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Survival Advantage and Comparable Toxicity in Reduced-Toxicity Treosulfan-Based versus Reduced-Intensity Busulfan-Based Conditioning Regimen in Myelodysplastic Syndrome and Acute Myeloid Leukemia Patients after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Treosulfan has been incorporated in conditioning regimens for sustained remission without substantial toxicity and treatment-related mortality (TRM). We aimed to analyze the safety and efficacy of a fludarabine 150 mg/m^2 and treosulfan 42 g/m^2 (FluTreo) conditioning regimen in medically infirm patients. Outcomes were compared with those of a similar historical group treated with fludarabine 150 mg/m^2 to 180 mg/m^2, busulfan 6.4 mg/kg, and antithymocyte globulin (ATG) 5 mg/kg to 7.5 mg/kg (FluBuATG). Thirty-one consecutive patients with acute myeloid leukemia (AML; n = 21), myelodysplastic syndrome (MDS; n = 6), or treatment-related AML (n = 4) received FluTreo conditioning. The historical group consisted of 26 consecutive patients treated with FluBuATG. In the FluTreo group, engraftment was prompt in all patients and 74% achieved >99% donor chimerism by day +30. No grades III or IV organ toxicities were noted. One-year cumulative incidences (CI) of acute and chronic graft-versus-host disease (GVHD) were 19.4% and 58.4%. The groups were similar for age, disease risk, lines of treatment, hematopoietic cell transplantation–specific comorbidity index, and acute or chronic GVHD incidence, except that there were more matched unrelated donor recipients in the FluTreo group ($P < .001$). With 20 (range, 2 to 36) months follow-up for FluTreo and 14 (range, 2 to 136) for FluBuATG, the 1-year cumulative overall survival (OS) probability was 76% versus 57%, respectively ($P = .026$); 1-year disease-free survival (DFS) was 79% versus 38% ($P < .001$). In multivariate analysis, the only significantly favorable factor for OS and DFS was FluTreo ($P = .010$ and $P = .012$). The CI of relapse mortality was markedly decreased in FluTreo versus FluBuATG (7.4% versus 42.3%, $P < .001$). In conclusion, the treosulfan-based regimen resulted in favorable OS and DFS with acceptable toxicity and low relapse rates compared with busulfan-based conditioning.

INTRODUCTION

Allogeneic (allo) hematopoietic stem cell transplantation (HCT) has become a curative therapy for hematological malignancies over the last 50 years. The aggressive standard myeloablative conditioning regimens are based mainly on total body irradiation (TBI) or busulfan and may result in multiple organ toxicity and high treatment-related mortality (TRM). Prolonged time to engraftment and prolonged use of immunosuppression result in increased risk for bacterial, viral, and fungal infections. The serious short- and long-term side effects of myeloablative regimens warranted the exploration of less toxic reduced-intensity conditioning (RIC) regimens [1].

In addition to its application in patients considered unsuitable for standard "classic" myeloablative HCT because of comorbidities, RIC alloHCT is increasingly being used as an alternative approach in older patients who would otherwise not be eligible for transplantation [2]. Indeed, acute

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myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are primarily diseases of the elderly, with a median patient age at diagnosis of 70 years. High-risk MDS and AML are aggressive diseases, with AML patients having a 5-year relative survival rate of 5% to 15% [3].

However, currently used RIC regimens have limitations, compared with conventional regimens, such as increased relapse and TRM rates. In addition, RIC regimens have not yet reached a plateau in survival rates [4-8]. Therefore, the optimal pretransplantation regimen for MDS and/or AML patients older than 55 years remains to be determined. In an effort to optimally tailor transplantation to individual patients, diverse protocols have been introduced for different disease entities, patient status, and degrees of remission. Treosulfan has gained much interest for the excellent toxicity profile in both RIC and myeloablative regimens [9-14].

We hypothesized that a reduced-toxicity regimen of fludarabine 150 mg/m^2, treosulfan 14 g/m^2, and antithymocyte globulin (ATG) 5 mg/kg (FluTreoATG) would achieve favorable outcomes in AML and/or MDS patients older than 55 years of age. The current study was designed to explore both safety and efficacy of FluTreoATG in medically infirm patients. Furthermore, we compared the outcome with a similar control population treated with fludarabine 150 mg/m^2, busulfan 6.4 mg/kg, antithymocyte globulin 5 mg/kg to 7.5 mg/kg (FluBuATG) reduced-intensity conditioning, which had been used in older patients and those with medical comorbidities.

PATIENTS AND METHODS

Study Population

We studied consecutive patients undergoing alloHCT from January 2002 to September 2015 in our Joint Accreditation Committee-International Society for Cellular Therapy and European Group for Blood and Marrow Transplant–accredited unit who met the following selection criteria: (1) age at HCT between 55 and 65 years; (2) HCT-CI >2 (medically infirm patients); (3) diagnosis of de novo or treatment-related AML or MDS without active disease after chemotherapy; (4) available sibling or unrelated donor (8/8 allele matched or 7/8 allele or antigen mismatched by molecular typing of HLA-A, -B, -C, -DRB1); (5) peripheral blood stem cells as the graft source; and (6) FluTreo or FluBuATG as the conditioning regimen.

