A Study of Human Leukocyte Antigen Mismatched Cellular Therapy (Stem Cell Microtransplantation) in High-Risk Myelodysplastic Syndrome or Transformed Acute Myelogenous Leukemia

KAI-XUN HU,a QI-YUN SUN,a MEI GUO,a JUN-XIAO QIAO,b CHANG-LIN YU,a JIAN-HUI QIAO,a ZHENG DONG,a WAN-JUN SUN,b HONG-LI ZUO,a YA-JING HUANG,a BO CAI,a HUI-SHENG Ai

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ABSTRACT

The treatment outcomes of myelodysplastic syndrome (MDS) and transformed acute myelogenous leukemia (tAML) remain very unsatisfactory. We designed a combination of human leukocyte antigen (HLA)-mismatched hematopoietic stem cell microtransplantation (MST) with chemotherapy for patients with MDS and tAML and evaluated its effects and toxicity. Patients were between 13 and 79 years old. Patients with MDS (n = 21) were given HLA-mismatched MST combined with decitabine and cytarabine; patients with tAML (n = 22) were given HLA-mismatched MST combined with decitabine and cytarabine, and also mitoxantrone. Patients in complete remission (CR) also received MST plus decitabine and medium-dose cytarabine chemotherapy without graft-versus-host disease (GVHD) prophylaxis. The overall response rate of the patients with MDS was significantly higher than that of those with tAML (81% vs. 50%; p = .03). The CR rates were 52.4% and 36.4% in the two groups, respectively. There was no difference in the cytogenetic CR rate between the MDS and tAML groups (85.7% vs. 70%, respectively; p = .7). The 24-month overall survival of the patients with MDS was significantly higher than that of the patients with tAML (84.7% and 34.1%, respectively; p = .003). The median recovery times of neutrophils and platelets were, respectively, 14 and 17 days in the patients with MDS, and 16 and 19 days in those with tAML. The treatment-related mortality rates were 4.8% and 18.2%, respectively, in the MDS and tAML groups (p = .34). No GVHD was observed in any patient. Microtransplantation combined with decitabine and chemotherapy may provide a novel, effective, and safe treatment for high-risk MDS and tAML.

SIGNIFICANCE

Microtransplantation (MST) refers to regular chemotherapy combined with granulocyte colony-stimulating factor-mobilized peripheral blood stem cell infusion of human leukocyte antigen-mismatched donor cells without using immunosuppressive agents. It aims to support hematopoietic recovery and perform graft-versus-leukemia (GVL) effects but differs from traditional allogeneic stem cell transplantation because the rate of donor cell chimerism is low and there is no graft-versus-host disease (GVHD) risk. Thus, a trial was designed to evaluate the safety and efficacy of MST in patients with myelodysplastic syndrome and those with transformed acute myelogenous leukemia. Higher complete remission and cytogenetic complete response rates were observed, and the treatment improved disease progress-free survival, sped hematopoietic recovery, and avoided GVHD.

INTRODUCTION

Despite the widespread use of DNA methylation inhibitors such as decitabine or azacytidine, and of hematopoietic allogeneic stem cell transplantation, the outcome of myelodysplastic syndrome (MDS), especially in patients whose MDS has transformed to acute myeloid leukemia (tAML), remains unsatisfactory [1–4]. There is a low complete remission (CR) rate and poor overall survival [1]. Large phase II cohort studies or randomized phase III trials of decitabine with or without other chemotherapy drugs, such as low-doseage cytarabine combined with anthracycline, showed a low CR rate (approximately 9%–37%) and progression-free survival (PFS) and overall survival (OS) of 6–12 and 10–19 months, respectively [2, 3]. Moreover, myelosuppression is a
major adverse outcome of the combination of decitabine or deci-
tabine plus other drugs, which largely limits its use, particularly in
patients with prolonged cytopenia; delay or termination of subse-
quent treatment cycles may occur, and frequently occurs [4–6].

Allogeneic stem cell transplantation (alloSCT), including non-
myeloablative (NST) or reduced-intensity conditioning (RIC), has
some curative effects in patients with MDS. However, both RIC
and NST have been associated with severe complications, such
as significant graft-versus-host disease (GVHD) [7], lack of suitable
related HLA-matched donors, and age limitations (the median age
of patients with MDS at diagnosis is 70 years) [8–14].

