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Study of Kidney Function Impairment after Reduced-Intensity Conditioning Allogeneic Hematopoietic Stem Cell Transplantation. A Single-Center Experience

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Acute renal failure (ARF) is a life-threatening complication after allogeneic stem cell transplantation (Allo-HSCT). Identification of ARF risk factors could be useful to develop preventive strategies for patients at high risk. The goal of this study was to evaluate the incidence and risk factors of ARF after reduced intensity conditioning Allo-HSCT (Allo-RIC). We included 188 consecutive patients who underwent Allo-RIC in our center between January 1999 and December 2006. ARF was defined as a decrease of at least 25% in baseline estimated glomerular filtration rate (GFR) calculated by modification of diet in renal disease (MDRD) equation. Conditioning consisted of fludarabine (Flu) 150 mg/m^2 in combination with busulfan (Bu) 8-10 mg/kg (n = 61), melphalan (Mel) 140 mg/m^2 (n = 115), cyclophosphamide (Cy) 120 mg/kg (n = 7) or low-dose total-body irradiation (TBI) 2 Gy (n = 5). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A (CsA) alone (n = 3) or in addition to methotrexate (MTX; n = 132) or mycophenolate mofetil (MMF; n = 51). The cumulative incidence of ARF at 1 year was 52% (n = 97 patients) after Allo-RIC. Most cases (86%) occurred within the first 3 months, and the main cause was the administration of CsA (71%). The risk factors associated with ARF in multivariate analysis were: administration of MTX (hazard ratio [HR] 1.9, P =.02), more than 3 lines of therapy prior to Allo-RIC (HR 1.8, P = .01), diabetes mellitus (HR 2.1, P <.01), and GVHD grade III-IV (HR 2.1, P = .015). In multivariate analysis, ARF was an independent risk factor for 1-year nonrelapse mortality (NRM) (HR 3, 95% confidence interval [CI]: 1.5-6, P = .002). Patients who experienced ARF had lower 1-year overall survival (OS; 53% versus 74%, P < .05). ARF is a frequent complication in patients after Allo-RIC, and it has a negative impact on outcome. Identification of ARF risk factors could help to avoid exposure to nephrotoxic drugs during the follow-up in patients at high risk.

Biol Blood Marrow Transplant 15: 21-29 (2009) © *2009 American Society for Blood and Marrow Transplantation*

KEY WORDS: Kidney function, Kidney injury, Acute renal failure, HSCT, Reduced-intensity conditioning Allo-RIC

INTRODUCTION

Myeloablative allogeneic hematopoietic stem cell transplantation (Allo-HSCT) with high-dose chemotherapy conditioning is an effective treatment for several neoplastic disorders. However, the nonhematologic toxicity limits the application to young (<55 years) and fit patients. Reduced-intensity conditioning allogeneic stem cell transplantation (Allo-RIC) regimens have been designed to reduce toxicity and allow stem cell transplantation in the elderly, in patients with comorbidities, and in those who have been heavily pretreated. Despite a reduction in conditioning intensity, complications such as graft-versus-host disease (GVHD), infections, and drug-related toxicity may still lead to organ injury in these older or debilitated patients. Organ damage contributes to morbidity and mortality and, for this reason, remains an important issue in the Allo-RIC setting. Both the intensity of conditioning and also the type of drug combinations may influence the different patterns of organ damage in Allo-HSCT [1].

An adequate kidney function is crucial for a management of life-threatening complications of Allo-HSCT. In consequence, acute renal failure (ARF)

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Financial disclosure: See Acknowledgments on page 28.

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Received July 23, 2008; accepted October 13, 2008
1083-8791/09/151-0001$36.00/0
doi:10.1016/j.bbmt.2008.10.011

has been associated with higher nonrelapse mortality (NRM) after myeloablative Allo-HSCT [2-4]. ARF frequently develops together with other posttransplant complications such as GVHD, respiratory infections, drug-related toxicities, and comorbidities, leading to a multiorgan dysfunction syndrome (MODS) in a high number of these patients [4-6]. As a result, ARF requiring dialysis occurs in a high proportion of these patients and leads to a high mortality rate, ranging from 75% to 100% [7-9].

Although the incidence and severity of ARF after Allo-RIC seems lower than in myeloablative regimens [10], incidences of severe ARF of about 30% to 40% have been reported [11,12]. Furthermore, it seems that severe ARF is associated with lower survival in low-dose totaldy irradiation (TBI)-based Allo-RIC regimens [11,12]. Of note, the impact of ARF in patients undergoing Allo-RIC may be of highest importance, as these patients usually have poorer performance status and other comorbidities.

