Allogeneic hematopoietic cell transplantation from unrelated donors in multiple myeloma: study from the italian bone marrow donor registry.

Allogeneic Hematopoietic Cell Transplantation from Unrelated Donors in Multiple Myeloma: Study from the Italian Bone Marrow Donor Registry

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Abstract

To evaluate trends in allografting from unrelated donors, we conducted a study on 196 consecutive myeloma patients transplanted between 2000 and 2009 in Italy. Twenty-eight percent, 37%, and 35%, respectively, received myeloablative, reduced-intensity, and nonmyeloablative conditioning. In these 3 cohorts, 1-year and 5-year transplantation-related mortalities were 28.8% and 37.0%, 20.3% and 31.3%, and 25.0% and 30.3%, respectively ($P = .745$). Median overall survival (OS) and event-free survival from transplantation for the 3 cohorts were 29 and 10 months, 11 and 6 months, and 32 and 13 months, respectively ($P = .039$ and $P = .049$). Overall cumulative incidences of acute and chronic graft-versus-host-disease (GVHD) were 46.1% and 51.1%. By Cox multivariate analyses, chronic GVHD was significantly associated with longer OS (hazard ratio [HR], .51; $P = .009$), whereas the use of peripheral blood stem cells was borderline significant (HR, .55; $P = .051$). Better response posttransplantation was associated with longer event-free survival (HR, 2.13 to 4.25; $P < .001$). Acute GVHD was associated with poorer OS (HR, 2.53; $P = .001$). This analysis showed a strong association of acute and chronic GVHD and depth of response posttransplantation with clinical outcomes. Long-term disease control remains challenging regardless of the conditioning. In the light of these results, prospective trials may be designed to better define the role of allografting from unrelated donors in myeloma.

Introduction

Indications for allografting in the treatment of hematological malignancies have greatly changed over the past decade. Several changes in transplantation procedures and better supportive care have also contributed to significantly improve clinical outcomes [1]. Recent activity surveys by the European Group for Blood and Marrow Transplantation (EBMT) have shown that the number of allografts performed from unrelated donors is currently higher that those from HLA-identical siblings in Europe 2 and 3. As for plasma cell disorders, 569 allografts were performed in 2009 with a remarkable increase as compared with 2004 [2]. In particular, 546 allografts were performed for multiple myeloma in 2010 and over 50% were from unrelated donors [3]. Unfortunately, only a minority of patient were enrolled in prospective clinical trials.

To observe trends and to report clinical outcomes in allografting from unrelated donors for the treatment of multiple myeloma in Italy, we conducted a retrospective study through the Italian Bone Marrow Donor Registry (IBMDR) over a 10-year period from 2000 to 2009 (http://ClinicalTrials.gov; NCT01440556).

Methods

Patients

From 2000 through 2009, 196 patients, median age 51 years (range, 32 to 67 years), underwent transplanted from an unrelated donor in Italy. Clinical data were retrieved from the central data management system Project Manager Internet Server (ProMISe) used by the EBMT and from the IBMDR where patients are followed longitudinally with at least yearly follow-up. Furthermore, patient forms for specific queries were sent to each participating center to complete data collection. The study was approved by the Italian Committee for Unrelated Donor Marrow Transplantation and by the institutional review board of the coordinating center, San Giovanni Battista Hospital, University of Torino, Torino, Italy, according to the Declaration of Helsinki (http://ClinicalTrials.gov; NCT01440556).

Statistical Analysis

Primary endpoints were overall survival (OS) from diagnosis and from the allograft and event-free survival (EFS) from the allograft. OS was defined as the date from diagnosis and from the allograft to death from any cause, whereas EFS was defined as the date from the allograft to disease progression/relapse or death from any cause, whichever occurred first. Alive patients without progression/relapse were censored as of March 31, 2012. Patient characteristics were compared with Fisher's exact test for categorical variables and with Mann-Whitney test for continuous variables. Survivals were calculated by the Kaplan-Meier method and analyzed by the Cox proportional hazards model, comparing the 2 arms by the Wald test and calculating 95% confidence intervals (CIs) 4 and 5.

Univariate and multivariate analyses were performed for the following variables: Durie-Salmon stage, number of previous chemotherapy lines (>2 versus ≤2), exposure to "new drugs" (thalidomide, lenalidomide, bortezomib) before the allograft, disease status at transplantation, HLA-matched alleles (≤8/10 versus 9/10 versus 10/10), recipient–donor gender combinations, stem cell source (bone marrow versus peripheral blood stem cells [PBSCs]), conditioning (nonmyeloablative versus reduced intensity versus myeloablative), acute graft-versus-host disease (GVHD), chronic GVHD, best response posttransplantation, and year of transplantation (2006 to 2009 versus 2003 to 2005 versus 2000 to 2002). Conditionings were defined as myeloablative, reduced intensity or nonmyeloablative as previously described [6].