Recently, our clinical studies and other data have shown that
human leukocyte antigen (HLA)-mismatched microtransplanta-
tion (MST) using cytarabine and HLA-mismatched granulocyte
colonystimulating factor-mobilized donor peripheral blood stem
cell (GPBSC) infusion did not require GVHD prophylaxis [15, 16].
MST resulted in donor microchimerism, improved survival, and
avoided GVHD. However, it is unclear whether MST in combina-
tion with decitabine and cytarabine chemotherapy can improve the
outcomes of patients with advanced MDS, especially those with
TAML. Therefore, to evaluate its effects and toxicity, we designed a combination of MST with decitabine and chemother-
apy as a novel therapy for patients with MDS and tAML.

**Materials and Methods**

The study involved eligible patients with MDS or tAML, between
13 and 79 years of age, who were recruited between September
2010 and October 2013. Their diagnoses were morphologically
confirmed according to World Health Organization (WHO) crite-
ria. Cytogenetic analyses on pretreatment bone marrow samples
were performed at diagnosis using standard banding techniques
and classification was made according to the International System
of Human Cytogenetic Nomenclature [17]. Molecular markers such
as AML1-ETO, PML-RARa, NPM1, and FLT3-ITD were also analyzed.

The criteria for eligibility were as follows: primary or
treatment-related MDS or chronic myelomonocytic leukemia
irrespective of white blood cell counts (according to the 2008
WHO classification of MDS or TAML) [18]; International Prognostic
Scoring System intermediate 2, or high risk [18]; and Eastern Co-
operative Oncology Group performance status of 0–2. Patients
who had HLA-matched related donors and received alloSCT were
excluded from the study.

The study protocol was approved by the Human Ethics Com-
mittee of the Affiliated Hospital of the Academy of Military Med-
ical Sciences, Beijing, and the Second Artillery General Hospital,
Beijing, before the start of enrollment at each center, and was
conducted in accordance with the Declaration of Helsinki. All pa-

tients and donors provided written informed consent before en-
rollment in the study. This trial was registered with ClinicalTrials.
gov (NCT01674985; http://www.clinicaltrials.gov).

Before MST, donor and recipient HLA-A, -B, -C, -DRB1, -DQB1
alleles were genotyped by sequence-specific priming polymerase
chain reaction (Thermo Fisher Scientific, Waltham, MA, USA,
https://www.thermofisher.com). Of the 43 patients/donor pairs,
4 were matched in 0 of 10 HLA loci, 12 were matched in 1–4 of
10 loci; 22 in 5 of 10; and 5 in 6–7 of 10 HLA loci. Of the 43
patient/donor relationships, 16 were the sons of patients, 9 were
dughters, 4 were sisters, 3 were brothers, 2 were the fathers, 1
was a cousin, 1 a granddaughter, 1 a grandson, 1 a nephew, 2 were
nieces, and 3 were unrelated.

**Treatment Design**

**Induction Therapy**

The patients with MDS were given a 3-hour infusion of decitabine
(25 mg/m²) daily for 4 days in combination with cytarabine
(150 mg/m²) daily for 7 days as a short infusion, followed by intrave-
nous infusion of GPBSCs 24 hours after each completed cycle of
cytarabine therapy. The patients with tAML were additionally
given mitoxantrone (8 mg/m²) daily for 3 days. Mandatory bone
marrow aspiration was performed on day 28 or at the time of he-
matopoietic recovery after the treatment. If a patient failed to
achieve CR, additional cycles of the same induction therapy were
permitted, depending on the patient’s medical condition (Fig. 1).

**Postremission Treatment**

Patients achieving CR received 4 further courses of postremission
therapy with decitabine (25 mg/m² daily for 4 days) and medium-
dose cytarabine therapy (2 g/m² infused over 3 hours every 12
hours intravenously on days 1, 2, and 3) followed by infusion of
HLA-mismatched GPBSCs 24 hours after each cycle of cytarabine
chemotherapy. If the patient was older than 65 years, the dose of
cytarabine was reduced to 1.0 g/m² for 6 doses. No GVHD, cyto-
megalovirus (CMV), or Pneumocystis carinii prophylaxis was used
before or after the MST therapy. Follow-up to assess for GVHD
occurred at least once every 4–6 weeks in the first 12 months,
then every 3 months after completing therapy for up to 2 years.
The antigens of CMV and Epstein-Barr virus (EBV) were detected
from patients and donors before treatment. If patients had a high
fever after first treatment, the antigens of CMV and EBV were de-
tected repeatedly.

