severe cGVHD (B) in the RTC children donor group and the MSD group.



Supplementary Figure 7. The cumulative incidences of TRM (A), and relapse (B) in the RTC children donor group and the MSD group.



Supplementary Figure 8. The probability of disease-free survival (A), and overall survival (B) in the RTC children donor group and the MSD group.