HLA-mismatched micro-transplantation as post-remission treatment compared to autologous hematopoietic stem cell transplantation or consolidation with single agent cytarabine for favorable or intermediate risk acute myeloid leukemia

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Research Article

Keywords: Acute myeloid leukemia, first complete remission, post-remission treatment, HLA-mismatched stem cell micro-transplantation, autologous stem cell transplantation, cytarabine single agent

Posted Date: May 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1664364/v1

Abstract

There was some heterogenity in low or intermediate risk acute myeloid leukemia (AML) stratified by European LeukemiaNet (ELN), the optimal post-remission treatment for an individual favorable and intermediate risk genetics AML patient has not yet been established. HLA-mismatched stem cell micro-transplantation (MST), a novel apporoach of transplantation, which may improve outcomes and avoid graft versus host disease (GVHD) in first complete remission (CR1) AML patients. We retrospectively analyzed the efficacy, safety and survival of the 63 patients with favorable or intermediate risk AML received MST, autologous stem cell transplantation (ASCT) or cytarabine single agent (CSA) as post-remission treatment from January 2014 to August 2021. Neutrophil recovery time was shorter in the MST group than CSA group. There was no significant difference in three groups of infection and bleeding. The 2-year cumulative incidences of relapse were 27.27%, 29.41% and 41.67% in the MST, ASCT and CSA groups, respectively. During the period of follow-up, there were 21 patients (33.3%) died to relapse, including 6(9.52%), 5(7.94%) and 10 (15.84%) deaths in MST, ASCT and CSA groups, respectively. The estimated overall survival (OS) and relapse free survival (RFS) at 2 years were 62.2% vs 50.0% (P = 0.101) and 57.1% vs 50.0% (P = 0.136) in MST and CSA group (P = 0.101) for patients over 60 years. The estimated OS at 2 years was 100.0%, 66.2%, and 69.1% in MST, ASCT and CSA group (MST vs CSA, P = 0.044), meanwhile, the estimated RFS at 2 years was 100.0%, 65.4%, and 59.8% (MST vs CSA, P = 0.050) in patients ≤ 60 years. We concluded that MST, ASCT and CSA were all acceptable options for favorable and intermediate risk AML patients as post-remission treatment. Moreover, MST could not only improve the prognosis of the elderly but also prolong the OS and RFS of low or intermediate-risk patients ≤ 60 years.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy characterized by the proliferation of myeloid blasts and abnormally differentiation[1, 2]. AML represents 1.2% of all new cancer cases in the U.S in 2019, and the five years survival for these patients is less than 28.3%[1]. Therefore, how to choose appropriate treatment options to prolong the long-term survival of AML patients is the key that needs to be solved at present. Recently, advances of new treatment regimens including cytotoxic chemotherapy, novel targeted agents and cellular therapies have improved the prognosis of AML patients[1].

The “3 + 7” regimen consisting of anthracycline and cytarabine remained unchanged for decades in induction therapy for AML, the post-remission treatment needs to be stratified according to the risk status. According to the National Comprehensive Cancer Network (NCCN) and European LeukemiaNet (ELN) 2017 risk stratification, favorable, intermediate and high risk groups were invovled. high-dose cytarabine chemotherapy, hematopoietic stem cell transplantation, immunotherapy, hypomethylating drug maintenance therapy, etc., can be selected for AML patients in the favorable or intermediate risk group[3]. In addition, HLA-mismatched hematopoietic stem cell micro-transplantation (MST), a novel

protocol, was found to be capable of donor micro-chimerism, precluding graft versus host disease (GVHD), and improving survival [4]. MST could prolong the leukemia-free survival (LFS) of elderly AML patients and overall survival (OS) of intermediate-risk young AML patients[4, 5].

However, there is a lack of definitive study to confirm which treatment option is more effective in low-intermediate risk AML. The present study retrospectively analyzed the date of 63 patients to compare the difference in efficacy and safety of MST and autologous stem cell transplantation or chemotherapy alone as post-remission treatment in favorable and intermediate risk AML patients.

Patients And Methods

Patient population

Sixty-three AML patients who were diagnosed and treated between January 2014 and August 2021 in Huan' an No.1 People's Hospital of Nanjing Medical University. The age of the patients was range from 20 years and 80 years. The retrospective study was approved by the Institutional Review Committee of Huan' an No.1 People's Hospital. The diagnosis of AML was established according to the 2008 and 2016 WHO diagnostic criteria[6, 7]. 63 patients received MST, autologous hematopoietic stem cell transplantation (ASCT) or cytarabine single agent (CSA) for consolidation therapy after complete remission (CR) by induction chemotherapy.

Treatment regimens

The patients achieving CR were divided into three groups, according to the post-remission therapy, 22 patients were assigned to receive two or three cycles of the MST as a post-remission therapy, 17 patients chose ASCT and 24 patients recived CSA for consolidation therapy. The peripheral blood MST (PBMST) regimen consisted of a median dose cytarabine (0.5 g/m^2 to 2.5 g/m^2 per 12 hours intravenously on days 1, 2, 3) according to age followed by infusion of HLA mismatched peripheral blood stem cell 48 hours after each course of the cytarabine chemotherapy, with three months intervals between two cycles (Figure 1). 7 patients without available donors were recevied HLA mismatched umbilical cord blood stem cell MST (CBMST), which consisted of decitabine (15 mg/m^2 every day on days 1 to 5) or azacitidine (75 mg/m^2 every day on days 1 to 5) and median cytarabine (1.0 g/m^2 per 12 hours intravenously on days 1 to 2) followed by infusion HLA mismatched umbilical cord blood stem cell 24 hours after chemotherapy[8], with three months intervals between two courses, EA regimen (cytarabine 0.1 g/m^2 every day on days 1 to 7 and etoposide 0.1 g/m^2 every day on days 1 to 7) was given in the interval as consolidation chemotherapy (Figure 2). The preconditioning regimen for ASCT was BuCy (busulfan 0.8 mg/m^2 per 6 hours on days 1 to 4 and cyclophosphamide 60 mg/kg every day on days 1 to 2). 24 patients recived 4 to 6 cycles of median or high dose of cytarabine (2.0 g/m^2 to 3.0 g/m^2) for consolidation.