Patients receiving FluBuATG were analyzed as a historical control population. Patients' medical history, clinical evaluation, and course were recorded in detail. To assess comorbidity risk, we used the HCT-CI by Sorror et al. [15]. Disease risk was also determined by the disease risk index (DRI) described by Armand et al. [16] and disease phase (early or advanced) was determined either according to previous treatment lines (>2) or to MDS progression. Our institutional review board approved this study and all patients gave a written informed consent in accordance with the Helsinki Declaration.

Conditioning Regimen

The FluTreo myeloablative reduced-toxicity conditioning regimen consisted of fludarabine 150 mg/m^2 (i.v. for 5 consecutive days) and treosulfan 42 g/m^2 (i.v. infused over 1 hour for 3 consecutive days). FluTreo patients with unrelated donors received 5 mg/kg of rabbit ATG. The control group received the RIC regimen, FluBuATG, which consisted of fludarabine 150 mg/m^2 to 180 mg/m^2, busulfan 6.4 mg/kg, and ATG 5 mg/kg to 7.5 mg/kg. To avoid reactions to ATG, methylprednisolone 80 mg every 8 hours was given on the ATG infusion days in both groups and was quickly tapered.

Prophylactic granulocyte colony–stimulating factor after transplantation was routinely used in both regimens. Supportive care also comprised of prophylactic platelet transfusion if platelet counts decreased to $<20 \times 10^9$/L or prophylactic red blood cell transfusion if hemoglobin levels decreased to <8 g/dL. All patients received supportive treatment against bacterial, fungal, and viral infections. Trimethoprim-sulfamethoxazole was used as prophylaxis against *Pneumocystis jirovecii* infection. Patients also received pre-emptive treatment for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) reactivation after close molecular monitoring. CMV and EBV infection and disease were managed according to international standards [17,18].

GVHD Prophylaxis

Assessment and grading of acute graft-versus-host disease (GVHD) were performed according to criteria suggested by Glucksberg et al., while chronic GVHD was assessed and graded according to Sullivan et al. criteria [19,20]. Transplant recipients received traditional cyclosporine (CSA) and mycophenolate mofetil until day +45 after transplantation (sibling and unrelated donor) for GVHD prophylaxis. Plasma CSA concentration was maintained between 100 ng/mL and 200 ng/mL until day +90 in sibling transplantations and +150 in matched unrelated donor transplantations. CSA dose was tapered by 5% every week if there were no signs of chronic GVHD.

Chimerism

Chimerism evaluation in unfractionated bone marrow with STR (short tandem repeat) fragment analysis was performed regularly (on days +14, +30, +60, +90) in both groups. Donor chimerism ≥99% was considered *complete donor chimerism*.

Statistical Analysis

Data were analyzed using the statistical program SPSS 22.0 (ISPSS Statistics for Windows, Version 22.0. IBM Corp, Armonk, NY). Continuous variables were described as median and range and categorical variables as frequencies. Continuous variables were assessed for normality and compared using Student's *t*-test or the Mann-Whitney test. Categorical variables were compared using the chi-square test. Multivariate analysis was performed by logistic regression model. The Kaplan-Meier method was used for survival analysis and the log-rank test for survival curves comparison. Cumulative incidence of competing events analysis was performed using the EZR software (http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) [21]. Statistical significance was assessed by the Gray test and Fine and Gray regression modeling. The level of statistical significance was defined at .05.

RESULTS

Study Population

We studied 31 patients treated with FluTreo between October 2013 and April 2016 and 26 in the control FluBuATG group who underwent transplantation between 2002 and 2012. A comparison of patient characteristics at transplantation for the 2 groups is shown in Table 1. No significant

Table 1
Characteristics at Transplantation in the Two Groups

Characteristic	FluTreo (n = 31)	FluBuATG (n = 26)	*P*
Age, median (range), yr	55 (25-65)	56 (26-63)	.936
Disease diagnosis			.994
AML de novo	21	20	
Secondary AML	4	1	
MDS	6	5	
Previous lines of treatment, median (range)	3 (1-6)	2 (0-4)	.104
Disease			.255
AML de novo			
CR1	8	16	
Late CR1	7	1	
CR2	6	3	
Secondary AML			
CR1	4	1	
High-risk MDS	6	5	
Phase			.977
Advanced	18	15	
Early	13	11	
DRI			.333
Low	—	1	
Intermediate	17	16	
High	14	9	
Donor			<.001
Sibling	12	22	
Unrelated	19	4	
8/8 HLA matching	11	4	
CD34			.266
>6	15	10	
<6	16	16	

Continuous variables are expressed as median (range).
CR indicates complete remission.