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Extended Mycophenolate Mofetil and Shortened Cyclosporine Failed to Reduce Graft-versus-Host Disease after Unrelated Hematopoietic Cell Transplantation with Nonmyeloablative Conditioning

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Abstract

We previously reported data from 103 patients with hematological malignancies (median age 54 years) who received peripheral blood stem cell (PBSC) grafts from HLA-matched unrelated donors after nonmyeloablative conditioning and were given postgrafting immunosuppression consisting of mycophenolate mofetil (MMF; administered from day 0 until day +40 with taper through day +96) and cyclosporine (CSP; given from day -3 to day +100, with taper through day 180) (historical patients). The incidences of grade II-IV acute and extensive chronic graft-versus-host disease (GVHD) were 52% and 49%, respectively, and the 1-year probabilities of relapse, nonrelapse mortality, and progression-free survival were 26%, 18%, and 56%, respectively. Here, we treated 71 patients with hematological malignancies (median age 56 years) with unrelated PBSC grafts and investigated whether postgrafting immunosuppression with an extended course of MMF, given at

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full dosing until day 150 and then tapered through day 180, and a shortened course of CSP, through day 80, would promote tolerance induction and reduce the incidence of GVHD (current patients). We observed 77% grade II-IV acute and 45% extensive chronic GVHD (P=0.03, and P=0.43, respectively, in current compared to historical patients). The 1-year probabilities of relapse, nonrelapse mortality, and progression-free survival were 23%, 29%, and 47%, respectively, (P=0.89, P=0.02, and P=0.08 compared to the historical patients). We conclude that postgrafting immunosuppression with extended MMF and shortened CSP failed to decrease the incidence of GVHD among unrelated PBSC recipients given nonmyeloablative conditioning.

INTRODUCTION

In order to extend allogeneic hematopoietic cell transplantation (HCT) from unrelated donors (URD) to include older patients with hematological malignancies, those with comorbid conditions, and those who had failed high-dose HCT, several groups of investigators have developed reduced-intensity or nonmyeloablative conditioning regimens [1-5], which have relied mainly or exclusively on immune-mediated graft-versus-tumor effects for tumor eradication [6-9]. Based on experimental canine studies [10] and on subsequent clinical trials in HLA-identical sibling recipients [8], we investigated a nonmyeloablative regimen consisting of fludarabine, 3×30 mg/m^2, and 2 Gy total body irradiation (TBI) for unrelated HCT [5, 11-13]. Postgrafting immunosuppression included mycophenolate mofetil (MMF) and cyclosporine (CSP).

In a previous prospective study, MMF was given at 15 mg/kg orally thrice daily, from the evening of day 0 through day +40 with taper through day +96, and CSP was given at 5 mg/kg orally twice daily, from day -3 to day 100, with taper through day 180 [14]. Sustained engraftment was achieved in 95% patients, and cumulative incidences of grade II-IV acute GVHD and extensive chronic GVHD were 52% and 49%, respectively. Two-year probabilities of progression-free survival, relapse, and nonrelapse mortality were 49%, 31%, and 19%, respectively.

Several studies have suggested that CSP prevented activation-induced death of T cells, and thus potentially delayed the eradication of alloreactive donor T-cells, preventing tolerance induction [15-18]. Conversely, antimetabolites such as MMF could delete alloreactive T cells by inducing apoptosis [19,20], thereby favoring tolerance induction. Based on these experimental findings, we investigated whether earlier discontinuation of CSP at day 80 along with prolonged MMF administration (taper initiated at day 150) would decrease the incidence of GVHD after nonmyeloablative unrelated HCT.