Mobilization and acquisition of donor peripheral stem cells and source of umbilical cord blood stem cells

The mobilization of HLA-mismatched donor peripheral stem cells was subcutaneously injected with 5-7 μg/kg granulocyte colony stimulating factor (G-CSF), per 12 hours a day for 5 days. The acquistion of donor cells was performed by a COM.TEC cell separator (Germany Fresenius Company), the fresh donor cells were used in first cycle, the remaining cells were stored in a -80℃ refrigerator. The number of mononuclear cells per infusion was≥3.0×10^8/kg. HLA-mismatched umbilical cord blood stem cells were derived from the cord blood bank of Shandong, China.

Response criteria and evaluation

Responses were evaluated according to standard criteria defined by the the National Comprehensive Cancer Network Guidelines for AML (www.nccn.org). CR was defined as the disappearance of clinical symptoms and recovery of normal hematopoiesis, with neutrophil absolute counts ≥1.0×10^9/L, platelets ≥100×10^9/L, bone marrow blasts ≤5%, and no evidence of extramedullary leukemia. Relapse was defined as the recurrence of leukemic blasts in the peripheral blood, ≥ 5% blasts in bone marrow after CR excluding bone marrow regeneration after consolidation chemotherapy or other causes, or evidence of extramedullary leukemia. Relapse free survival (RFS) was defined as time from CR to relapse or death from any cause. The OS was measured as the time from initial diagnosis until death of any reasons.

Statistical analysis

SPSS 22.0 (SPSS Inc., Chicago, Illinois) and GraphPad Prism 5.0 (Windows, GraphPad Software, La Jolla, California, USA) software was used for all the statistical analyses. The ANOVA test and Pearson Chi-Square test were used to assess the probability of significant differences of age and gender. Survival data was analyzed by means of the log-rank test and the Kaplan-Meier method. Statistical significance was defined as P 0.05.

Results

Patient characteristics

The patient characteristics were summarized in Table 1. Sixty-three patients were enrolled between 2014 and 2021 with a median follow-up time of 23.5 months, 21 months, and 11.5 months in MST, ASCT, and CSA treatment groups, respectively. All eligible AML patients who received “3+7” chemotherapy regimen consisted of cytarabine 100 mg/m^2 daily for 7 days by intravenous infusion and idrubicin (10 mg/m^2) or daunorubicin (60 mg/m^2) or CAG regimen (aclarubicin hydrochloride 20 mg/d for 4 days, cytarabine 10 mg/m^2 per 12 hours intravenously for 14 days, G-CSF 200 μg/m^2 daily subcutaneously for 14 days until the white blood cell counts were greater than 20×10^9/L) achieved CR. The median age in three groups were 64 years (range 20-80), 42 years (23-58), and 51 years (range 30-65), most of the patients who received MST were over 60 years old. According to the French-American-British classification, M1, M2, M4, and M5 were included. According to ELN 2017 risk stratification for AML[9], patients with t(8;21),

t(16;16) or inv(16), *RUNX1/RUNX1T1*, *CBFB/MYH11,* mutated *NPM1* without *FLT3-ITD or with FLT3-ITD^{low}*, biallelic mutated *CEBPA* were defined as favorable risk, and patients with mutated *NPM1* and *FLT3-ITD^{high}*, wild type *NPM1* without *FLT3-ITD or with FLT3-ITD^{low}*, t(9;11), *MLLT3-KMT2A*, cytogenetic abnormalities not classified as favorable or adverse were defined as intermediate risk[9]. There were no significant differences among the three treatment groups in physical status score, blood counts and bone marrow blasts ratio.

Treatment response and complications

In MST group, the median transfusion total nucleated cells (TNC) dose and CD34 positive cell dose of grafts were 3.01 (range 0.28-5.40)×10^8/kg and 0.80 (range 0.07-4.07)×10^6/kg (Table 3). In ASCT group, the median transfusion mononuclear cells (MNC) dose and $CD34^+$ cell dose of grafts were 4.11 (range 2.69-10.37)×10^8/kg and 3.14 (range 1.74-5.65)×10^6/kg. The minimal residual disease (MRD) after induction therapy of two patients was positve in MST group, while MRD was negative in both the ASCT group and the CSA group. Neutrophil recovery time was shorter in the MST group than in the CSA group (median time to neutrophil recovery, 11(9-15) days vs 13(11-18) days, P = 0.003) (Table 2). There was no significantly difference between the MST group and the ASCT group of neutrophil recovery time and platelet recovery time (P = 0.342 and P = 0.259, respectively). The most common complication was hematologic toxicity, including infection and bleeding, with no significant difference in incidence among the three groups. There was no any grades of GVHD suffered in the MST group (Table 2).

Relapse and non-relapse related to mortality

The median follow-up time in MST, ASCT, and CSA treatment groups were 23.5 months, 21 months, and 11.5 months, respectively. The 2-year cumulative incidences of relapse were 27.27% and 29.41% in the MST and ASCT groups (P = 0.581). The 2-year cumulative incidence of relapse in the CSA group was 41.67% higher than that of the MST and ASCT groups, but there was no significant difference. Up to the date of follow-up, there were 21 patients (33.3%) died to relapse, including 6(9.52%), 5(7.94%) and 10 (15.84) deaths in MST, ASCT and CSA groups, respectively. There was no treatment-related death and non-relapse-related mortality in the three groups.

