Microtransplantation improves the outcome of older patients with newly diagnosed acute myeloid leukaemia: a single-centre study with long-term follow-up

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Article

Keywords: Microtransplantation, Older patients, Acute myeloid leukaemia.

Posted Date: March 29th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1212388/v2

Abstract

This retrospective single-centre study was to validate the efficacy and safety of microtransplantation in the treatment of older patients with acute myeloid leukemia (AML). Microtransplantation combines chemotherapy and human leukocyte antigen (HLA)-mismatched peripheral blood stem cell infusion without graft-versus-host disease (GVHD) prophylaxis. Totally, 26 newly diagnosed AML patients who received microtransplantation therapy were enrolled in our study from April 2008 to April 2018. The deadline date of follow-up was December 31, 2019. Patients were divided into 2 age groups: 60 ~ 70 years (n = 17) and > 70 years (n = 9). The study analyzed the data of complete remission (CR) rate, overall survival (OS), leukemia free survival (LFS), hematopoietic recovery time, and treatment related toxicities. 10 patients were still alive with complete remission (CR) on the deadline date, and the median overall survival (OS) was 64 months. The CR, relapse and nonrelapse mortality rates were 84.6%, 38.5% and 30%, respectively. Both OS ($p < 0.0001$) and leukaemia free survival (LFS) ($p < 0.0001$) were significantly higher in the younger group than in the older group. The median times of neutrophil and platelet recovery were 12 days and 14 days, respectively. These data showed that MST could be an alternative treatment for older AML patients.

Introduction

AML impacts older adults, at a median age of 68 years [1]. Most older AML patients have very poor outcomes, with a 5-year relative survival rate of only 12.5% [2, 3]. Older AML patients usually can choose only nonintensive treatment without full-dose chemotherapy or transplantation [4, 5], and the median survival of older AML patients receiving low-dose chemotherapy is no longer than 16 weeks [6–9]. Therefore, nonintensive treatment does not improve the outcome of older AML patients.

Recently, many new molecule-targeted drugs and transplantation innovations have greatly prolonged their overall survival [10–13]. Microtransplantation (MST) combines the infusion of HLA-mismatched donor granulocyte colony-stimulating factor–mobilized peripheral blood stem cells (G-PBSCs) with appropriate-dose chemotherapy but without a conditioning regimen or immunosuppressive drugs. Compared to the control group, MST statistically improved the CR rate to 80.0% and the 2-year LFS rate to 38.9% with rapid haematopoietic recovery in older AML patients [14]. Some centres have reported that MST could improve the outcomes of AML patients [15–20]. However, other institutions did not find similar efficacy of MST in treating AML patients [21, 22]. Briefly, more studies need to be conducted to validate the efficacy and safety of MST in treating older AML patients.

To validate the efficacy and safety of MST, we evaluated the rates of CR, OS and LFS as well as GVHD and the treatment-related toxic effects of older AML patients receiving MST therapy in our single centre study.

Methods

Patients and Donors

In total, 26 patients (≥ 60 years) with newly diagnosed AML were enrolled in our study from April 2008 to April 2018. The deadline for follow-up was December 31, 2019. One patient was lost to follow-up after CR2 with 30-month OS and 27-month LFS. The diagnosis was defined by World Health Organization criteria consisting of primary AML or a history of myelodysplasia syndrome, except acute promyelocytic leukaemia [23,24]. The prognostic risk groups were defined by cytogenetics and gene mutation according to the NCCN 2017 criteria [25]. The standard risk group included patients with favourable and intermediate prognoses; the high-risk group included patients with poor prognoses. Donor selection criteria were as follows: healthy adults without previous history of cancers or critical basic diseases, aged from 18 to 55 years, related or unrelated to patients. Before transplantation, donor and recipient HLA-A, -B,-C, -DR, -DQ, and -DP alleles were typed by polymerase chain reaction (PCR) with a sequence-specific priming-based molecular method (Invitrogen). The acceptable level of HLA mismatch was 5/12-7/12[14,17, 20].