In view of these concerns, we assessed renal function as estimated glomerular filtration rates (GFR) calculated by modification of diet in renal disease (MDRD) equation. We report our experience in a large cohort of patients who underwent Allo-RIC in a single center. We analyzed ARF incidence and risk factors, and also the impact of developing ARF on outcome. To the best of our knowledge, the incidence and risk factors of ARF after fludarabine (Flu) plus an alkylating agent (busulfan (Bu) or melphalan (Mel))-based conditioning Allo-RIC have not been systematically analyzed.

PATIENTS AND METHODS

Patients

We included 188 consecutive patients who underwent Allo-RIC in our institution between January 1999 and December 2006. The reason to use Allo-RIC was age older than 50 years (n = 131), the presence of severe comorbidities (n = 29), or to have had undergone prior stem cell transplantation (SCT; n = 28). The sources of donor hematopoietic cells were granulocyte-colony stimulating factor (G-CSF)-stimulated peripheral blood hematopoietic cells in most cases (94%) and bone marrow in the remainder (6%). Patient characteristics are detailed in Table 2.

Conditioning Regimen and GVHD Prophylaxis

We used conditioning regimens as described elsewhere [13]. Briefly, Flu 150 mg/m^2 was combined with Bu 8-10 mg/kg for myelogenous neoplasm (n = 61), Mel 70-140 mg/m^2 for lymphoid neoplasm including multiple myeloma (MM; n = 115), with Cy clophosfamide (CFM) 120 mg/kg for solid tumors (n = 7) or with low-dose TBI 2 Gy for chronic myelogenous leukemia (CML) (n = 4). One patient with lymphoblastic lymphoma was treated with CFM and low-dose TBI as RIC. GVHD prophylaxis consisted of cyclosporine A (CsA) from day −7 in all except 2 patients who received tacrolimus. The dose was adjusted to blood levels (between 200 and 300 μg/mL). Methotrexate (MTX) (n = 132) was administered on days +1, +3, and +6 days (10 mg/m^2) with folinic acid rescue. Myophenolate mofetil (MMF) was used instead of MTX in 51 patients; it was started on day 0 (at least 10 hours after the infusion of progenitors) at a dose of 1g 3 times daily (15 mg/kg/8 hours). MMF was continued until day +30 and then tapered.

ARF Assessment

All patients were hospitalized for the procedure. Daily blood analyses were performed from the day of admission until discharge. Thereafter, blood analyses were performed weekly during the first 100 days and monthly if no complications appeared. GFR was calculated by MDRD equation as follows: {GFR (mL/min per 1.73 m^2) =186 * PCr −1.154 *age −0.203 (* 0.742 if female)} [14,15]. These parameters were measured on days −9, +15, +30, +60, +120, +180, +360, and whenever an increase in baseline creatinine was detected. ARF was classified on the basis of estimated GFR, as in previous HSCT studies [10-12,16]. ARF was defined as a decrease of at least 25% of baseline GFR when creatinine levels rise above the standard values. ARF gradation is shown in Table 1. ARF caused by baseline disease progression was excluded from the analysis, as this was considered a competitive event. We also excluded ARF in the context of MODS when it was the last event before death.

Statistical Data

The main endpoints of the study were the incidence of ARF, the identification of its risk factors, and the impact of developing ARF on acute and chronic GVHD (aGVDH, cGVHD), overall survival (OS), NRM, and relapse. The probability of OS was estimated from the time of transplantation using Kaplan-Meier curves [17], whereas NRM and relapse were calculated using cumulative incidence estimates, taking into account the competing risk structure [18,19]. Other posttransplantation outcomes that were calculated using

Table 1. Classification of Grades of Severity of ARF

Grade 0	Decrease in estimated GFR < 25% of the baseline value
Grade 1	Correspond to a less than 2-fold rise in serum creatinine concentration with a decrease in estimated GFR >25% but <50% of the baseline value.
Grade 2	A decrease in estimate GFR >50% of baseline GFR but not requiring dialysis
Grade 3	grade 2 parameters but requiring dialysis

AFR indicates aute renal failure; GFR, glomerular filtration rate.