Survival

The median for OS time was 5 years in all patients. The estimated OS at 2 years was 72.9%, 66.2%, and 65.5% in MST, ASCT and CSA group (χ^2 = 3.079, P = 0.215) (Fig. 3A and 3B). The estimated RFS at 2 years was 68.7%, 59.9%, and 57.4% in MST, ASCT and CSA group (χ^2 = 2.159, P = 0.340) (Fig. 3C and 3D). These results showed that MST and ASCT could not improve the OS and RFS of low or intermediate-risk AML patients compared to CSA. For patients over 60 years of age, the estimated OS and RFS at 2 years was 58.3% and 54.2%, respectively, and the estimated OS at 2 years was 62.2% and 50.0% in MST and CSA group (P = 0.101), the estimated RFS at 2 years was 57.1% and 50.0% (P = 0.136) (Fig 4A-D). For patients under 60 years of age, the estimated OS and RFS at 2 years was 74.6% and 67.7%, and the

estimated OS at 2 years was 100.0%, 66.2%, and 69.1% in MST, ASCT and CSA group (MST vs CSA, *P* = 0.044), the estimated RFS at 2 years was 100.0%, 65.4%, and 59.8% (MST vs CSA, *P* = 0.050) (Fig 4E-H). The median for RFS and OS time were 19 months and 40 months in CBMST group, and RFS and OS time were both undefined in PBMST group (Fig 5). Compared to CSA, MST could prolong the OS and RFS in low or intermediate-risk AML patients with age less than 60 years. However, prospective randomized controlled studies with a great number of patients are needed for further investigation.

Discussion

In decades, recent advances of the remission induction treatment strategies for the specific subtype of AML, have significantly improved the rates of CR and OS. However, almost all AML patients will relapse during their first CR peroid without appropriate post-remission therapy[10], even favorable and intermediate risk according to ELN 2017 risk stratification for AML. ELN recommended 2–4 cycles of intermediate-dose cytarabine for favorable-risk genetics younger AML patients (18–60/65 years) eligible for intensive chemotherapy, and allogenic hematopoietic stem cell transplantation (allo-HSCT) from matched-related or unrelated donor, 2–4 cycles of intermediate-dose cytarabine (IDAC), high-dose therapy and ASCT for the intermediate-risk genetics patients. For older patients (≥60/65 years) eligible for intensive chemotherapy, 2–3 cycles of intermediate-dose cytarabine (HiDAC), allo-HSCT in patients with low HCT-Comorbidity Index, or investigational therapy could be chose[9]. Inaddition to, previous studies have also showed that MST as a post-remission therapy may improve outcomes and avoid GVHD in CR1 AML patients[11]. Owing to the heterogeneity of AML and a paucity of randomized controlled trial data with large samples, Nevertheless, the optimal post-remission treatemt for an individual favorable and intermediate risk genetics AML patient has not yet been established[10]. The retrospective study was to compare the difference in efficacy and safety of MST and ASCT or CSA as post-remission treatment in favorable and intermediate risk AML patients.

Many studies have explored the optimal post-remission strategy for favorable and intermediate risk AML patients. The majority of favorable risk AML patients recevied IDAC or HiDAC for consilidation therapy in CR1 according to ELN 2017[9]. However, the preferred dose of cytarabine and the optimal number of cycles necessary to acquire the best outcomes are unknown. It was recently reported that the 3-year risk of relapse was significantly higher in IDAC compared to HiDAC, HiDAC is the preferred dose for single agent cytarabine consilidation in younger, favourable-risk AML[12]. A meta-analysis also compared the efficacy of HiDAC to IDAC or low-dose cytarabine as post-remission for AML patients including 9 studies. HiDAC was benefit from RFS in the favorable risk group, but it did not translate into an OS benefit[13]. Moreover, CPX-351, hypomethylating agents, targeted agents (i.e. gemtuzumab ozogamicin) were also used as post-remission treatment for AML patients, there was no material OS benefit from these regimens[14–17]. ASCT is feasible when matched sibling donor is not available for patients with favorable and intermediate risk AML in CR1, but the MRD status before HSCT is a key factor to determine whether a patient is suitable for ASCT and to predict the outcome after transplantation[18–20]. Clinical studies have showed that MST could improve remission rates and OS with rapid hematopoietic recovery and without

GVHD in AML patients, particularly in elderly patients, although the precise mechanism of MST is still unclear[5, 21, 22]. The majority of MST patients were received HLA-mismatched peripheral blood stem cells from donors, but for AML patients without available donors, CBMST was also an optimal option[8], the two regimens both implied low risk procedure with chemotherapy and with no risk of GVHD, the HLA were both mismathcded[5, 8]. In the study, 7 patients were treatment with CBMST and 15 patients were treatment with PBMST, the median for RFS and OS time were 19 months and 40 months in CBMST group, and RFS and OS time were both undefined in PBMST group.

In this study, sixty-three patients were enrolled between 2014 and 2021 with a median follow-up time of 23.5 months, 21 months, and 11.5 months in MST, ASCT, and CSA treatment groups, respectively. There were no significant differences in baseline characteristic among the three groups, except for age, the median age in MST group was 64 years (range 20–80), which showed that MST could improve the outcomes of older AML patients with low or intermediate risk without increasing treatment-related toxicity, it was consistent with previous report[23]. Compared to CSA, neutrophil recovery time was shorter in the MST group (median time to neutrophil recovery, 11(9–15) days vs 13(11–18) days, $P = 0.003$), rapid neutrophil recovery can significantly reduce the incidence of infections in the granulocytosis phase. There was no significant difference in three groups of the most common complication including infection and bleeding, and there was no grade of GVHD in MST group.