PATIENTS AND METHODS

Eligibility criteria

Eligibility criteria were those previously reported [14]. Briefly, patients were included in this multi-institutional international protocol if they had hematological malignancies treatable by unrelated HCT and were older than 50 years. Younger patients were candidates if they were considered at risk for transplant-related mortality with myeloablative conditioning because of medical comorbidities or preceding failed high-dose HCT or if they refused conventional HCT. Seventy-one patients were enrolled from October 2003 to January 2005. Their characteristics are shown in Table 1. Briefly, median age was 56 (range, 15-75) years. Diagnoses were acute myeloid leukemia (n=20), myelodysplastic syndrome (n=14), non-Hodgkin lymphoma (n=11), fludarabine-refractory chronic lymphocytic leukemia (n=8), multiple myeloma (n=6), chronic myeloid leukemia (n=5), Hodgkin lymphoma (n=4), myeloproliferative disorders (n=2), and acute lymphoblastic leukemia (n=1). Forty-seven patients were $\geq$ 50 years old, 16 had failed

high-dose HCT, seven had planned tandem autologous-allogeneic HCT, and one had morbid obesity. Sixty-nine percent of the patients had HCT-comorbidity index (HCT-CI) scores ≥ 1, including 41% who had scores ≥ 3. Patients received HCT at 10 centers including the FHCRC (n=35), Emory University in Atlanta (n=10), University of Leipzig (Germany, n=6), University of Tuebingen (Germany, n=4), Oregon Health & Science University in Portland (n=4), Rocky Mountain Cancer Center in Denver (n=3), University of Utah in Salt Lake City (n=3), VA Puget Sound Health Care System in Seattle (n=2), Medical College Wisconsin in Milwaukee (n=2), and Stanford University in Palo Alto (n=2). The protocol was approved by the Institutional Review Boards (IRB) at the FHCRC and each of the collaborating sites. All patients signed consent forms approved by the local IRB.

Stem cell source and HLA matching

All patients were given peripheral blood stem cells (PBSC). Compatibility between patients and donors for HLA-A, -B,-C,-DRB1 and -DQB1 alleles was assessed by high-resolution DNA techniques [5]. Sixty-five pairs were matched at the allelic levels for all 10 alleles at HLA-A, -B,-C, -DRB1 and -DQB1, while six pairs were mismatched for a single HLA-A (n=2), HLA-B (n=3), or HLA-C (n=1) allele.

Conditioning regimen and postgrafting immunosuppression

Conditioning included fludarabine, 30 mg/m^2/day on days -4, -3, and -2, in all patients. Sixty-eight received 2 Gy TBI (day 0), while three patients with chronic myeloid leukemia (CML) were given 3 Gy TBI in an attempt to reduce the risk of graft rejection. Postgrafting MMF was given at 15 mg/kg orally thrice daily from the evening of day 0 until day +30, at 15 mg/kg orally twice daily from day 31 until day 150, and then tapered from day 150 until day 180. CSP was given at 5 mg/kg orally twice daily from day -3 to day +80 and then discontinued without taper at day 80 in the absence of GVHD.

GVHD Grading and Therapy, and Supportive Care

Diagnosis, clinical grading and treatment of GVHD were performed according to established criteria [21]. Treatment of GVHD was based on the attending physicians' assessment of the severity of GVHD. Initial treatment usually consisted of prednisolone, 1-2 mg/kg/day with taper initiated within 14 days. If already discontinued, CSP was usually resumed at full doses. Steroid-refractory acute GVHD was treated per available investigational protocols or other salvage regimens. Extensive chronic GVHD was usually treated with prednisone (1 mg/kg) with or without alternate-day CSP [22].

Standard prophylaxis against infections was used [23]. Patients with chronic GVHD requiring systemic immunosuppressive therapy remained on prophylaxis for Pneumocystis carinii and pneumococcal infections.

Disease-dependent restaging after HCT occurred monthly for the first 3 months and then at 6 months, 1 year, and yearly thereafter. Percentages of donor-host chimerism were assessed by fluorescent in situ hybridization for X and Y chromosomes (FISH) in recipients of sex-mismatched HCT, or by polymerase chain reaction (PCR)–based amplification of variable-number tandem repeat (VNTR) or short-tandem repeat (STR) sequences unique to donors and hosts if patients and donors were sex-mismatched [13].

