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Sirolimus and Mycophenolate Mofetil as Calcineurin Inhibitor–Free Graft-versus-Host Disease Prophylaxis for Reduced-Intensity Conditioning Umbilical Cord Blood Transplantation

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A B S T R A C T

The use of calcineurin inhibitors (CNIs) to reduce the risk of graft-versus-host disease (GVHD) after hematopoietic cell transplantation (HCT) requires intensive post-transplantation toxicity monitoring. Sirolimus-based GVHD prophylaxis is associated with a favorable toxicity profile and requires less intensive monitoring. However, the efficacy of sirolimus-based regimen compared with CNI-based regimen has not been evaluated in the setting of reduced-intensity conditioning (RIC) double umbilical cord blood (UCB) HCT. We compared outcomes of patients receiving sirolimus/mycophenolate mofetil (MMF) (n = 37) or cyclosporine (CSA)/MMF (n = 123) in an ongoing phase II study of RIC UCB transplantation. In multiple regression analysis, sirolimus/MMF did not influence the risk of grades II to IV or grades III and IV acute GVHD. In addition, there was no association between type of GVHD prophylaxis and hematopoietic engraftment. Infection density analysis found a significantly lower risk of infections with sirolimus/MMF between days +46 and +180 after HCT compared with CSA/MMF (3.4 versus 6.3 per 1000 patient-days, $P = .03$); however, no difference was observed before day +45. Sirolimus/MMF use resulted in no thrombotic microangiopathy, fewer instances of elevated serum creatinine >2 mg/dL (14% versus 45%; $P < .01$), and similar rates of sinusoidal obstruction syndrome (2.7% versus 4%; $P = .68$), compared with CSA/MMF. Disease-free survival at 1 year was 51% for sirolimus/MMF and 41% for CSA/MMF ($P = .41$), and sirolimus/MMF use did not influence the risk of nonrelapse mortality or survival. In conclusion, sirolimus/MMF GVHD prophylaxis was better tolerated and resulted in similar rates of GVHD and survival as compared to CSA/MMF after RIC double UCB transplantation.

INTRODUCTION

Sirolimus is a mammalian target of rapamycin (mTOR) inhibitor with immunosuppressive properties. Sirolimus has been shown to permit relative expansion of thymic-derived regulatory T cells and the preferential inhibition of effector T cell function [1-4]. In addition, sirolimus has been found to be effective in preventing graft-versus-host disease (GVHD) both in rodent models [5,6] and in human studies [4,7-9]. Calcineurin inhibitors (CNIs) can successfully reduce the risk of GVHD; however, their use requires intensive post-transplantation monitoring of side effects, such as nephrotoxicity, electrolyte imbalances, hypertension, posterior reversible encephalopathy syndrome, and transplantation-associated thrombotic microangiopathy (TMA). Given sirolimus's overall favorable side effect profile, less frequent need for drug level monitoring, and lower cost compared with CNIs [10,11], it has been increasingly used for the past decade as an immunosuppressive agent both after solid-organ transplantation and allogeneic (allo) hematopoietic cell transplantation (HCT) [4,7,12-14]. In addition, the direct antineoplastic activity of sirolimus via mTOR pathway inhibition makes it a particularly attractive GVHD prophylaxis drug for recipients of alloHCT with hematological malignancies, especially in the reduced-intensity conditioning (RIC) setting,

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where relapse remains the main cause of treatment failure [7,15]. Despite the recently increased use of sirolimus in alloHCT for GVHD prophylaxis, most studies have examined sirolimus in combination with CNIs in mainly adult related or unrelated donor HCT [8,16-23]. No studies have compared sirolimus-based and CNI-based GVHD prophylaxis in recipients of RIC double umbilical cord blood (UCB) HCT. The present study compares the outcomes of GVHD prophylaxis with cyclosporine (CSA)/mycophenolate mofetil (MMF) or sirolimus/MMF after RIC double UCB HCT.

METHODS

Study Design and Patient Eligibility

We performed a secondary analysis of data from the ongoing phase II study of RIC double UCB HCT. The protocol for GVHD prophylaxis was originally CSA/MMF; however, it was amended to use sirolimus/MMF in September 2012. Eligible patients were those ≤75 years old with no available matched sibling donor, who had a Karnofsky score >60% and adequate organ functions (cardiac left ventricular ejection fraction ≥35%, pulmonary diffusing capacity of the lungs for carbon monoxide (DLCO) >30% predicted, liver transaminases <5 times and total bilirubin <3 times the upper limit of normal, serum creatinine ≤2.0 mg/dL, as described) [24]. Patients with previous alloHCT and those receiving experimental cellular therapies were excluded. The protocol was approved by the University of Minnesota institutional review board. All patients/guardians provided written informed consent. The study was registered at clinicaltrials.gov as NCT00305682.

Treatments

Sirolimus was administered once daily, with 8 mg to 12 mg oral loading dose on day –3, followed by 4 mg daily dose with target trough levels 3 ug/L to 12 ug/L until day +100, followed by a tapering of the dose by day +180. CSA was administered twice daily, with initial dose of 2.5 mg/kg intravenously (i.v.) on day –3, then was continued either i.v. or orally until day +100 to maintain a target trough level between 200 ng/mL and 400 ng/mL, followed by a tapering of the dose by day +180. All patients received MMF at 1.5 g twice daily between days –3 and +30; MMF was delivered intravenously initially and then orally in the same dose.