The 2-year cumulative incidences of relapse were 27.27% and 29.41% in the MST and ASCT groups ($P = 0.581$), and the 2-year cumulative incidence of relapse in CSA group was 41.67% higher than that of MST and ASCT groups. During the period of follow-up, there were 21 patients (33.3%) died to relapse. The estimated OS and RFS at 2 years were 62.2% vs 50.0% ($P = 0.101$) and 57.1% vs 50.0% ($P = 0.136$) in MST and CSA group ($P = 0.101$) for patients over 60 years. The estimated OS at 2 years was 100.0%, 66.2%, and 69.1% in MST, ASCT and CSA group (MST vs CSA, $P = 0.044$), the estimated RFS at 2 years was 100.0%, 65.4%, and 59.8% (MST vs CSA, $P = 0.050$) in patients ≤ 60 years. These results suggested that MST could improve the outcomes of favorable and intermediate AML patients over 60 years and prolong the OS and RFS for patients ≤ 60 years.

Our results analyzed that MST, ASCT and CSA were all acceptable options for favorable and intermediate risk AML patients as post-remission treatment. However, what option is the optimal for different individuals as post-remission regimen? Guo *et al*[24] first reported that MST increased the 2-year OS rate from 11–39% in older patients with AML, then a long term follow-up study showed that LFS and OS rates were 84.4% and 89.5% in low risk AML patients treated with MST as post-remission consolidation[11]. Particularly in older AML patients, MST achieved a high CR rate and 1-year OS[21]. Moreover, in recent years, MST for refractory secondary AML and the immunomodulatory agent lenlidomide combined with MST for AML have been reported[25, 26]. Compare to HLA-matched sibling donor (MSD) transplantetion, OS and LFS of MST were inferior to MSD transplantation for favorable and intermediate risk AML patients in CR1[27]. Our results indicated that MST as post-remission treatment may be suitable for elderly patients and younger patients without an available donor for allo-HSCT suffered favorable and

intermediate risk AML in CR1. The potential mechanisms of MST were direct cytotoxicity mediated by transferred alloreactine or tumor-speicific donor cells, rejection of donor cells and concomitant cytokine release, and donor CD4 + cells enhanced host cytotoxic T cells responses[5, 21, 28–31]. Nevertheless, the precise mechnism of MST remains unclear so far. Prospective randomized controlled design with large samples and basic experiments for mechanism of MST need to be further investigated. Reseachs in recent years have showed that ASCT is the acceptable option for post-remission treatment with favorable and intermediate risk AML in CR1, especially for favorable risk patients. Compared to ASCT, allo-HSCT should be the preferred post-remission strategy for intermediate risk AML patients[20, 32–34]. Furthermore, it was reported that the regimen of repeated courses of HiDAC and idarubicin with limited autologous CD34 positive peripheral blood stem cell support was proved feasible and effective in non-high risk AML patients[35]. Therefore, ASCT should be used as post-remission treatment for younger AML patients in CR1 with favorable risk and intermediate risk in the absence of an available donor, whose MRD were negative. However, the limitations of our study were the small samples size and not the prospective randomized controlled study.

In conclusion, MST could not only improve the prognosis of the elderly but also prolong the OS and RFS of favorable or intermediate risk patients ≤ 60 years. MST, ASCT and CSA were all acceptable options for favorable and intermediate risk AML patients as post-remission treatment. MST is more suitable for elderly patients and younger patients without an available donor suffered favorable and intermediate risk AML in CR1, and ASCT is the preferred stragegy for younger favorable risk AML patients in CR1 with MRD negative. Further investigations need to be comfirmed the conclusion.

Declarations

Acknowledgements

Not applicable

Funding

This work was funded by Science and Technology Fund of Jiangsu Commission of Health (grant #H2018085 and H2019082).

Availability of data and materials

Not applicable

Authors' contributions

SD T, CL W and L Y conceptualized the original idea, designed the experiments, and analyzed the data. SD T wrote the paper. LX S, D Z, Y D, Y C, BH D and ZM H collected the patients' information, treated patients with the regimens, and analyzed the data with statistics software. CLW and L Y revised the manuscript. All authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Committee of The Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University (KY-2022-031-01) and individual consent for this retrospective analysis was waived.

Consent for publication

As this was a retrospective study, patient consent was waived, and anonymity was ensured.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Patient characteristics, treatment regimens and outcomes according to three different consolidation treatments

istics at on	MST (n = 22)	ASCT (n = 17)	CSA (n = 24)	*P* value
an (range)	64（20-80）	42（23-58）	51（30-65）	0.038*
(M/F)	（7/15）	（8/9）	（14/10）	0.196*
%)				0.127*
	12（54.54）	14（82.35）	13（54.16）	
	10（45.46）	3（17.64）	11（45.84）	
^{9}/L)	3.03（0.26-116.12）	6.03（1.27-196.21）	40.43（0.94-222.09）	0.433*
	94（49-132）	85（40-107）	86（39-116）	0.764*
	68（28-270）	33（8-229）	29（5-233）	0.433*
/L)	212（148-1609）	180（15-924）	252（85-914）	0.352*
ification				
	1（4.54%）	1（5.88%）	6（25%）	NA
	9（40.92%）	8（47.05%）	13（54.16%）	NA
	1（4.54%）	1（5.88%）	1（4.16%）	NA
	11（50.00%）	7（41.19%）	4（16.68%）	NA
ow blasts, (%)	48.50（26.00-83.50）	56.00（27.50-95.00）	69.25（21.00-99.00）	0.413*
ic risk, n (%)				0.134**
e	2（9.09）	6（35.29）	5（20.83）	
liate	20（90.91）	11（64.71）	19（79.17）	
risk, n (%)				0.141**
e	5（22.73）	9（52.94）	10（41.67）	
liate	17（77.27）	8（47.06）	14（58.33）	
reach CR, n (%)				0.291*
	20（90.91）	13（76.47）	22（91.67）	
	2（9.09）	4（23.53）	2（8.33）	
MRD before MAC				0.146**
n (%)	2（9.09）	0	0	
, n (%)	20（90.91）	17（100）	24（100）	
er MAC, n (%)				
	16（72.73）	12（70.59）	14（58.33）	0.540**
	6（27.27）	5（29.41）	10（41.67）	0.540**