Table 2. Demographics and Baseline Comorbid Conditions in Patients When Categorized by ARF

Variables	ARF at 1 Year (n = 97)	Without ARF (n= 91)	*P* Value
Median age in years (range)	55 (18-71)	53 (18-73)	.6
Sex Male n, (%)	63 (65)	55 (60)	.3
Unrelated Donor, n (%)	19 (19)	13 (14)	.5
Underlying disease, n (%)			ns
• Acute leukemia/MDS/MPS	31 (32)	38 (41)	
• CLL	11 (11)	5 (5)	
• NHL	22 (22)	17 (19)	
• HD	16 (16)	9 (11)	
• MM	11 (11)	18 (20)	
• Solid tumors and others	6 (5)	4 (4)	
Number of Prior therapies, mean ± SD	2.6 ± 1.5	2.4 ± 1.4	.5
Baseline GFR (mL/min/1.73 m^2), mean ± SD	75.6 ± 17	75.4 ± 24	.9
Prior CRD, n (%)	22 (23)	25 (27)	.6
HSTC source BM, n (%)	8 (8)	4 (5)	.3
Comorbidities, n (%)			
• Diabetes	15 (15)	7 (8)	.1
• HTA	24 (25)	16 (17)	.2
• Cardiomyopathy	17 (17)	11 (12)	.3
Advanced disease status at HSCT, n (%)	70 (72)	61 (67)	.5
Mean levels of CsA (ng/mL) +/− SD			
• During day +15	183 ± 62	184 ± 62	.9
• During day +30	202 ± 61	209 ± 58	.4
Median follow-up in days (range)	479 (8-2947)	933 (48-2759)	.01
Cumulative Incidence of relapse at 1 year, % (95% CI)	20 (13-29)	26 (18-37)	.5
Overall survival at 1 year	54%	70%	.04

ARF indicates acute renal failure; MDS, myelodysplastic syndrome; MPS, myeloproliferative syndrome; GFR, glomerular filtration rate; CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; HD, Hodgkin disease; MM, multiple myeloma; SD, standard deviation; N, number; CRD, chronic renal dysfunction; HSCT, hematopoietic stem cell transplantation; BM, bone marrow source; HTA, arterial hypertension; CsA, cyclosporine A; GVHD, graft-versus-host disease.

cumulative incidence estimates were hematopoietic recovery, ARF, and GVHD. Univariate analyses of the association of various clinical risk factors with these latter posttransplantation outcomes were calculated using univariate Cox regression models, whereas the log-rank test was used for OS [18,19]. Multivariate analyses were performed by Cox proportional hazards regression, with inclusion of those variables with a value of $P < .1$ in the prior univariate testing. The assumption of proportional hazards over time was tested for all explanatory covariates using a time-dependent covariate. To analyze the impact of ARF and GVHD in Allo-RIC outcome, these variables were entered as time-dependent covariates. Quantitative variables that were found to have an impact on any outcome were reanalyzed as categoric variables. Tests of significance were 2-sided, with significance level of $P = .05$ or less. All statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL), with the exception of the cumulative incidence analyses, which were carried out with NCSS 2004 (Number Cruncher Statistical System, Kaysville, UT). If ARF, aGVHD, or cGVHD were found to have an impact on posttransplantation outcomes in the final multivariate Cox analysis, plots were constructed to visually illustrate the effects of each variables on these outcomes, as described elsewhere [20].

RESULTS

Patients Characteristics

No demographic differences were seen between the 2 groups of patients when categorized as with or without ARF (Table 2). Comorbidity conditions were equally distributed between the 2 groups. Sex, age, diagnosis, disease status, type of donor, type of transplant, conditioning regimen, and a number of prior transplants did not differ between patients with and without ARF.

ARF: Incidence, Etiology, and Risk Factors

After a median follow-up of 49 months (range: 4-98) for survivors, 97 patients developed ARF for a 1-year cumulative incidence of 52% (95% confidence interval [CI] 45-60). The median time to the onset of ARF was 31 days (range: 0-320 days). ARF occurred mainly within the first 3 months after Allo-RIC, as 79 (81%) of 97 patients developed ARF before day +100. Most of the patients (86%) developed grade 1 ARF, 10% developed grade 2, and only 4% developed grade 3.

The causes of ARF are shown in Table 3. ARF was directly attributable to CsA in 69 (71%) patients. In 21% of these patients, however, the cause of ARF was attributed to CsA in addition to other transplant-related complications such as GVHD, absence of fluid intake, dehydration, and antimicrobial drugs (amphotericin and aminoglucoside). We did not find any correlation

Table 3. Etiology and Grades of ARF

Main Causes of ARF	n	%
CsA alone	48	50
CsA + sinusoidal obstruction syndrome	3	3
CsA + dehydration	9	9
CsA + GVHD	4	4
CsA + antimicrobial therapy	5	5.2
Total CsA	*69*	*71*
Multiorgan failure	3	3.1
Microangiopathy	8	8.2
Dehydration	6	6.2
Adenovirus interstitial nephritis	1	1
Bilateral litiasis obstruction	1	1
Diverse pharmacological toxicity	3	3.1
Undetermined causes	6	6.2
Total	*97*	*100*
Grade of ARF	n	%
Grade 1	84	86
Grade 2	9	10
Grade 3	4	4

CsA indicates cyclosporine A; ARF, acute renal failure; GVHD, graft-versus-host disease.

between the median of CsA blood levels at +15 and +30 days and the development of ARF.