We used institutional guidelines for UCB graft selection with both units 4/6- to 6/6-matched to the patient and to each other [24]. Minimum required total nucleated cell dose at cryopreservation was 1.5×10^7/kg per unit. The RIC conditioning regimen consisted of fludarabine at a dose of 30 mg/m^2 daily for 5 days, cyclophosphamide at a single dose of 50 mg/kg, and total body irradiation (TBI) at a dose of 200 cGy as a single fraction. Antithymocyte globulin (ATG) at a dose of 15 mg/kg twice daily for 3 days was given to patients receiving no immunosuppressive chemotherapy within 3 months [24,25]. Supportive care has been previously described and did not change over the 2 time periods of the study [24,25].

Definitions and Endpoints

The primary study endpoint was the incidence of acute GVHD at day +100 graded, as previously described [26,27]. Secondary endpoints included neutrophil and platelet engraftment, nonrelapse mortality (NRM) at day +180, relapse, disease-free (DFS), and overall survival (OS) at 1 year. Exploratory endpoints included infections within post-transplantation intervals of days 0 to +45 and days +46 to +180. Bacterial, fungal, and viral infectious episodes were previously described [25]. Patient, disease, and transplantation characteristics included age, sex, year of transplantation, disease diagnosis, disease risk, hematopoietic stem cell transplantation comorbidity index (HCT-CI), prior history of autologous transplantation, recipient cytomegalovirus (CMV) serological status, HLA disparity by worst unit matching, ATG use, infused total nucleated cell dose, and total CD34$^+$ cell dose. Disease risk was defined as either standard or high risk at HCT using America Society for Blood and Marrow Transplantation 2006 risk scoring schema [28]. HCT-CI was assessed before alloHCT [29]. Patient outcomes are reported as of April 2015. *Neutrophil engraftment* was defined as absolute neutrophil counts recovery of $>.5 \times 10^9$/L for 3 consecutive measures by day +42, and *platelet engraftment* as platelet count recovery >20,000 by day +180 and platelet transfusion-free for at least 7 days. *DFS* was defined as being alive without malignancy relapse or progression after HCT. *OS* was defined as the time from HCT to death from any cause.

Statistical Analysis

Comparisons between GVHD prophylaxis cohorts were completed with the log-rank test. OS and DFS were estimated by Kaplan-Meier curves with 95% confidence intervals (CI) derived from the standard errors [30]. NRM was analyzed using cumulative incidence treating relapse as a competing risk. Relapse was analyzed using cumulative incidence treating death as a competing risk. Neutrophil and platelet engraftment were analyzed using cumulative incidence treating nonevent death as a competing risk [31]. Fine and Gray proportional hazards regression was used to assess the independent effect of the indices on NRM, relapse, and engraftment [32]. Factors considered in the regression models included HLA disparity considering the worst matched UCB units (4/6 versus 5/6 + 6/6), age (<60 versus 60+), disease (acute leukemia versus lymphoma versus other), disease risk (standard versus high risk), gender (male versus female), Karnofsky performance status at baseline (60% to 80% versus 90% to 100%), HCT-CI (0 versus 1 or 2 versus ≥3), recipient CMV serostatus (positive versus negative), prior auto transplantation (yes versus no), conditioning (ATG versus no ATG), Human Herpesvirus 6 (HHV6) reactivation (no versus prior outcome), and grades II to IV acute GVHD as a time-dependent variable. Backward selection was used to build prognostic factor models for all endpoints. A P value of ≤.05 was considered significant for remaining in the model; however, GVHD prophylaxis was included in all models. The cumulative density function was used to estimate the infection density per 1000 patient days to account for multiple infections per patient. The Mantel-Haenszel test was used to compare the frequency of bacterial, fungal, and viral infections between 2 GVHD prophylaxis types for person-years data. The analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

The patient, disease, and transplantation characteristics of sirolimus/MMF-treated patients (n = 37) and CSA/MMF-treated patients (n = 137) are summarized in Table 1. The year of transplantation differed between the 2 groups because alloHCT recipients received sirolimus/MMF GVHD prophylaxis after 2012. Patients in the sirolimus/MMF cohort were older (median age, 61 versus 53 years; $P < .01$), but they had less comorbid conditions at transplantation than the CSA/MMF cohort (HCT-CI ≥3, 27% versus 55%; $P < .01$). However, the remaining patient, disease, and treatment characteristics

Table 1
Patient Characteristics

Variable	Sirolimus/MMF n = 37	CSA/MMF n = 123	P Value*
Age, median, range, yr	61 (22-69)	53 (21-69)	<.01
Male	28 (76)	74 (60)	.09
Year of HCT			<.01
2006-2009	0 (0)	98 (80)	
2010-2014	37 (100)	25 (20)	
HLA disparity (worst match)			.42
4/6	20 (60)	59 (49)	
5/6	14 (38)	53 (43)	
6/6	3 (8)	11 (9)	
ATG in conditioning	17 (46)	48 (39)	.45
Diagnosis			.40
Acute leukemia	17 (46)	55 (45)	
Lymphoma	6 (16)	32 (26)	
Other†	14 (38)	36 (29)	
Disease risk			.68
Standard	16 (43)	58 (47)	
High	21 (57)	65 (53)	
Prior auto-HCT	6 (16)	26 (21)	.51
HCT-CI			<.01
0	11 (30)	32 (26)	
1-2	15 (41)	21 (17)	
≥ 3	10 (27)	67 (55)	
CMV seropositive	19 (51)	82 (67)	.05
Total TNC, median (range), × 10^8/kg)	.4 (.3-.8)	.4 (.2-.7)	.16
Total CD34, median (range), × 10^6/kg	.5 (.2-1.8)	.4 (.1-1.3)	.34

Data presented are n (%), unless otherwise indicated.

* P value for between-treatment comparisons. Continuous variables were analyzed by general Wilcoxon test. Categorical variables were analyzed by chi-square.

† Other includes diagnoses of myelodysplastic syndromes and plasma cell disorders.