Note: *ANOVA test, **Pearson Chi-Square test, M, male; F, female; WBC, white blood cells; Hb, hemoglobin; PLT, platelet; LDH, lactic dehydrogenase; FAB, French-American-British; CR, compete remission; MST, HLA-mismatched stem cell micro-transplantation; ACST, autologous stem cell transplantation; CSA, cytarabine single agent; MRD, Minimal residual disease; MAC, the abbreviation for MST, ASCT and CSA

Table 2 Clinical outcomes after different post-remission treatments

eristics	MST (n = 22)	ASCT (n = 17)	CSA (n = 24)	*P* value
neutrophil recovery, days	11(9-15)	11(10-12)	13(11-18)	0.003*
	13(9-19)	13(10-21)	15(11-18)	0.076*
platelet recovery, days (range)	0	0	0	
nt-related mortality, n (%)	20(90.90)	17(100)	21(87.5)	0.335**
, n (%)	5(22.73)	4(23.53)	7(29.16)	0.863**
nage, n (%)	0	0	0	
host disease, n (%)	23.5	21	11.5	
ollow-up, months (range)	Undefined	Undefined	32	0.287*
dian (months)	Undefined	Undefined	59	0.221*
ian (months)				

Note: *ANOVA test, **Pearson Chi-Square test, LFS, leukemia free survival; OS, overall survival; MST, HLA-mismatched stem cell micro-transplantation; ACST, autologous stem cell transplantation; CSA, cytarabine single agent

Table 3 The characteristics and clinical outcomes of 22 patients received MST

Characteristic	Cases (n)	Ration (%)
Graft type		
Umbilical cord blood	7	31.82
Peripheral blood	15	68.18
HLA match		
≥ 6/12	10	45.45
6/12	12	54.55
Median TNCs,$\times 10^8$/kg (range)	3.01(0.29-5.40)	
Median CD34+ cells,$\times 10^6$/kg (range)	0.80(0.07-4.07)	
Infused cycles		
1-2	8	36.36
≥ 3	14	63.64
Complications		
Infection	20	90.90
Hemorrhage	5	9.10
Other	1	4.54
GVHD	0	0
OS, range (months)	(5-74)	
RFS, range(months)	(3-72)	

Note: HLA, Histocompatibility antigen; TNC, Total nucleated cells; GVHD, Graft versus host disease; RFS, relapse free survival; OS, overall survival; MST, HLA-mismatched stem cell micro-transplantation