Response criteria were defined as complete remission (CR), partial remission (PR), and stable and progressive disease (SD-PD) according to the International Uniform Response Criteria for multiple myeloma [7]. Best response posttransplantation and acute and chronic GVHD were treated as time-dependent variables. Moreover, to fully evaluate the confounding role of "disease status at transplantation" and "best response posttransplantation" in multivariate analyses, the previous Cox multivariate models were also estimated omitting these 2 variables. Cumulative incidences of grades II to IV acute GVHD, overall, limited and extensive chronic GVHD, and transplantation-related mortality (TRM) were estimated by the Fine and Gray competing risk regression models as previously described [8]. TRM was defined as death without previous relapse. Death without acute GVHD was considered a competing risk for acute GVHD, whereas death without chronic GVHD for overall chronic GVHD, limited and extensive chronic GVHD, and relapse was considered a competing event for TRM.

All *P* values were 2-sided at the conventional 5% significance level. Follow-up was updated as of March 31, 2012. Data were analyzed as of November 2012 by IBM SPSS 21.0. (Armonk, NY) and R 3.0.0 (R Foundation for Statistical Computing, Vienna, Austria) package cmprsk.

Results

Study Population

Over the 10-year study period (January 2000 to October 2009), 649 unrelated volunteer donor searches for myeloma patients were started through the IBMDR. As of October 31, 2009, 196 patients received transplantations after identifying a suitable unrelated donor at 34 centers; 3 patients received 2 allografts for a total of 199 transplantations. Median time from the start of the donor search to transplantation was 7 months. Patient characteristics are reported in Table 1.

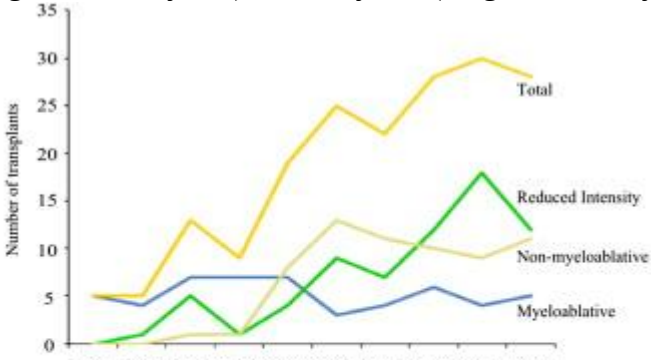
Table 1.
Characteristics of Patients Who Underwent an Allograft from an Unrelated Donor

Characteristic	**Number**
Study period	2000-2009
Patients	196
Allografts	199
Median age, yr (range)	51 (32-67)
Male	120 (60%)
Myeloma stage at diagnosis (Durie & Salmon)∗	
Stage I-II	42 (21%)
Stage III	140 (70%)
Myeloma isotype	
IgG	115 (58%)
IgA	34 (17%)
IgM	1 (<1%)
Bence Jones	33 (16%)
Nonsecretory	3 (1%)
Conditioning∗	
Myeloablative	52 (28%)
Nonmyeloablative	64 (35%)
Reduced intensity	69 (37%)
Therapy lines before transplant∗	
≤2	86 (43%)
>2	99 (50%)
Recipient–donor HLA matched alleles	
10/10	102 (52%)
9/10	62 (31%)
≤8/10	34 (17%)
Median time from diagnosis to transplant, mo	33 (range 5-171)

∗
Data not reported in 14 transplants.

Patients were also divided into 3 cohorts depending on the year of transplantation: 26 in 2000 to 2002, 57 in 2003 to 2005, and 116 in 2006 to 2009. Patients were also divided by conditioning regimen: 52 were assigned the myeloablative conditioning regimen, 69 the reduced intensity, and 64 the nonmyeloablative (conditioning regimen was unknown in 14 transplantations) (Figure 1).

Patient median age at transplantation for the 3 cohorts was 45 years (range, 32 to 63 years), 53 years (range, 33 to 65 years), and 55 years (range, 38 to 67 years), respectively ($P < .001$).



Transplants			
Myeloablative	16	17	19
Reduced Intensity	6	14	49
Non-myeloablative	1	22	41
Missing data	3	4	7
Total	26	57	116

Figure 1.
Number of allografts by year and trends in conditioning regimens over the study period.