Persistent, progressive, or relapsed malignancies in the absence of severe manifestations of acute and chronic GVHD were treated by rapid taper and discontinuation of systemic immunosuppression in order to initiate graft-versus-tumor effects. In addition, two patients with low (<30%) donor T-cell chimerism were given pentostatin (4mg/m^2), followed two days

later by donor lymphocyte infusion (DLI) on a separate protocol as preliminarily reported [24], in an attempt to avert graft rejection [25,26]).

Statistical analyses—Data were analyzed as of 4/18/2006. Overall and progression-free survivals were calculated by the Kaplan-Meier method. Cumulative incidence estimates were calculated for graft rejection, graft failure, acute and chronic GVHD, life-threatening GVHD, steroid initiation, progression/relapse, and nonrelapse mortality. Hazard ratios were estimated by Cox regression models. In order to better compare the outcomes between the two protocols, multivariate models adjusting for pre-transplant risk factors were constructed. Pre-transplant risks factors included in the models were aggressive versus indolent disease, HLA-mismatch between donors and recipients versus not, patient CMV status, patient age (over 50 versus not), female to male recipient versus not, and comorbidity at HCT [assessed by the HCT-comorbidity index (HCT-CI) [27]]. By protocol, graft failure was defined as Common Toxicity Criteria (CTC) grade IV thrombocytopenia and neutropenia persisting/occurring after day 21, lasting more than 2 weeks and refractory to hematopoietic growth factors. Graft rejection was defined as the inability to detect or loss of detection of ≥ 5% donor T-cells [26]. All p-values refer to hazard ratio comparisons, and are 2-sided.

RESULTS

Engraftment

Median donor T-cell chimerism levels on days 28, 180, and 365 after HCT were 89%, 99%, and 100%, respectively, in current patients, versus 92%, 99%, and 100% in historical patients. Sustained engraftment was achieved in 68 current patients (96%) versus in 98 historical patients (95%). Two of 3 current CML patients conditioned with 3 Gy TBI had either protocol defined primary graft failure (without fulfilling the protocol's criteria for graft rejection (see below), or graft rejection (defined as the inability to detect or loss of detection of ≥ 5% donor T-cells).

GVHD

The cumulative incidences of grade II-IV and grade III-IV acute GVHD were 77% and 26% among current patients versus 52% (P=0.03; *P*=0.02 after adjusting for pre-transplant risk factors [Table 2]) and 15% (P=0.11; *P*=0.16 after adjusting for pre-transplant risk factors [Table 2]) among historical patients, respectively (Figure 1A). Specifically, grades II, III and IV acute GVHD were seen in 51%, 16% and 10% of current patients, respectively, versus 38%, 11% and 4% of historical patients, respectively. One of the 7 current cases of grade IV acute GVHD occurred after abrupt discontinuation of postgrafting immunosuppression for progressive disease, and another after pentostatin (4 mg/m^2) and DLI for prevention of graft rejection. Three additional cases of grade IV acute GVHD occurred after discontinuation of CSP on day 80. Seven of 11 historical patients mismatched with their donor for a single HLA-class I allele experienced grade II-IV acute GVHD (including one patient with grade IV acute GVHD), while 5 of 6 current patients who mismatched with their donor for a single HLA-class 1 allele had grade II-IV acute GVHD (including one patient with grade IV acute GVHD). The 1-year cumulative incidence of extensive chronic GVHD was 45% among current patients versus 49% among historical patients (P=0.43; *P*=0.48 after adjusting for pre-transplant risk factors [Table 2]) (Figure 1B).

Relapse, nonrelapse mortality, survival

The current and historical 1-year cumulative incidences of relapse/progression were similar: 23% versus 26%, respectively (*P*=0.89; *P*=0.50 after adjusting for pre-transplant risk factors [Table 2]). However, the current 1-year cumulative incidence of nonrelapse mortality was higher, 29%, as compared to the historical one of 18% (*P*=0.02; *P*=0.03 after adjusting pre-transplant risk factors [Table 2]). In order to determine whether abrupt CSP discontinuation