Figures

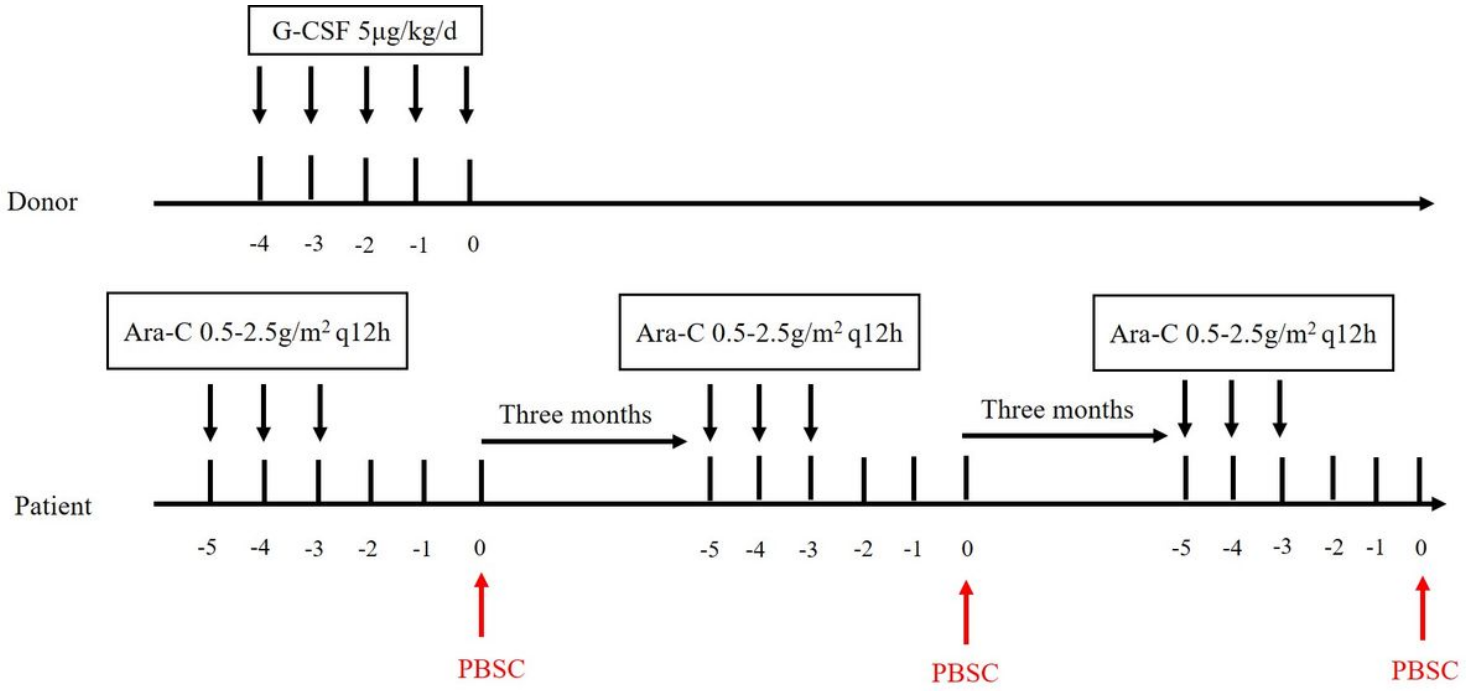

Figure 1

Treatment schedule of MST infusion of HLA mismatched peripheral blood stem cell. The donors were subcutaneously injected with 5-7 μg/kg granulocyte colony stimulating factor, per 12 hours a day for 5 days for mobilization. The patients were received a median dose cytarabine (0.5 g/m^2 to 2.5 g/m^2 per 12 hours intravenously on days 1, 2, 3) according to age followed by infusion of HLA mismatched peripheral blood stem cell 48 hours after each course of the cytarabine chemotherapy, with three months intervals between two cycles.

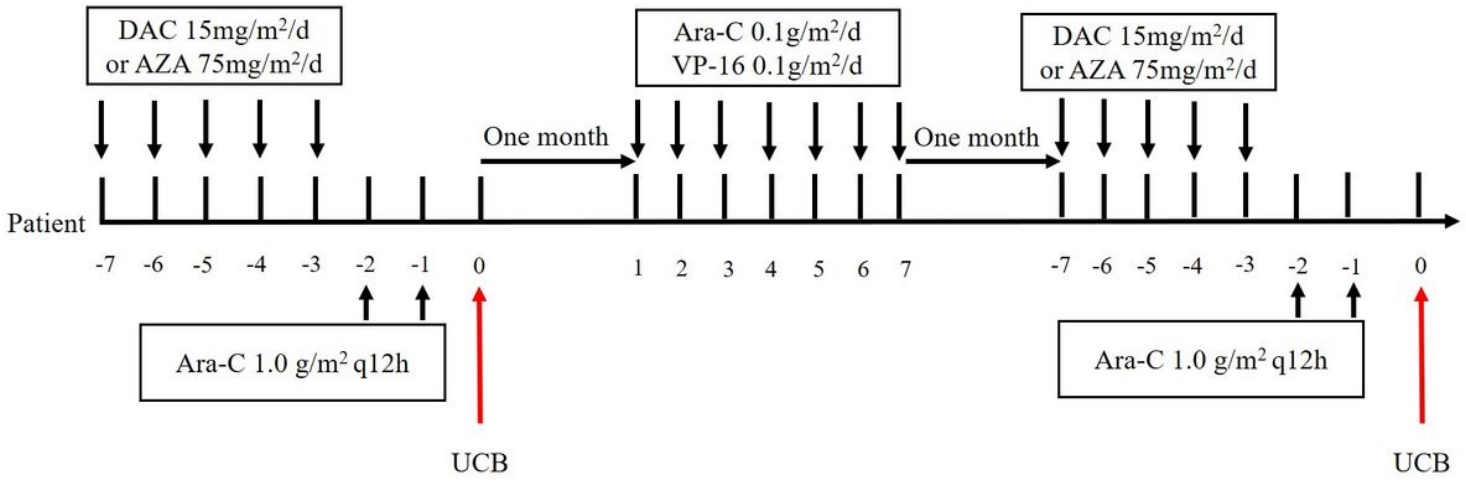

Figure 2

Treatment regimen of MST infusion of HLA mismatched umbilical cord blood stem cell. Umbilical cord blood stem cells were derived from the Cord blood bank of Shandong, China. The patients were treated decitabine (15 mg/m^2 every day on days 1 to 5) or azacitidine (75 mg/m^2 every day on days 1 to 5) and

median cytarabine (1.0 g/m^2 per 12 hours intravenously on days 1 to 2) followed by infusion HLA mismatched umbilical cord blood stem cell 24 hours after chemotherapy, with three months intervals between two courses, EA regimen (cytarabine 0.1 g/m^2 every day on days 1 to 7 and etoposide 0.1 g/m^2 every day on days 1 to 7) was given in the interval as consolidation chemotherapy.