MST

One course of MST included chemotherapy and the infusion of G-PBSCs. For induction chemotherapy, idarubicin hydrochloride (8-10 mg/m^2) or mitoxantrone hydrochloride (6-8 mg/m^2) was used for 3 days, and cytarabine (100-150 mg/m^2) was used for 7 days. The interval between the infusion of G-PBSCs and the completion of cytarabine was 24 hours. Patients without CR need the 2nd induction chemotherapy. For postremission therapy, patients need more than 2 courses of MST. Each course of MST included cytarabine (1.0-1.5 g/m^2 for 6 doses) and an infusion of G-PBSCs. Generally, the interval between the courses was 3 months. Patients 60-70 years old without a high comorbidity index will be suggested to receive allogeneic haematopoietic stem cell transplantation (allo-HSCT). In this study, patients 60-70 years old who had no suitable donors for allo-HSCT or were not willing to receive allo-HSCT were recommended to receive MST therapy. No patient received any GVHD prophylaxis. Patients received subcutaneous G-CSF and intravenous infusion of antibiotics for infection prophylaxis when their absolute neutrophil count was <0.5×10^9/L. Support treatment, including transfusion and nutrition, was administered if necessary. Patients who relapsed during the treatment were considered to have therapy failure and received identical reinduction chemotherapy or terminated MST.

Mobilization and Apheresis of Donor Peripheral Mononuclear Cells

The HLA-mismatched donor was subcutaneously injected with 5 μg/kg G-CSF (Kirin Corp) twice a day for 5 days, and a leukocyte count up to approximately 50×10^9/L was suitable for apheresis peripheral mononuclear cells with a CS-3000S cell separator (Baxter). G-PBSCs from donors were equally divided for each course of MST. Usually, fresh G-PBSCs are used in the first course of MST, and other stem cells cryopreserved in liquid nitrogen are used in the subsequent courses of MST.

Detection of Donor Microchimerism

The level of haematopoietic donor microchimerism was detected by InDel assay, which could detect donor-specific cells at levels of 0.01% to 0.001%. Microchimerism detections were generally performed during white blood cell count recovery before each new cycle of therapy. If the donor microchimerism was positive, we performed an InDel assay to monitor donor microchimerism until negative after completing therapy continuously.

Primary Endpoints

According to the 2021 version of the NCCN Guidelines Insights: Acute myeloid leukaemia, primary endpoints such as CR, relapse, early death, the cumulative incidence of relapse, NRM, OS and LFS were elaborated in detail as follows [26]. GVHD was defined according to published criteria [27]. Patients with CR had less than 5% blasts in bone marrow, no circulating blasts or blasts with Auer rods, and no extramedullary disease. Moreover, peripheral blood had more than 1.0×10^9/L neutrophils and more than 100×10^9/L platelets; additionally, MRD (minimal residual disease) was detected by multiparameter flow cytometry (MFC) was negative. Patients with relapse had more than 5% blasts in bone marrow, any blast in blood or extramedullary organs, or positive molecular markers. Patients who died within 4 weeks of the beginning of chemotherapy defined early death. The cumulative incidence of relapse was measured from the date of CR to the date of relapse; if patients were not known to have relapsed, they were censored on the date when they were last assessed; if patients died without relapse, they were counted as a competing cause of failure. NRM: any cause for death except relapse. OS: the time between confirmation of diagnosis and death; if patients were not known to have died at last follow-up, they were censored on the date they were last known to be alive. LFS: the time between CR and relapse or death from any cause; if patients were not known to have relapsed or died at last follow-up, they were censored on the date they were last assessed. The start time point of ANC and Plts count recovery was defined as the first of 3 consecutive days in which the ANC was < 2×10^9/L and the platelet count was < 100×10^9/L after completing the last dose of chemotherapy. The end time point of ANC and Plts count recovery was defined as the first of 3 consecutive days in which the ANC was > 0.5×10^9/L and the platelet count was > 30×10^9/L as previously described [14].

Statistical Analysis

The independence of the categorical parameters was calculated using an accurate chi-square test or the correct Fisher's test. The log-rank test was used to analyse survival data, and the Kaplan–Meier method was used to draw survival curves. Data on primary endpoints were evaluated by univariate and multivariate Cox proportional hazards regression models. A significant difference was identified as p 0.05. SPSS 21.0 software (IBM, Armonk, NY, USA, http://www-01.ibm.com) was used in all statistical analyses.

Results

Characteristics of patients and donors

In total, 26 patients were divided into the 60-70 year old group and the >70 year old group (Table 1). 84.6% of donors were related to patients. The donors of the 60~70 year old group were much younger than those of the >70 year old group (p = 0.0006). Compared to the >70 year old group, more patients in the 60-70 year old group received more than 3 courses of MST therapy (p = 0.0008). In summary, except for donor age and MST courses, there were no significant differences in most characteristics between the two age groups.