Therapy Lines

Most patients were heavily pretreated and received a median of 3 (range, 1 to 7) lines of therapy before the allograft. One hundred fifty of 196 patients (76%) also received so-called new drugs: 71 of 150 (47%) received thalidomide and/or lenalidomide, 28 of 150 (19%) received only bortezomib, and 51 of 150 (33%) received both thalidomide/lenalidomide and bortezomib. One hundred seventy-five of 196 patients (89%) had received at least 1 autograft; 12 of 196 (6%) had not undergone an autograft (data were missing in 9 patients [4%]). Median time from diagnosis and from the autograft to the unrelated donor allograft was 16 months (range, 2 to 150) and 33 months (range, 5 to 171), respectively.

Conditioning Regimens, Stem Cell Source, and GVHD Prophylaxis

Conditioning regimens

Myeloablative regimens consisted primarily of cyclophosphamide–total body irradiation (TBI) and cyclophoshamide–busulfan. Some patients received high-dose busulfan associated with melphalan, fludarabine, or thiotepa–fludarabine. Other regimens included melphalan–cyclophosphamide–TBI, melphalan–TBI, and treosulphan–fludarabine. Nonmyeloablative regimens consisted of low-dose TBI (200 cGy) with fludarabine. Reduced-intensity regimens consisted of melphalan–fludarabine based or thiotepa–cyclophosphamide based conditionings. The use of myeloablative regimens remained steady during the study period, whereas reduced-intensity and nonmyeloablative regimens remarkably increased over the years (Figure 1, Table 2).

Table 2.
Transplant Characteristics of 3 Patient Cohorts Defined by Year of Transplant and Conditioning Regimen

Year of Transplant	Stem Cell Source No. of Transplants	Therapy Lines Before Transplant No. of Patients	Use of ATG No. of Transplants	Conditioning Regimen∗ No. of Transplants
	BM vs. PBSC	≤2 vs. >2	Yes vs. No	M vs. R vs. NM
2000-2002	21 (84%) vs. 5 (19%)	14 (54%) vs. 12 (46%)	18 (70%) vs. 8 (30%)	16 (70%) vs. 6 (26%) vs. 1 (4%)
2003-2005	12 (21%) vs. 45 (79%)	23 (40%) vs. 34 (60%)	29 (51%) vs. 28 (49%)	17 (32%) vs. 14 (26%) vs. 22 (42%)
2006-2009	16 (14%) vs. 100 (86%)	61 (53%) vs. 55 (47%)	63 (55%) vs. 53 (45%)	19 (17%) vs. 49 (45%) vs. 41 (38%)

Conditioning Regimen∗	Stem Cell Source No. of Transplants	Therapy Lines Before Transplant No. of Patients	Use of ATG No. of Transplants	Year of Transplant No. of Transplants
	BM vs. PBSC	≤2 vs. >2	Yes vs. No	2000-2002 vs. 2003-2005 vs. 2006-2009
Myeloablative	24 (46%) vs. 28 (54%)	23 (44%) vs. 29 (56%)	45 (86%) vs. 7 (14%)	16 (31%) vs. 17 (33%) vs. 19 (36%)
Reduced intensity	18 (26%) vs. 51 (74%)	33 (48%) vs. 36 (52%)	53 (77%) vs. 16 (23%)	6 (9%) vs. 14 (20%) vs. 49 (71%)
Nonmyeloablative	0 (0%) vs. 64 (100%)	30 (47%) vs. 34 (53%)	10 (16%) vs. 54 (84%)	1 (2%) vs. 22 (34%) vs. 41 (64%)

BM indicates bone marrow; M, myeloablative; R, reduced intensity; NM, nonmyeloablative vs., versus.

∗

Conditioning regimen was unknown in 14 transplants.

Stem cell source

PBSCs were the most frequently used stem cell source: They were used in 150 of 199 transplants (75%), whereas bone marrow was used in 49 of 199 transplants (25%). Bone marrow was primarily associated with myeloablative regimens in earlier years, whereas PBSCs were mostly used in reduced-intensity and in all nonmyeloablative regimens in recent years (Figure 1, Table 2).

GVHD prophylaxis

Myeloablative and reduced-intensity regimens were associated with cyclosporine–methothrexate based GVHD prophylaxis, whereas nonmyeloablative regimens were associated with cyclosporine–mycophenolate mophetil prophylaxis. Moreover, antithymocyte globulin (ATG) was used in 110 of 199 transplants (55%) as part of GVHD prophylaxis (Table 2).

Transplant-Related Toxicity and Mortality

Overall cumulative incidence of acute grades II to IV GVHD was 46.1%, whereas chronic GVHD was 51.1% (Figure 2A, B). The cumulative incidences of acute and chronic GVHD by type of conditioning were 41.2% and 42.9%, 50.0% and 40.1%, and 49.2% and 66.4% for myeloablative, reduced-intensity, and nonmyeloablative regimens, respectively. No statistically significant difference in acute GVHD cumulative incidence among the 3 cohorts was found (P = .803), whereas for chronic GVHD a borderline difference was observed (P = .052).