on day 80 was in part responsible for the increased current nonrelapse mortality, we compared nonrelapse mortality in patients with grade II-IV acute GVHD before day 80, who therefore were continued on CSP, and in patients without grade II-IV acute GVHD on day 80 whose CSP was discontinued. Current and historical nonrelapse mortalities were comparable in patients with acute GVHD before day 80 [HR 1.12 (0.4-3.2), P=0.83], while nonrelapse mortality was higher in current patients without grade II-IV acute GVHD on day 80 [HR 10.1 (3.4-30), P<0.0001] (Figure 1C). Current causes of death in these patients included grade III (n=1) or grade IV (n=4) acute GVHD, chronic GVHD (n=3), graft failure (n=2), infection (n=1), pulmonary embolism (n=1), chronic heart failure (n=1), and unknown (n=1). Taken together, these data suggested that early CSP discontinuation on day 80 contributed to higher nonrelapse mortality.

The current 1-year overall and progression-free survivals were 55% and 47% versus 68% (*P*=0.06; *P*=0.05 after adjusting for pre-transplant risk factors) and 56% (*P*=0.08; *P*=0.05 after adjusting for pre-transplant risk factors [Table 2]), respectively, among historical patients (Figure 1D).

DISCUSSION

GVHD with or without infection has been the leading cause of nonrelapse mortality after transplantation following nonmyeloablative conditioning [9,28]. Since CSP [15-18] but not MMF inhibited activation-induced death of T-cells [19,20], we reasoned that early CSP discontinuation combined with extended MMF administration might help promoting tolerance induction, and reduce the incidences of late acute and chronic GVHD.

However, we observed that prolonging MMF and truncating CSP administration failed to reduce GVHD. On the contrary, while chronic GVHD was comparable in the two protocols, grade II-IV acute GVHD was significantly more frequent among current than historical patients. There are two possible explanations for this finding. First, from day 28 to day 40, MMF was given b.i.d. in current versus t.i.d. in historical patients. That explanation is unlikely, however, given that t.i.d. MMF administration, while apparently effective in reducing the risk of graft rejection, did not alter the GVHD incidence compared to original b.i.d. MMF administration [5]. Second, and most likely, our hypothesis of tolerance induction through early discontinuation of the calcineurin inhibitor and continuation of the antimetabolite was incorrect. As a result, more current than historical patients developed acute GVHD after day 80 including four with grade IV GVHD. Apparently, administration of a calcineurin inhibitor for at least 6 months after HCT is needed for successful establishment of graft-host-tolerance. This concept is in agreement with the recent observation by Burroughs *et al.* in patients given grafts from related donors that extending CSP administration through day 180 compared to CSP discontinuation at earlier time points reduced the incidence of grade III-IV acute GVHD from 15–20% to <5% [29].

Likely, as a result of the increase in acute GVHD, nonrelapse mortality in current patients was significantly higher than among historical patients. The increase in nonrelapse mortality occurred among patients without acute GVHD on day 80, while it was similar among patients who experienced acute GVHD before day 80 and, therefore, continued receiving CSP. Strong associations between acute GVHD and nonrelapse mortality have been reported by us and others after nonmyeloablative or reduced-intensity conditioning [9,30-34]. Not surprisingly, the increased nonrelapse mortality among current patients translated into both decreased overall and progression-free survivals compared to historical patients.

The increased incidence of grade II-IV acute GVHD in current patients did not translate into lower risk of relapse. We acknowledge that caution is in order when comparing relapse

incidences between the two groups of patients given the heterogeneity of underlying diseases. However, this observation is in agreement with previous studies by our group [9] and by others [30,35,36], showing that occurrence of grade II-IV acute GVHD was not significantly associated with lower risk of relapse after nonmyeloablative conditioning. In contrast, occurrence of chronic GVHD has been significantly associated with lower risk of relapse after nonmyeloablative conditioning, particularly in patients with acute myeloid leukemia or myelodysplastic syndrome [9,35,36].