Concerning the risk factors for ARF, demographic baseline characteristics and severe aGVHD were analyzed. Univariate and multivariate proportional hazard ratio models are shown in Table 4. The analyses were performed at +100 and +180 days and 1 year after the Allo-RIC. At day +100 the variables associated with higher risk of ARF were: diabetes mellitus (DM) (HR 2.1, CI 95% 1.2-3.8; $P = .007$), having received more than 3 prior lines of therapy (HR 1.8, CI 95% 1.1-2.9; $P = .01$), and the use of MTX as GVHD prophylaxis (HR 1.9, CI 95% 1.1-3.5; $P = .02$). The impact of MTX and the number of prior therapies were no longer observed after day +100. The impact of acute GVHD (aGVHD) grade III-IV appears as the only risk factor after day +100, (HR 2.1, CI 95% 1.2-3.7 and HR 2, CI 1-3.5 at +180 days and 1 year, respectively, $P < .02$).

GVHD

Although severe aGVHD appeared as a risk factor for ARF, grade II-IV aGVHD occurred in 34% (95% CI 26-44) of patients who developed previously ARF compared to 25% (95% CI 17-37) of patients without ARF ($P = .1$). Patients who developed ARF had a similar cumulative incidence of cGVHD (72% versus 62%, $P = .3$, respectively). The severity of cGVHD was not significantly different between the 2 groups [41% (95% CI 29-58) and 30% (95% CI 19-47), for patients with and without ARF (p=0.2)].

NRM

Fifty-five (29%) patients died because of NRM after a median follow-up of 518 days (range: 8-2947). Median time to death was 115 days (range: 8-1072). The +100, +180 days, and 1-year cumulative

Table 4. Cumulate Incidence and Multivariate Cox Regression Hazard Models Analysis of Risk Factors for ARF

	ARF											
	Day +100 (N = 79)				Day +180 (N = 90)				1 Year (N = 97)			
	Univariate Analysis		Cox. Regr		Univariate Analysis		Cox Regr.		Univariate Analysis		Cox Regr.	
Variables	Cumulative incidence % (95% CI)	*P* Value	HR (95% CI)	*P* Value	Cumulative incidence % (95% CI)	*P* Value	HR (95% CI)	*P* Value	Cumulative incidence % (95% CI)	*P* Value	HR (95% CI)	*P* Value
Conditioning regimen												
• Melphalan	48 (40-59)		—		51 (43-62)		—		56 (48-66)		—	
• Busulfan+others	25 (16-38)	.01	—		37 (31-52)	.053	—		43 (32-58)	.087	—	
Acute GVHD prophylaxis												
• MTX	46 (38-56)		1.9 (1.1-3.5)	.01	49 (41-59)		—		53 (45-63)			
• Without	9 (4-21)	.02	—		40 (29-56)	.1	—		50 (34-62)	.26	NA	
Donor												
• Related	39 (32-48)				44 (37-53)				44 (37-53)			
• Unrelated	47 (33-68)	.5	NA		58 (43-79)	.3	NA		58 (43-79)	.3	NA	
Diagnosis												
• Myeloid disease	26 (17-39)		—		37 (27-51)		—		44 (33-58)		—	
• Lymphoid disease	48 (40-59)	.01	—		51 (42-62)	.051	—		56 (47-66)	.081	—	
Status Disease												
• Advanced	45 (37-55)		—		49 (41-58)				54 (46-64)			
• Nonadvanced	32 (21-47)	.065	—		41 (30-56)	.2	NA		46 (35-62)	.19	NA	
No. therapies before HSCT												
• <3 lines	32 (23-48)		—		40 (31-52)		—		47 (38-59)		—	
• 3 or more lines	50 (40-62)	.02	1.8 (1.1-2.9)	.01	52 (43-64)	.08	1.5 (0.97-2.5)	.065	57 (47-68)	.095	—	
Comorbidities												
• Diabetes*												
- yes	65 (47-91)		2,1 (1.2-3.8)	.007	65 (47-91)		1.5 (0.98-3)	.08	71 (53-95)		—	
- no	38 (31-46)	.018	—		44 (37-53)	.037	—		49 (42-58)	.035	—	
• HTA												
- yes	43 (30-62)				51 (37-69)				59 (42-58)			
- no	40 (33-49)	.9	NA		45 (38-54)	.7	NA		50 (43-59)	.56	NA	
• Cardiomyopathy												
- yes	37 (23-60)				52 (36-75)				59 (43-81)			
- no	41 (34-50)	.7	NA		45 (38-54)	.7	NA		50 (43-59)	.5	NA	
Acute GVHD III-IV												
• yes	64 (45-91)		—		78 (60-100)		2,1 (1.2-3.7)	.015	78 (60-100)		2 (1-3.5)	.019
• no	38 (30-47)	.048	—		44 (36-53)	.01			51 (43-61)	.02	—	

ARF indicates acute renal failure; CI, confidence interval; COX. Regr, Cox regression hazard model; HR, hazard ratio; GVHD, graft-versus-host disease; MTX, methotrexate, No., number; HTA, arterial hypertension.