Response to induction chemotherapy

The CR rate of all patients was 84.6%, in which 2 patients achieved CR after 2 courses of induction chemotherapy (Table 2). A total of 94.1% of patients from the 60~70 year old group and 66.7% of patients from the >70 year old group achieved CR. There was no significant difference in overall CR rates between the two age groups. All patients with standard risk achieved CR, but 76.5% of patients with high risk achieved CR.

Total death rate, early death rate and causes of death

In this study, the total death rate and the early death rate were 57.7% and 15.4%, respectively (Table 2). The total death rate of the 60-70 year old group was much lower than that of the > 70 year old group (p = 0.002). In total, 30.8% of patients died of relapse, 15.4% died of severe infection, and 11.5% died of organ failure. Fewer patients died of severe infection in the 60-70 year old group than those in the >70 year old group (p = 0.008).

Haematopoietic recovery and adverse events

The median neutrophil and platelet recovery times were 12 days and 14 days after induction chemotherapy, respectively. The adverse events of the patients are summarized in Supplementary Table 1. The constipation rate of the >70 year old group was significantly higher than that of the 60-70 year old group (p = 0.002). The pulmonary infection rate of the >70 year old group was higher than that of the 60-70 year old group (p = 0.009).

OS and LFS

The median follow-up time was 20.5 months (range, 1-135 months). In particular, 10 patients were still alive with CR on December 31, 2019, and the median OS was 64 months. The OS rate of all patients was 41.3% (Table 2). The OS rate of the 60-70 year old group was significantly higher than that of the >70 year old group (p< 0.0001). The Kaplan–Meier analyses showed that patients from the 60-70 year old group, the standard risk group and the group receiving more than 3 courses of MST had much longer OS times than their corresponding groups (p < 0.0001, p = 0.0155, and p = 0.0009) (Figure 1 A, C and D).

The LFS rate was 52.4% (Table 2). All 10 leukaemia-free patients were from the 60-70 year old group. Therefore, the LFS rate of the 60-70 year old group was higher than that of the >70 year old group (p< 0.0001). In the Kaplan–Meier analysis, patients from the 60-70 year old group and the group receiving

more than 3 courses of MST had much longer LFS times than their corresponding groups ($p < 0.0001$ and $p = 0.0056$) (Figure 2 A and D).

Relapse and nonrelapse mortality

During follow-up, 38.5% of patients experienced relapse (Table 2). The median relapse time of these 8 patients was 8.5 months (range, 4-20 months). The relapse rate of the 60-70 year old group was lower than that of the >70 year old group (21.0% vs. 83.3%, $p = 0.0002$). Thirty percent of patients died of nonrelapse diseases, including 5 patients with severe pulmonary infection, 1 patient with cerebral haemorrhage and 1 patient with acute GVHD (Table 2). Compared to the >70 year old group, the 60-70 year old group had a much lower cumulative incidence of NRM (18.1% vs. 100%, $p = 0.0296$).

Donor microchimerism and GVHD

96.2% of patients had negative donor microchimerism. Only one 62-year-old female patient was diagnosed with severe acute GVHD with high fever, rash, diarrhoea and severe hyperbilirubinemia, and mixed donor chimerism was detected after 4 courses of MST therapy. The donor of the patient was her 28-year-old daughter. The patient was infused with MNCs (3.84×10^8/kg), $CD34^+$ (3.21×10^6/kg) and $CD3^+$ (0.76×10^8/kg) in each course of MST therapy. The chimaerism rate increased from negative to 7.973%, reaching 25.809% after one week. The patient failed to respond to anti-GVHD treatment and died of multiorgan failure at Day 44 after the fourth MST.

Univariate Cox proportional regression analyses

Univariate Cox proportional regression analysis showed that patient age, donor age, risk and the number of courses of MST therapy might be factors for OS (Supplementary Figure 1A). Patient age, risk and the number of courses of MST therapy might be factors for LFS (Supplementary Figure 1B). Patient age and the infused MNC dose might be factors affecting the cumulative incidence of relapse (Supplementary Figure 1C). The number of courses of MST therapy might affect the cumulative incidence of NRM (Supplementary Figure 1D).

Discussion

The current study summarized the experience of MST therapy for newly diagnosed AML patients aged 60 to 85 years. Complete remission and haematopoietic recovery as soon as possible are vital in treating AML [28-30]. Our data showed that the overall CR rate was 84.6% (22 of 26), and OS rates at 1year and 3 years were 65.4% and 41.3%, respectively (Table 2), indicating an equivalent efficacy compared to the results of other MST reports [14,17]. Additionally, the median neutrophil recovery time and platelet recovery time were 12 days and 14 days in MST, respectively, similar to other MST studies [14, 17]. Therefore, our experience showed that MST therapy could be an alternative treatment for older AML patients.