**Mobilization and Apheresis of Donor Peripheral
Mononuclear Cells**

Apheresis and mobilization of HLA-mismatched donor peripheral
mononuclear cells were performed as previously described [16].
After apheresis, the donor cells were aliquoted and cryopre-
served in liquid nitrogen; however, fresh donor cells were used
in the first course of treatment. Cell infusion was performed 24
hours after the chemotherapy course. The median numbers
(range) of mononuclear, CD34+, CD3+, and natural killer (NK) cells
infused per course were, respectively, 3.0 (2.9–4.8) × 10⁸, 2.0
(1.6–3.4) × 10⁸, 1.0 (0.8–2.4) × 10⁸, and 0.2 (0.03–0.8) × 10⁶ cells
per kilogram [16].

**Analysis of WT1/HLA-A*0201–CD8+ T Cells**

Of the 43 patients and/or their donors who had HLA-A*0201 or
HLA*2402, 22 were monitored for WT1/HLA-A*0201 or WT1/
HLA-A*2402 CD8+ T cells in peripheral blood before and after
MST, using a pentamer peptide antigen, as previously described.
A pentamer of an irrelevant peptide (SLNVTAVL; Proimmune,
Oxford, UK, https://www.proimmune.com) was used as a nega-
tive control.

**Detection of Donor Chimerism and Microchimerism**

**Chimerism Detection**

Hematopoietic donor chimerism was detected in all 43 patients
by a standard cytogenetic analysis and a semiquantitative PCR-
based analysis of the short tandem repeats, with the ability to de-
tect as few as 1% donor cells [19].

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Microchimerism Detection (Donor Cells <1%)  
Of the 43 patients who had male donors and were available for the detection of a Y chromosome, only 6 (all women) were consecutively monitored for donor microchimerism from peripheral blood cells and bone marrow cells. Real-time quantitative PCR was used to detect the sex-determining region of the Y chromosome, with a sensitivity of $10^{-9}$ cells, as previously described [15, 16]. These assays of chimerism and microchimerism were performed at white blood cell count recovery before each new cycle of therapy, at 4 weeks after the last round of consolidation, and, if still positive, every 3 months after completing therapy for up to 2 years.

Criteria of Response and Outcome Evaluation

Responses were determined according to the revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes [1, 2]. A CR required normalization of the bone marrow and peripheral blood with 5% or less marrow blasts, a granulocyte count of $1 \times 10^9$ cells per liter or more, and a platelet count of $100 \times 10^9$ cells per liter or more in peripheral blood lasting for at least 4 weeks. A PR is similar to CR except that persistent marrow blasts are greater than 5% but are reduced from 50% or more. A marrow CR (MR) is the reduction of marrow blasts to 5% or less without normalization of peripheral counts. For this study, overall response (OR) rate included CR, PR, MR, and hematopoietic improvement. Cytogenetic complete responses were defined as the disappearance of cytogenetic abnormality. The recovery time of neutrophils was defined as the first of 3 consecutive days in which the absolute neutrophil count was $>0.5 \times 10^9$ cells per liter, while that of platelets was defined as the first of 3 consecutive days in which the platelet count was $>50 \times 10^9$ cells per liter, as previously described [1, 2]. The response duration was dated from the first evidence of response until disease progression, as defined by the International Working Group. PFS was defined as the time from response to progression, relapse after attaining of CR or partial response, or death. OS was defined as the time from assignment to death or to the last date of the follow-up until October 2013. Acute GVHD and chronic GVHD were defined according to published criteria [20].

Statistical Analysis

SPSS 21 software (IBM, Armonk, NY, USA, http://www-01.ibm.com) was used for all statistical analyses. Survival data were analyzed by a log-rank test, and survival curves were created using the Kaplan-Meier method. Multivariate analysis of survival and CR were performed using Cox’s proportional hazards regression analysis. The independence of categorical parameters was calculated using either a chi-square or Fisher’s exact test. Statistical significance was defined as $p < .05$.