*DM was defined when patient needed insulin or oral antidiabetic therapy to control glycemia before transplant.

incidence of NRM for the whole group was 13% (95% CI: 9-19), 17% (95% CI: 12-23), and 23% (95% CI: 17-29), respectively. The most common causes of NRM were GVHD and infections (25 patients died from GVHD and infection, 17 from GVHD without infection, and 5 from infection without GVHD). The other deaths were attributed to central nervous system bleeding (n = 2), sinusoid obstruction syndromes (n = 2), sudden death (n = 2), progressive multifocal encephalopathy (n = 1), and microangiopathy (n = 1).

The variables associated with higher NRM at +100 days and 1 year in univariate analyses are shown in Table 5: in multivariate analyses, the variables associated with NRM were: MTX-GVHD prophylaxis (HR of 0.3 [CI 95% 0.2-0.6]) (P = .001), more than 3 prior therapies (HR of 3.3 [CI 95% 1.4-7.6]) (P = .001), DM (HR 3.2 [CI 95% 1.4-7.3]) (P = .03), aGVHD grade II-IV (HR 5.1 [CI 95% 2.3-11.2] (P = .001), and ARF (HR 3.4 [CI 95% 1.5-8.1] (P = .002) (Table 5). The effect of ARF, DM and aGVHD on NRM are shown in figures 1. a, b and c. The incidence of NRM at 1 year in patients who developed ARF was 33% compared to 12% for patients with normal renal function (P = .001). Moreover, the NRM was even higher in those patients who

Table 5. Cumulate Incidence and Multivariate Cox Regression Hazard Models analysis of Risk Factors for NRM

	Non Relapse Mortality (NRM)							
	Day +100				1-year			
	Univariate Analysis		Cox Regr.		Univariate Analysis		Cox Regr.	
Variables	Cumulative incidence % (95% CI)	*P* Value	HR (95% CI)	*P* Value	Cumulative incidence % (95% CI)	*P* Value	HR (95% CI)	*P* Value
Conditioning regimen								
• Melphalan	8 (4-15)				25 (18-34)			
• Busulfan	10 (5-21)	.7	NA		19 (12-32)	.8	NA	
Acute GVHD prophylaxis								
• MTX	13 (8-20)				16 (11-24)		0.3 (0.2-0.6)	.001
• Without	19 (12-33)	.3	NA		39 (28-54)	.003	–	
Diagnosis								
• Myelogenous disease	14 (7-25)				22 (15-35)			
• Lymphoid disease	7 (4-14)	.5	NA		24 (18-34)	.5	NA	
Status disease								
• Advanced	17 (11-25)		—		21 (15-30)			
• Nonadvanced	10 (5-22)	.1	—		21 (13-35)	.2	NA	
No. therapies before Allo-RIC								
• = or <3 lines	7 (4-15)		—		12 (6-20)		—	
• >3 lines	20 (14-31)	.02	3.3 (1.4-7.6)	.005	26 (18-36)	.059	2.9 (1.5-5.5)	.001
DONOR								
• Related	11 (7-17)		—		19 (13-26)		—	
• Unrelated	28 (16-49)	.036	—		43 (30-65)	.006	—	
Comorbidities								
• Diabetes								
- yes	36 (21-63)		3.2 (1.4-7.3)	.004	45 (29-72)		2.2 (1.1-4.4)	.03
- no	11 (7-17)	.003	—		20 (15-27)	.002	—	
• HTA								
- Yes	13 (6-28)				22 (13-40)			
- No	14 (10-21)	.9	NA		19 (14-26)	.8	NA	
• Cardiomyopathy								
- yes	11 (4-31)				25 (13-47)			
- no	14 (10-21)	.5	NA		19 (14-27)	.8	NA	
Acute GVHD II-IV								
• Yes	34 (24-49)		5.1 (2.3-11.2)	.001	46 (35-62)		4.3 (2.3-8.1)	<.001
• No	7 (4-13)	<.001	—		13 (8-20)	<.001	—	
Chronic GVHD								
• Limt/Ext	—		NA		13 (8-22)		—	
• No	—		—		7 (4-16)	.1	—	
ARF at day +100								
• Yes	25 (17-37)		3.4 (1.5-8.1)	.005	35 (26-48)			
• No	5 (2-12)	.002	—		14 (9-22)	.002	NT	
ARF at 1-year								
• Yes	—				33 (25-44)		3 (1.5-6)	.002
• No	—		NT		12 (7-21)	.001	—	

CI, indicates confidence interval; Cox. Regr, Cox regression hazard model; HR, hazard ratio; GVHD, graft-versus-host disease; MTX, methotrevate, No., number; HTA, arterial hypertension; Limt, limited; Ext, extended; ARF, acute renal failure; RIC, reduced intensity conditioning; NA, not applicable; NT, not tested.