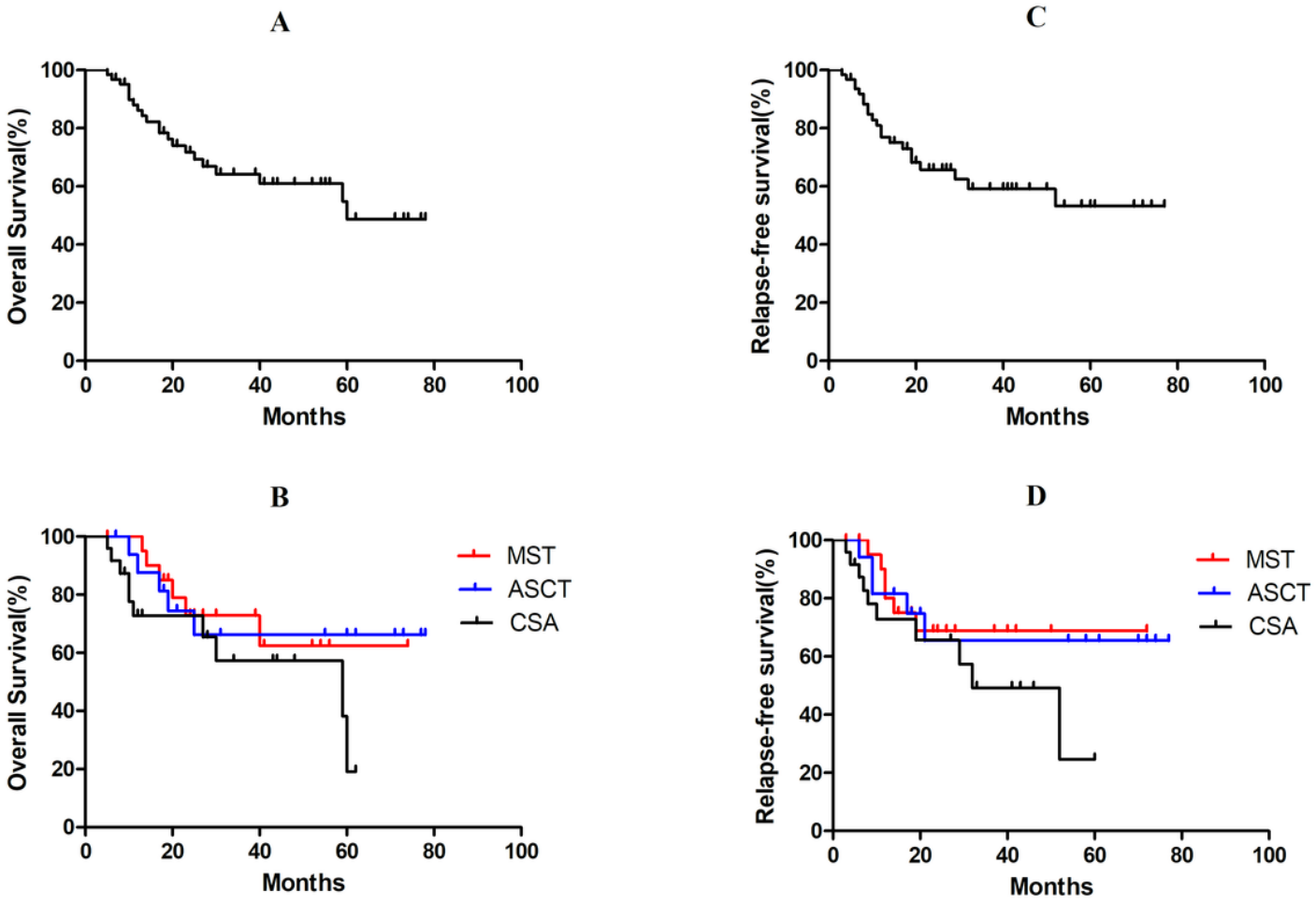

Figure 3

Survival analysis of all patients and different groups' patients. (A) The median for OS time was 5 years in 63 patients; (B) The estimated OS at 2 years was 72.9%, 66.2%, and 65.5% in MST group, ASCT group and CSA group (χ^2 = 3.079, P = 0.215); (C) The median for RFS time in all patients was undefined; (D) The estimated RFS at 2 years was 68.7%, 59.9%, and 57.4% in MST group, ASCT group and CSA group ($\chi 2$ = 2.159, P = 0.340).