RESULTS

Characteristics of the Patients

Of a total of 58 potential patients, only 43 were enrolled in the study. Of the 15 who were not enrolled, 3 died early, 3 refused to participate, 7 received other nonprotocol treatments, and for 2, the reasons were unknown.

The clinical characteristics of the 43 patients were comparable among the MDS and tAML groups (Table 1).

Response to Induction Chemotherapy

The OR rate for all patients was 65.1%, and that of patients with MDS was significantly higher than that of patients with tAML (81% vs. 50%; $p = .03$). The overall CR rate for all patients was 44.2%. The CR rate of the MDS and tAML groups was 52.4% and 36.4%, respectively ($p = .14$). The CR rate was not significantly different for patients 60 years and older versus patients younger than 60 years (45.5% vs. 42.9%; $p = .86$). Importantly, the cytogenetic CR rate for all patients was 76.5%; this was not significantly different between the MDS and tAML groups (85.7% and 70%, respectively; $p = .7$) (Table 2).

Hematopoietic Recovery

The median time for neutrophil recovery was not significantly different between the MDS and tAML groups (14 and 16 days, respectively). The median time for platelet recovery was also not significantly different between the groups (17 and 19 days, respectively).

Safety

The incidences of severe infection and/or hemorrhage were not significantly different between the MDS and tAML groups (Table 3). The treatment-related mortality rate was also not significantly different between the two groups (4.8% vs. 18.2%, respectively; $p = .34$) (Table 2). The main causes of death were pulmonary or intestinal infection and bleeding. There were no signs of acute or chronic GVHD, including unexplained skin rashes, diarrhea, or other symptoms (Table 3).

PFS and OS

The 19 patients who achieved complete remission, including of 11 patients with MDS and 8 with tAML, received high-dose cytarabine with decitabine as postremission chemotherapy. The 24-month PFS values in the MDS and tAML groups were 42.7% and 17.5%, respectively ($p = .17$) (Fig. 2). The 24-month OS of the
patients with MDS was significantly higher than that of those with tAML (84.7% and 34.1%, respectively; \(p = .003\)) (Fig. 2).

**Detection of Donor Microchimerism and WT1+CD8+ T Cells**

No full or mixed-donor chimerism was found in any patient. However, donor microchimerism was detected in 4 of the 6 assessable women, with between 0.0000697 and 0.56 gene copies per patient. Of the 22 patients with positive HLA-A*0201 or HLA*2402, 9 had a detectable WT1+CD8+ T-cell response between 0.11% and 0.48% after MST. In the remaining 13 patients, no WT1+CD8+ T cells were detected.

By multivariate analysis of the number of MNC, CD34+, CD3+, and NK cells infused, as well as the age and sex of donors or patients, the positive prognostic impact parameters were positive WT1+CD8+ T cell and high numbers of infused CD3 T cells. The OR rate was higher in patients with positive WT1+CD8+ T cells than in those with negative WT1+CD8+ T cells (88.9% vs. 61.5%, respectively; \(p = .04\)). The CR rate was also significantly higher in patients who received a high dose of donor T cells (>0.9 \(\times\) 10^6 cells per kilogram) in each course than those who received a lower dose (<0.9 \(\times\) 10^6 cells per kilogram; 59.1% vs. 28.6%; \(p = .04\)) (Table 4).

**DISCUSSION**

The outcome of MDS remains unsatisfactory, especially for tAML, although DNA methylation inhibitors and hematopoietic alloSCT are generally used. In the present study, the clinical results showed that MST with chemotherapy resulted not only in a higher CR rate and more rapid hematopoietic recovery but also in higher PFS and OS rates than previously reported in the literature for decitabine alone or combination with other chemotherapy agents in patients with MDS and those with tAML, in whom the overall CR rate was approximately 8%–35% [21, 22].

An interesting finding is that MST possibly improved the response rate of patients with MDS and patients with tAML; however, it should be explored further in a larger clinical trial. In this study, the CR rate and the overall response were 52.4% and 81%, respectively, in the patients with advanced MDS, which were higher than in patients with tAML (36.4% and 50%, respectively).
MST improved the cytogenetic CR rate (85.7% of patients with MDS and 70% of those with tAML). The first plausible explanation for these findings is that MST mediated antileukemic effects to improve treatment outcomes. Our previous studies proved that MST can induce specific antileukemic effects and improve survival in patients with AML [15, 16]. In this study, the positive effects of WT1+CD8+ cytotoxic T lymphocytes were observed in 9 of the 22 patients with positive HLA*0201 or HLA*2402. These patients showed a higher OR rate than those without WT1+CD8+ T cells, suggesting specific antileukemic effects. The patients who received a high dose of donor T cells (>0.9 x 10^8 cells per kilogram) showed a much higher CR rate than those with a lower dose of T cells.