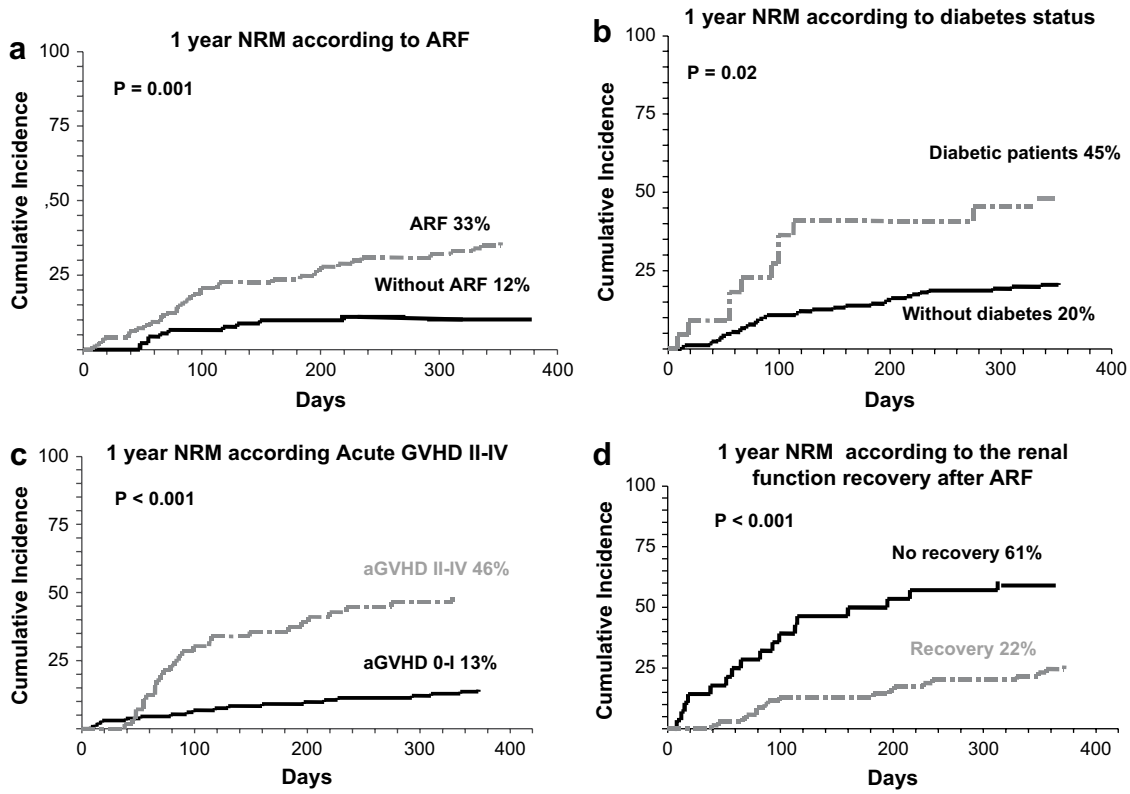

Figure 1. NRM curves corresponding to (a) ARF development, (b) diabetic status, (c) aGVHD grade II-IV, and (d) according to kidney function recovery.

did not recover normal kidney function (61%, 95% CI 45-82) than in those who did (22%, 95% CI 14-34) ($P \leq .001$) (Figure 1.d).

Relapse and OS

The cumulative incidence of relapse at median follow-up of 49 months was 30% (CI 95% 22-40) for the whole group. Patients who developed ARF had a 1-year cumulative incidence of relapse of 20% (95% CI 13-29) compared to 26% (95% CI 18-37) of patients without ARF ($P = .5$). The 1-year OS was lower for patients who developed ARF (54% versus 70%, $P = .04$, Figure 2.a). In addition, OS decreased according to the severity of ARF. Patients with ARF grade 2-3 had an OS at 1 year of 33% compared to 59% of patients with grade 1 and 70% of patients without ARF ($P = .003$) (Figure 2b).