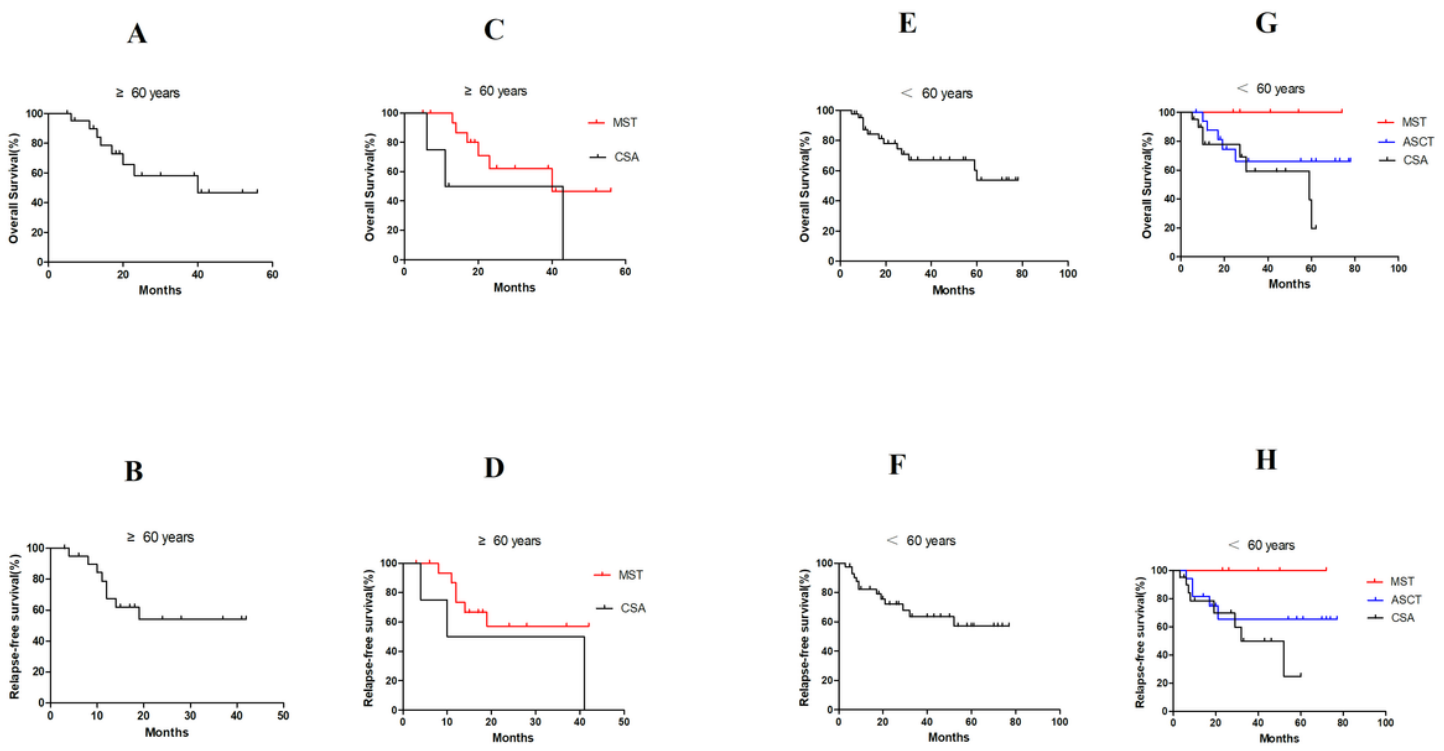

Figure 4

Survival analysis of patients over 60 years and under 60 years. For patients over 60 years of age, (A-B) the estimated OS and RFS at 2 years was 58.3% and 54.2%, respectively; (C) the estimated OS at 2 years was 62.2% and 50.0% in MST and CSA group (P = 0.101); (D) the estimated RFS at 2 years was 57.1% and 50.0% in MST and CSA group (P = 0.136). For patients under 60 years of age, (E-F) the estimated OS and RFS at 2 years was 74.6% and 67.7%; (G) the estimated OS at 2 years was 100.0%, 66.2%, and 69.1% in MST, ASCT and CSA group (MST vs CSA, P = 0.044); (H) the estimated RFS at 2 years was 100.0%, 65.4%, and 59.8% (MST vs CSA, P = 0.050).

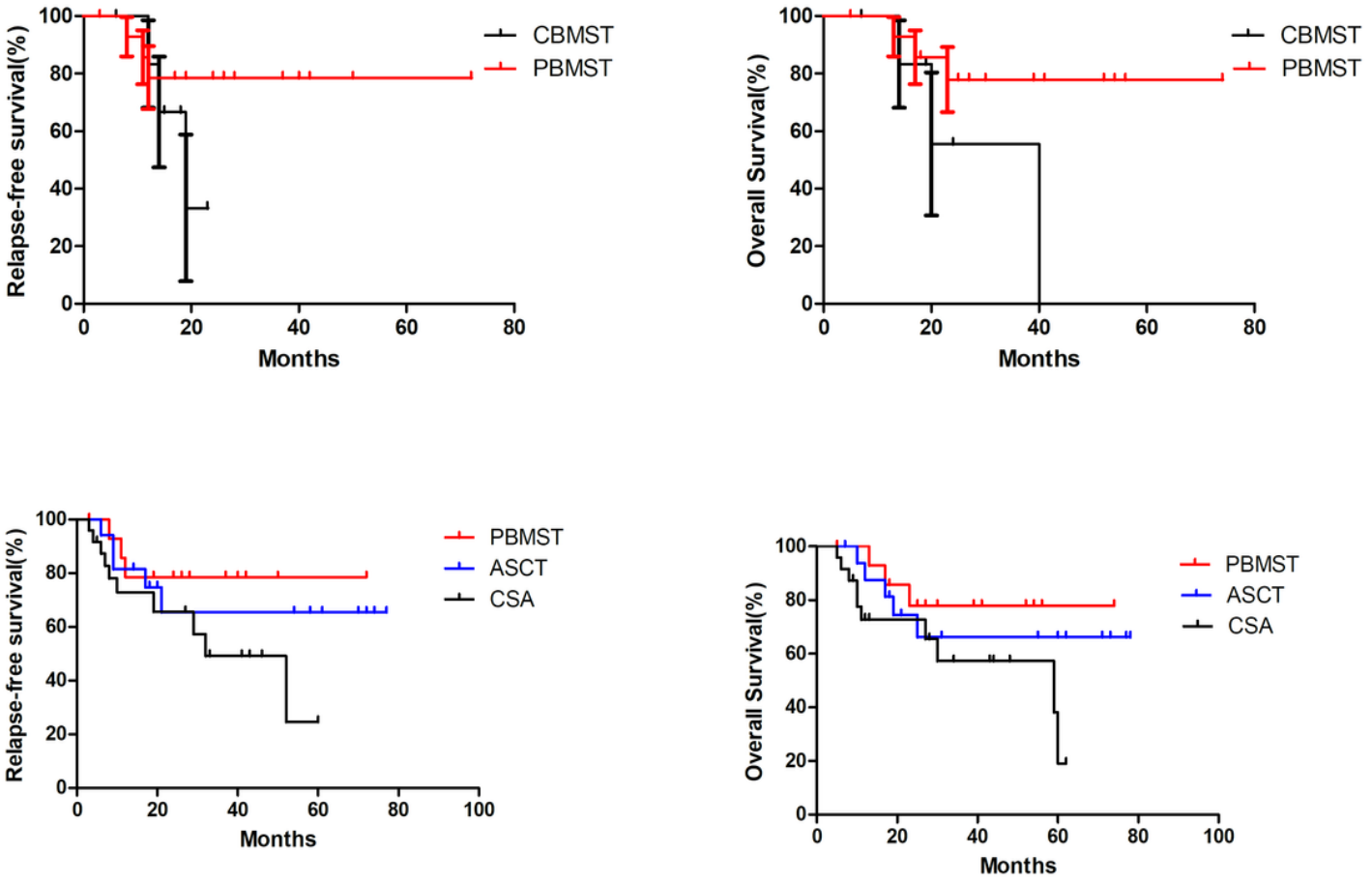

Figure 5

Survival analysis of PBMST and other groups' patients. (A) The median for RFS time was 19 months in CBMST group, and RFS time was undefined in PBMST group (χ^2 = 1.280, P = 0.257); (B) The median for OS time was 40 months in CBMST group, and RFS time was undefined in PBMST group (χ^2 = 2.430, P = 0.119); (C) The median for RFS time in PBMST and ASCT group were both undefined, and median survival in CSA was 59 months(χ^2 = 3.948, P = 0.138); (D) The estimated RFS at 2 years was 78.5%, 65.4%, and 65.6% in PBMST group, ASCT group and CSA (χ2 = 3.242, P = 0.197).