While 96% of current patients achieved sustained engraftment, similar to what was observed in the previous protocol (95%), two patients with CML had graft rejection/failure, even though the TBI dose had been increased from 2 Gy to 3 Gy. A high rate of graft rejection among CML patients given unrelated grafts after relatively more intense “reduced-intensity” conditioning has been reported by other investigators [1,37]. A graft failure rate of 44% (3 of 8 patients) was described after a reduced intensity conditioning regimen that combined fludarabine (150 mg/m^2), i.v. busulfan (6.6 mg/kg), and ATG [37], while 5 of 22 evaluable patients giving unrelated marrows after conditioning with 5.5 Gy TBI and cyclophosphamide also experienced graft failure [1].

In conclusion, postgrafting immunosuppression with extended MMF and shortened CSP increased the incidence of acute GVHD in unrelated HCT recipients given nonmyeloablative conditioning. It would appear that extending calcineurin inhibitors for six months is required for better control of GVHD. Extending that use beyond that time is of questionable value, given that a prospective randomized study comparing 6 vs. 24 months CSP administration failed to show differences in outcomes [38].

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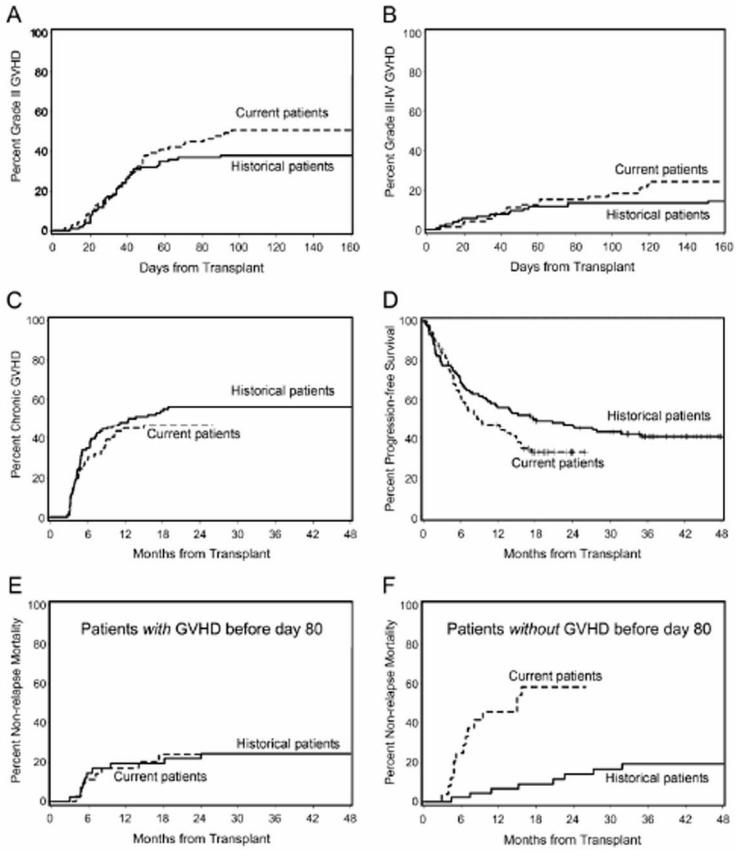

Figure 1.

Cumulative incidences of grades II acute GVHD **(A),** III-IV acute GVHD **(B)** and chronic extensive GVHD **(C)** in patients included in the current protocol (protocol #1668; extended MMF and truncated CSP, n=71), or in the historical protocol (protocol #1641; n=103). Progression-free survival in patients included in the current protocol or in the historical protocol **(D)**. Cumulative incidences of nonrelapse mortality in the current and in the historical protocols among patients who experienced **(E)** or did not experience **(F)** grade II-IV acute GVHD before day 80.