Patent age was still an important prognostic factor in this study. We found that patients aged 60-70 years had a much higher CR rate, lower death rate and longer OS time than those aged >70 years. In the >70 year old group, the median survival was 10 months, and the 1-year OS rate was 33.3%. Similarly, Kantarjian H et al. also reported that intensive chemotherapy did not benefit most older patients (age 70 years or older) with AML (median survival: 4.6 months, 1-year OS rate 28%) [29]. Although MST is a novel tool for treating AML patients aged > 70 years, chemotherapy in MST may be adjusted with tolerable medicines such as venetoclax and azacitidine.

In this MST study, patients with standard risk, including favourable and intermediate-risk patients, had higher CR rates (100% vs. 76.5%) and 1-year OS rates (82.4% vs. 33.3%) than those with high risk. In a case-control study, the 2-year OS (74.1% vs. 34.3%) and LFS rates (73.3% vs. 31.6%) of MST were inferior to those of allogeneic haematopoietic stem cell transplantation (HLA-matched sibling donor) for intermediate/high-risk AML in CR1 [31]. Therefore, we suggest that patients at high risk undergo allogeneic haematopoietic stem cell transplantation to improve prognosis.

As in other MST studies, our patients were encouraged to receive at least 2 courses of MST for postremission therapy. Guo Mei et al. reported that 3 courses of MST as postremission therapy for AML significantly improved the 6-year LFS and OS rates in the low-risk and intermediate-risk groups [20]. In another study, older AML patients who achieved CR received 2 to 3 courses of MST as postremission therapy and achieved a high 2-year OS rate [17]. Our study also found that more than 3 courses of MST therapies could prolong the OS time of older AML patients. Therefore, to a certain extent, more courses of MST therapy may provide longer-term benefits for older AML patients.

The infusion of donor stem cells might induce antileukaemic responses to MST therapy [32]. In MST therapy, the incompletely destroyed immune system of patients could reject most donor cells. Therefore, microchimerism exists in patients who receive sequential MST therapy in postremission treatment. Microchimerism was reported to be a potential reason for MST antileukaemia[33,34]. Additionally, an MST mouse model demonstrated that G-PBSC infusion might stimulate recipient-derived T-cell responses for indirect antitumour effects [35]. However, one patient in our study developed serious acute GVHD and died of multiorgan failure. If patients have a persistent high fever, rash, diarrhoea, hepatic injury and chimaerism higher than 1% at 1 week after stem cell infusion, we should pay close attention to the risk of GVHD [17]. At this time, we need to monitor the cytokines IL-6, IL-8, sTNFR1, sST2, Reg3α and elafin to predict the risk of GVHD. Generally, steroid therapy and CD25mab will be adopted, and intermission of microtransplantation will be extended for the patient when there is rising chimaerism.

Azacitidine has been primarily used to treat AML patients older than 60 years or those who cannot accept intensive conventional chemotherapy. Venetoclax combined with azacitidine has usually been used to treat older adults with primary or secondary AML who are ineligible for conventional chemotherapy [36]. The rates of CR or CR with incomplete haematologic recovery (CRi) were 54% for the low-dose cytarabine/venetoclax regimen and 67% for the azacitidine/venetoclax doublet, with a significant

extension in OS to a median of 10–18 months [37]. If we combine azacitidine and/or venetoclax with stem cell infusion as a new microtransplantation regimen in treating older AML patients, the drug resistance rate may be reduced, and patients may obtain higher CR rates and longer overall survival.

In conclusion, MST therapy could be an alternative treatment for older AML patients. Patients in the 60-70 year old group and the more than 3 courses of MST group had much better clinical outcomes. Further studies on optimizing the chemotherapy factor of MST and expanding donor sources will become as important as the mechanism of MST antileukaemia.

Declarations

Acknowledgments

This work was supported by the Science and Technology Plan Project of Beijing under Grant Z161100000516231, the Capital Health Research and Development of Special under Grant NO.2014-4-5081 and the Youth Development Program of Military Medical Science and Technology under Grant 16QNP029. Thanks for all authors for collecting, summarizing, analyzing data and writing paper.

Author contributions

WJ S, J L, and XM H were involved in the conception and design. J L and XM H were involved in the analysis and interpretation of the data. WJ S, J L, and XM H were involved in drafting the paper and revising it critically for intellectual content and the final approval of the version to be published. YK Y, YY Q, JN Z, PP L, and C Y collected data. All authors agree to be accountable for all aspects of the work.