DISCUSSION

The incidence of ARF in this cohort of patients undergoing Allo-RIC was (52%) similar to that observed in previous reports [2,4,5,7,9,12]. However, most patients with ARF (86%) developed grade 1 ARF, and grade 2-3 was observed only in 14% of patients. These results compares favorably with historic results with myeloablative regimens [6,10]. Nevertheless, 2 recent studies in nonmyeloablative Allo-HSCT have reported higher incidence of ARF (80%-90%) and a more severe form (30%-40% grade 2 or greater) [11,12]; this discrepancy compared to our study could be explained in part by the substantial differences in the conditioning regimens, GVHD prophylaxis, and especially by the much higher targeted dose of CsA than used in our study.

The main cause of ARF in our study was drug related (mainly the use of CsA), which has been previously reported as the main cause of ARF in the posttransplant setting [21]. By decreasing the CsA dose, kidney function returned to normal in most of our patients. As in other studies [2,4,12], we did not find any relationship between plasma levels of CsA and the development of ARF. Nevertheless, this could perhaps be explained by the adjustment of CsA levels to between 200-300 ng/mL.

Risk factors for the development of ARF had been delineated by several studies in a myeloablative Allo-HSCT setting [6,22,23]. However, Allo-RIC differs widely from myeloablative Allo-HSCT in terms of conditioning therapy, the patient's comorbidity profile, and posttransplantation-related complications. We identified 4 risk factors for ARF: (1) more than 3 lines of chemotherapy prior to Allo-RIC, (2) the use of MTX as GVHD prophylaxis regimen, (3) aGVHD grade III-IV, and (4) DM. MTX and number of prior chemotherapy have not been reported previously as risk factors for ARF in Allo-RIC. Heavily pretreated

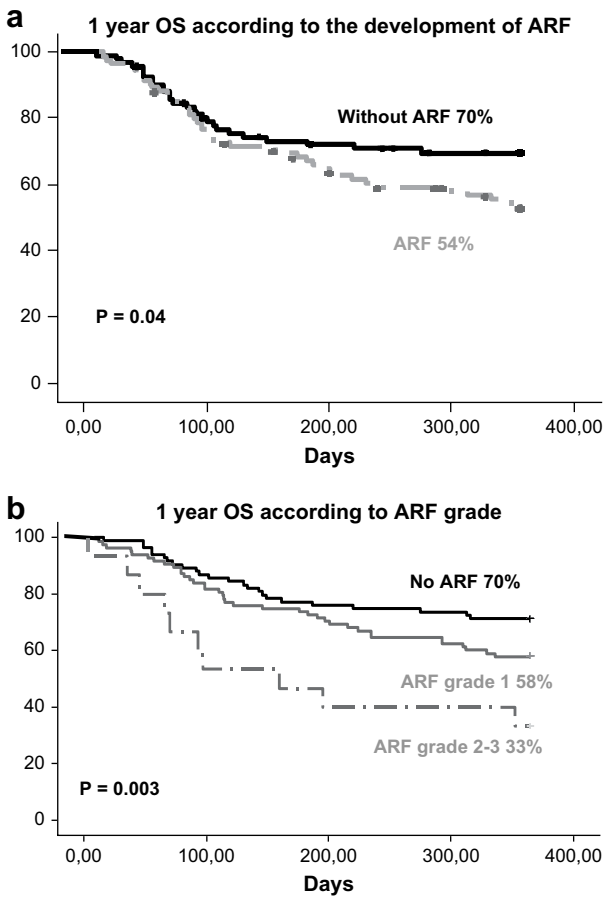

Figure 2. KM 1-year OS curves (a) according to ARF and (b) according to ARF grades.

patients may have had prior kidney damage, and although this may have been subclinical in the evaluation before SCT, it could predispose these patients to develop ARF in subsequent exposure to nephrotoxic drugs. MTX is a well-known nephrotoxic drug [24], even when it is used at low doses, and it is not surprising that it can be related to ARF in patients undergoing Allo-RIC. The absence of prior reports regarding the relationship between MTX and ARF in nonmyeloablative transplants seems to be related to the use of MMF instead of MTX as GVHD prophylaxis [9,11,12].

The relationship between ARF and cGVHD has been described by Parikh et al. [11], who showed that the development of ARF was associated with higher incidence of cGVHD, which may be because of the tapering of CsA [25] in those patients who develop ARF. In our study, as in the study by Kersting et al. [12], we found that the development of severe aGVHD was a risk factor for ARF, which could be related to the use of nephrotoxic drugs and the dehydration. Probably the relationship is bidirectional, and both complications are closely linked.