Table 1

Patients

Characteristic	Current patients (Protocol #1668) (n=71)	Historical patients (Protocol #1641) (n=103)	*P value*
Median patient age, y (range)	56 (15-75)	54 (17-69.6)	NS
Recipient gender, #M (%)/#F (%)	49/22	63/40	NS
Female donor / male recipient, # pts (%)	11 (15%)	21 (20%)	NS
Diagnosis at the time of nonmyeloablative conditioning, # (%) pts			
AML/ALL	21 (30)	24 (23)	
CR1-2	16 (23)	21 (20)	
CR>2	4 (6)	1 (1)	
> CR	1 (1)	2 (2)	
Chronic myeloid leukemia	5 (7)	5 (5)	
CP1	3 (4)	3 (3)	
CP2 or AP	2 (3)	2 (2)	
Fludarabine-refractory chronic lymphocytic leukemia	8 (11)	13 (13)	
Myelodysplastic syndrome	14 (20)	9 (9)	
RA	4 (6)	2 (2)	
RAEB/CR1	3 (4)	4 (4)	
tAML CR1/CR2	7 (10)	3 (3)	
Multiple myeloma	6 (8)	11 (11)	
CR/PR/Ref	2(3)/3(4)/1(1)	2(2)/6(6)/3(3)	
Non-Hodgkin lymphoma	11 (15)	24 (23)	
CR/PR	5(7)/1(1)	9(9)/6(6)	
Stable	0	1 (1)	
Ref/rel	5 (7)	6(6)/2(2)	
Hodgkin lymphoma	4 (6)	8 (8)	
CR/PR	1(1)/1(1)	1(1)/3(3)	
Ref/rel	2 (3)	1(1)/3(3)	
Myeloproliferative syndrome other than chronic myeloid leukemia	2 (3)	3 (3)	
Waldenströms macroglobulinemia	0	2 (2)	
Renal cell carcinoma	0	4 (4)	
Disease, # pts (%)			
Indolent*	31 (44)	40 (39)	NS
Aggressive†	40 (56)	63 (61)	
Comorbidity at HCT (HCT-CI score [27]), # pts (%)			
0	22 (31)	30 (29)	NS
1-2	20 (28)	38 (37)	
≥ 3	29 (41)	35 (34)	
Donor, # pts (%)			
HLA-allele Match	65 (92)	92 (89)	NS
1 allele HLA- Mismatch	6 (8)	11 (11)	
PBSC dose, median (range)			
$CD34^+$ cells ($\times 10^6$/kg recipient)	7.4 (1.1-30.0)	7.3 (0.8-26.3)	NS
T-cells ($\times 10^8$/kg recipient)	2.6 (0.8-6.7)	2.7 (0.3-9.3)	NS

*Defined as acute myeloid leukemia in first complete remission, acute lymphoblastic leukemia in first complete remission, myelodysplastic syndrome-refractory anemia, chronic myeloid leukemia in first chronic phase, chronic lymphoblastic leukemia, low-grade non Hodgkin lymphoma, multiple myeloma in partial or complete remission, and Waldenstrom macroglobulinemia.

†All other diagnoses.

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CR, complete remission; Rel, relapse; Ref, refractory; CP, chronic phase; AP, accelerated phase; RA, refractory anemia; RAEB, refractory anemia with blast excess; tAML, secondary AML; PBSC, G-CSF-mobilized peripheral blood stem cells.

Table 2

Outcomes for current (n=71) relative to historical (n=103) patients

Endpoint	Cumulative Incidence at 1 year		Adjusted* HR† (95% CI)	Adjusted* P-value
	Historical patients	Current patients		
Overall survival	68%	55%	1.58 (1.0-2.5)	0.05
Progresion-free survival	56%	47%	1.51 (1.0-2.3)	0.05
Relapse/progression	26%	23%	1.22 (0.7-2.2)	0.50
Nonrelapse mortality	18%	29%	1.93 (1.1-3.5)	0.03
Grade II-IV acute GVHD	52%	77%	1.67 (1.1-2.5)	0.02
Grade III-IV acute GVHD	15%	26%	1.65 (0.8-3.3)	0.16
Extensive chronic GVHD	49%	45%	0.85 (0.5-1.3)	0.48

*Adjusted for disease risk (aggressive versus indolent disease), one HLA-allele mismatch between donor and recipient or not, recipient CMV serostatus, recipient age (over 50 years old versus not), female donor to male recipient, and comorbidity at HCT (HCT-CI score 0,1-2, ≥ 3).

†HR for outcomes in current relative to historical patients. HR > 1 refers to worse outcomes.