Competing interests

The authors declare no competing interests.

Data availability

The datasets generated and analyzed in this study are available from the corresponding author upon reasonable request.

Ethics statements

The study involving human participants was reviewed and approved by the ethics committee of PLA Rocket Force Characteristic Medical Center. In accordance with the Helsinki Declaration, written informed consent for enrollment in this study was obtained from all of the patients or their legal guardians and the donors.

Publisher's Note

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Tables

Table 1-2 are available in the Supplementary Files section.

Figures

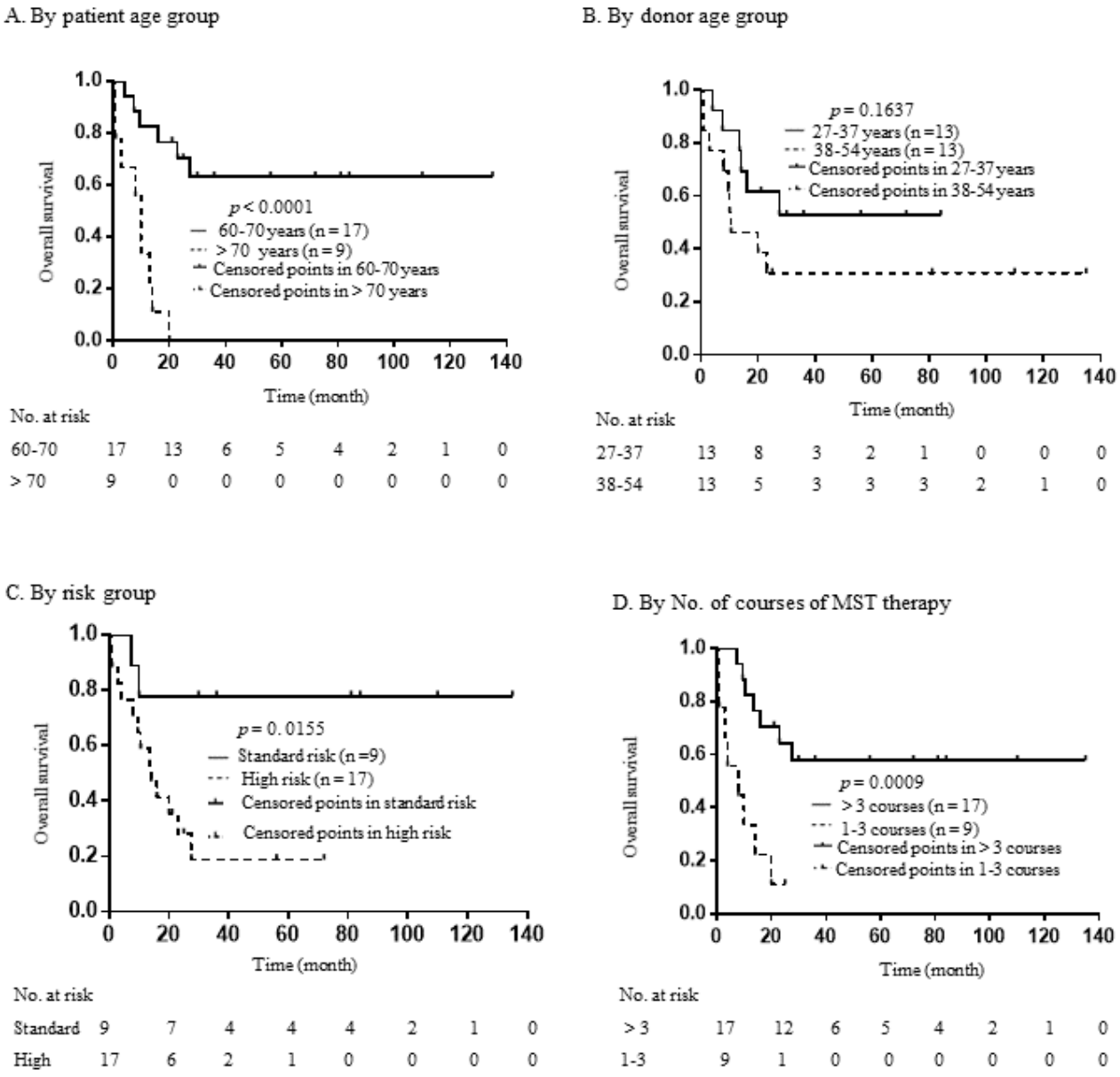

Figure 1

Overall survival of older AML patients after MST.