There is still no definitive, effective postremission therapy for patients with MDS who achieve CR. Several studies have shown that an additional 8–10 continuous courses of decitabine-only therapy for patients with CR of MDS may help delay progression of disease and improve overall survival; however, 2-year OS was still less than 20% [22]. In this study, we used MST and decitabine and medium-dose cytarabine chemotherapy as a postremission therapy for patients with CR of MDS. The results showed that the 24-month PFS and OS were 42.7% and 84.7%, respectively, in patients with MDS and 17.5% and 34.1% in patients with tAML. These results suggest that MST combined with decitabine and cytarabine as a postremission therapy may be effective in delaying disease progression and improving PFS and OS for patients with MDS and those with tAML [5, 23–25].

Particular attention has been paid to the risk of aggravated myelosuppression and delayed hematopoietic recovery when decitabine only is used, which is estimated to be in greater than 50% in these patients. In this study, the median periods of neutropenia and thrombocytopenia in patients with MDS were only 14 and 17 days, respectively. These recovery times are much shorter than those of patients who received decitabine alone, for whom the median days of neutropenia and thrombocytopenia were approximately 19–28 days or more [1, 3]. Furthermore; continuous monitoring of engraftment showed that the recovered neutrophils after MST were of recipient origin. These results are different from those of standard alloSCT or NST studies, in which a rapid neutrophil recovery was based on successful donor engraftment. Although the exact mechanism is still unclear, we hypothesize that the improvement in hematopoietic recovery by MST may be related to the GPBSCs containing a large number of hematopoietic stem and progenitor cells, where GPBSCs, in conjunction with granulocyte colony-stimulating factor, promoted hematopoietic recovery and stimulated cellular cytokine secretion.

Severe GVHD is the main complication following HLA-mismatched alloSCT with myeloablative or NST conditioning. Interestingly, in this study, no clinical signs of acute or chronic GVHD were observed, even though total numbers of mononuclear cells in the MST group were the 3–4 times than the number of mononuclear cells in the myeloablative or NST regimen. These results indicate that MST may separate clinical GVHD and GVL. Further investigation will be necessary to explore the mechanism responsible for the avoidance of GVHD [26].

\[\text{Table 4. Clinical responses of multiple facts}\]

| Patient characteristic | Patients, n | CR, n (%) | ORR, n (%) |
|------------------------|-------------|-----------|------------|
| Age <60 years          | 21          | 9 (42.9)  | 13 (61.9)  |
| Age ≥60 years          | 22          | 10 (45.5) | 15 (68.2)  |
| Age >70 years          | 10          | 4 (40)    | 7 (70)     |
| CTL positive           | 9           | 5 (55.6)  | 8 (88.9)   |
| CTL negative           | 13          | 3 (23.1)  | 8 (61.5)   |
| CD3 cells ≥0.9 x 10^8 per kilogram | 22 | 13 (59.1) | 16 (72.7) |
| CD3 cells <0.9 x 10^8 per kilogram | 21 | 6 (28.6)  | 12 (57.1)  |
| HLA allelic matches, 0–4/10 | 16 | 7 (43.7)  | 10 (62.5)  |
| HLA allelic matches, 5–7/10 | 27 | 12 (44.4)| 18 (66.7)  |

\*p < .05 for the difference between high- and low-dose CD3 cells groups or in CTL-positive and -negative groups.

Abbreviations: CR, complete remission; CTL, cytotoxic T lymphocyte; HLA, human leukocyte antigen; ORR, overall response rate.
CONCLUSION

MST in combination with decitabine and cytarabine chemotherapy resulted in higher rates of CR, cytogenetic CR, PFS, and rapid hematopoietic recovery, suggesting a safer and more effective treatment regimen than traditional chemotherapy for MDS and tAML. Further studies involving a larger cohort of patients and longer follow-up are warranted.

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