The impact of DM in the allo-HSCT is controversial. One study has shown that preexisting diabetes is associated, albeit weakly, with ARF [10], whereas a recent multivariate analysis by Kersting et al. [12], reported that the absence of preexisting vascular disease (including diabetes, myocardial infarction, angina pectoris, and cerebrovascular event) was an independent risk factor for the development of ARF. The authors considered that these controversial results could be explained by the fact that physicians monitored the CsA levels and creatinine more closely in this vulnerable group of patients. Moreover, in a recent study with patients that underwent an Allo-RIC, DM was not associated with ARF [9]. and the authors supported the use of RIC regimens for diabetic patients who were not eligible for myeloablative transplantation because of preexisting impaired renal function.

Our results, however, indicated that DM was a strong factor associated with the development of ARF throughout the transplant, although the significance is lower after day +100. Diabetic nephropathy is a leading cause of end-stage renal disease and CsA, which is the main cause of renal impairment in HSCT, has been associated with kidney impairment in diabetic patients [26]. It is also important to emphasize that CsA induces an abnormal glucose metabolism by decreasing insulin release and inducing peripheral insulin resistance in diabetic patients undergoing kidney transplantation [27]. Moreover, steroids commonly used in this setting could also impair glucose metabolism and may also lead to renal damage. Therefore, it is highly probable that diabetic status in conjunction with kidney (CsA) and glucose metabolism (steroids) injuries could have a synergic effect on renal damage. Taking all of this into account, it seems very important to closely monitor diabetic patients and, if possible, to avoid other known toxic drugs such as MTX or nonsteroid anti-inflammatory drugs. There is some evidence in heart transplantation that substituting CsA for sirolimus improves renal recovery compared to lower dose CsA plus sirolimus [28].

Other studies on autologous and allogeneic HSCT have found that the need for mechanical ventilation (MV) is the strongest risk factor associated with ARF and implies a high mortality rate [9,29]. However, MV, especially in the context of respiratory infections, is usually accompanied by exposure to antimicrobial drugs with a high nephrotoxic profile, leading to kidney failure. This setting often leads to dysfunction of other organs (liver, heart, bone marrow) and subsequent MODS. The association between MV and ARF is controversial in the above-mentioned studies, as it was not reported how many patients who needed MV had respiratory failure in the context of MODS. As well, liver failure has also been associated with severe ARF in myeloablative Allo-HSCT [22], without data about how many patients with liver dysfunction had MODS. Because MODS is a well-characterized

and unified syndrome that involves 2 or more organ systems [30], we did not consider each organ failure separately in the analysis. We considered MODS as a single entity because of the concomitant failure of multiple interreliant organ systems.

Although the development of an RIC regimen has allowed patients who are ineligible for standard Allo-HSCT to benefit from allogeneic therapy, NRM remains a significant obstacle to success with Allo-RIC. Our study showed that the development of ARF was strongly related to higher NRM and lower OS. These results are in line with preceding reports on myeloablative and RIC regimens [2,11]. All these reports enhance the suggestion that renal function is critical not only in Allo-HSCT but also in Allo-RIC patients. Moreover, as patients who undergo Allo-RIC are older and have other comorbidities, they are more vulnerable to complications. In our study, we also identified other variables as independent risk factors for NRM. These were DM, aGHVD, no MTX as GVHD prophylaxis, and more than 3 lines of chemotherapy before Allo-RIC. In our study, MTX appears to be protective against NRM, whereas it is associated with increased ARF; this apparent contradiction can be explained by the fact that MTX shows collinearity with an HLA matched sibling donor, whereas MMF show collinearity with unrelated donors (URD). One hundred twenty-five (80%) of 156 patients with HLA familiar donor received MTX as GVHD prophylaxis by only 7 (22%) of 32 patients with URD ($P < .0001$). In our study, URD had a higher cumulative incidence NRM compared to an HLA matched sibling donor: (43% [95% CI 30-65]) veresus (19% [95% CI 13-26]), respectively ($P = .006$).

In conclusion, we found that the incidence of severe ARF seems to be lower in Fludarabine plus alkylating agent-based RIC than myeloablative regimens. Despite this, ARF remains a life-threatening complication in this setting. DM, the use of MTX, having received more than 3 lines of treatments before transplant, and the development of severe aGVHD are the main risk factors associated with ARF in the patients undergoing Allo-RIC. The development of preventive strategies to avoid ARF is required in these patients.

ACKNOWLEDGMENTS

Special thanks to Carolyn Newey for her invaluable language aid in the manuscript drafting. J.L.Piñana is supported by grants from the Instituto de Salud Carlos III (CM06/00139, Ministerio de Sanidad, Spain).

Financial disclosure: This work is supported by the Ferrer Salat award from the fundación de investigación Sant Pau, Barcelone, Spain.

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