Overall survival analyses of AML patients were performed by dividing patients into 2 groups according to patient age (A), donor age (B), risk (C) or the NO. of courses of MST therapy (D).

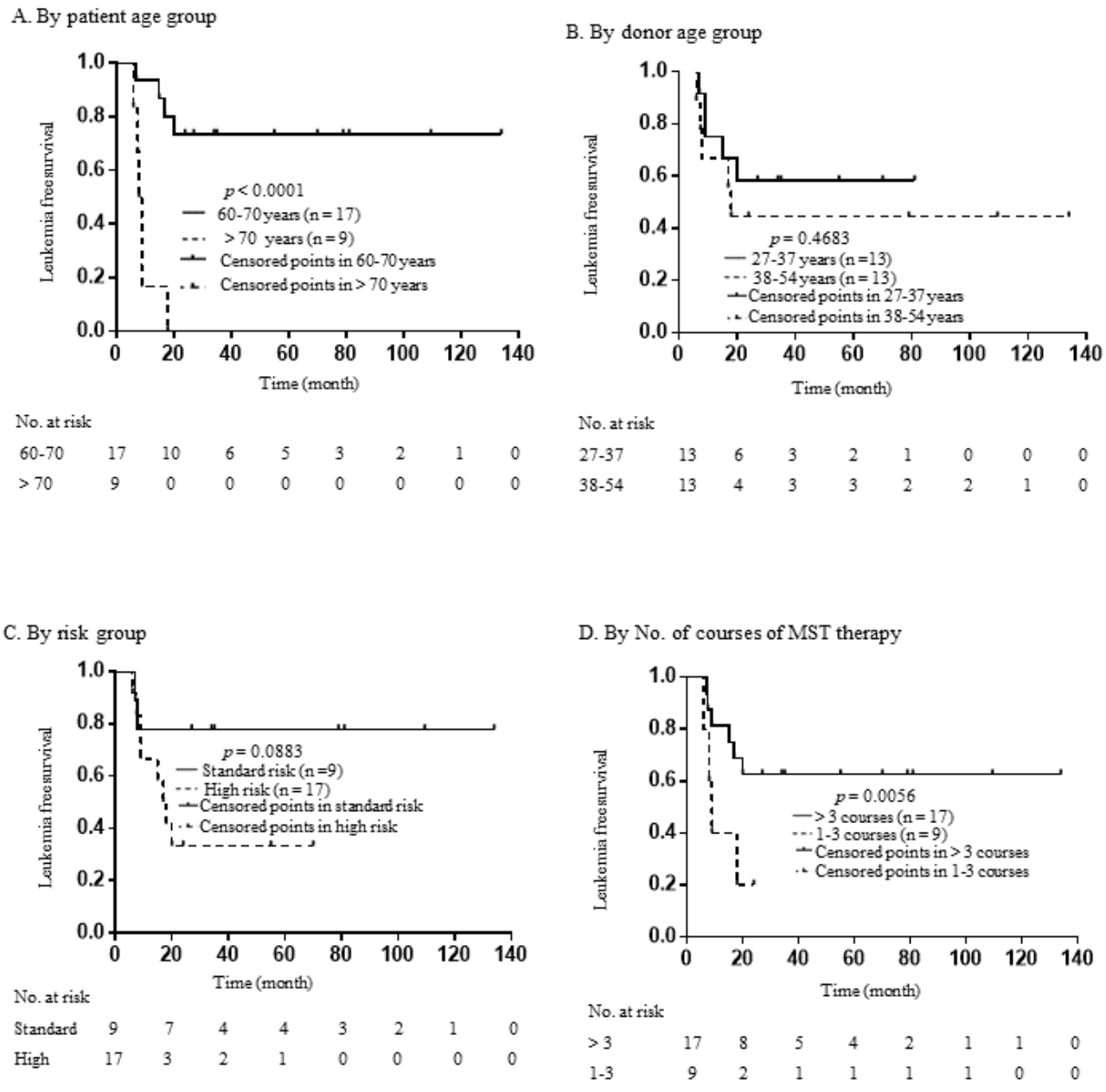

Figure 2

Leukemia free survival of older AML patients after MST.

Leukemia free survival analyses of AML patients were performed by dividing patients into 2 groups according to patient age (A), donor age (B), risk (C) or the NO. of courses of MST therapy (D).

Supplementary Files

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