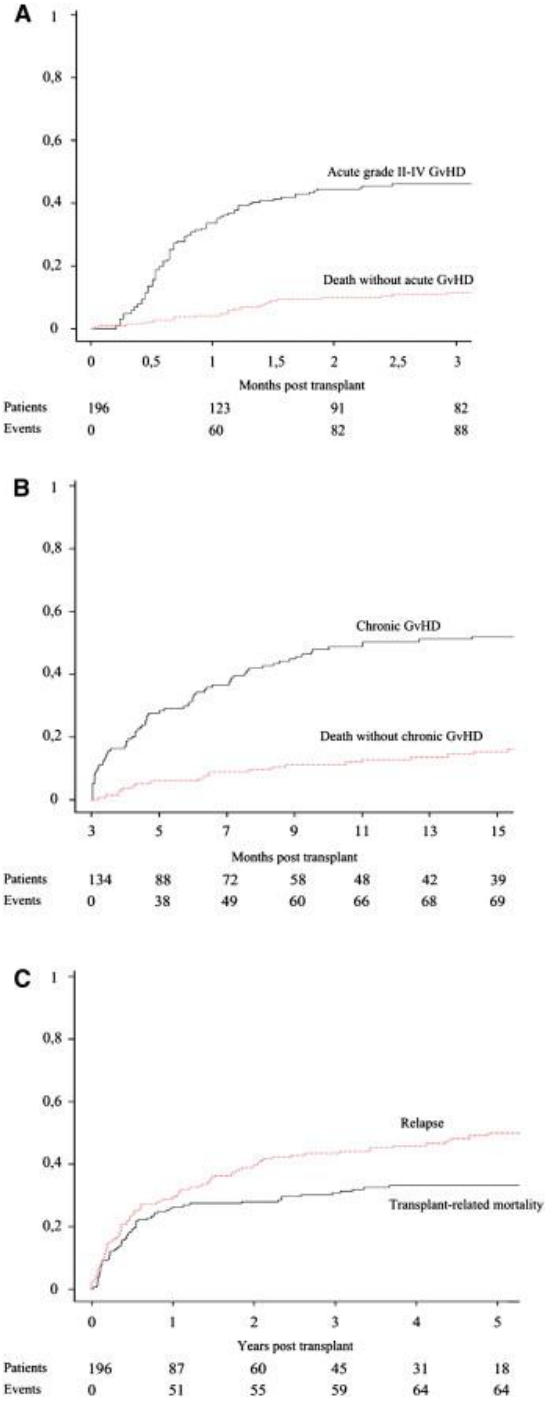


Figure 2.
(A) Cumulative incidence of acute grades II-IV GVHD. (B) Cumulative incidence of chronic GVHD. (C) Cumulative incidence of TRM.

Overall cumulative incidence of TRM was 25.8% at 1 year and 33.2% at 5 years posttransplantation, and the cumulative incidence of its competing event (relapse) was 28.8% and 50.0%, respectively (Figure 2C). One-year and 5-year TRM was 28.8% and 37.0%, 20.3% and 31.3%, and 25.0% and 30.3% for myeloablative, reduced-intensity, and nonmyeloablative regimens, respectively (P = .745), whereas 1-year and 5-year cumulative incidences of relapse were 21.2% and 46.0%, 42.1% and 54.3%, and 20.3% and 45.7%, respectively (P = .259).

Disease Response

At the time of the allograft, 29 of 196 patients (14.8%) were in CR and 87 of 196 (44.4%) in PR. Stratified by conditioning, patients in CR, PR, and SD-PD were 3 of 52 (6%), 23 of 52 (44%), and 26 of 52 (50%) for myeloablative; 9 of 69 (13%), 28 of 69 (41%), and 32 of 69 (46%) for reduced-intensity; and 15 of 64 (23%), 29 of 64 (45%), and 20 of 64 (31%) for nonmyeloablative regimens, respectively (P = .052). After a median follow-up from transplantation of 57 months (range, 3 to 128), CR and PR in patients who survived at least 3 months after transplant were 40% and 39%, respectively, for an overall response rate of 79%.

Clinical Outcomes

At a median follow-up of 93 months (range, 25 to 189) from diagnosis, median OS from diagnosis of the entire study population was 67 months, whereas at a median follow-up of 57 months (range, 3 to 128) posttransplantation, median OS and EFS from the allograft were 15 and 7 months, respectively (Figure 3A). Overall, 57 of 196 patients died of disease progression, whereas 71 of 196 died of transplant-related causes.

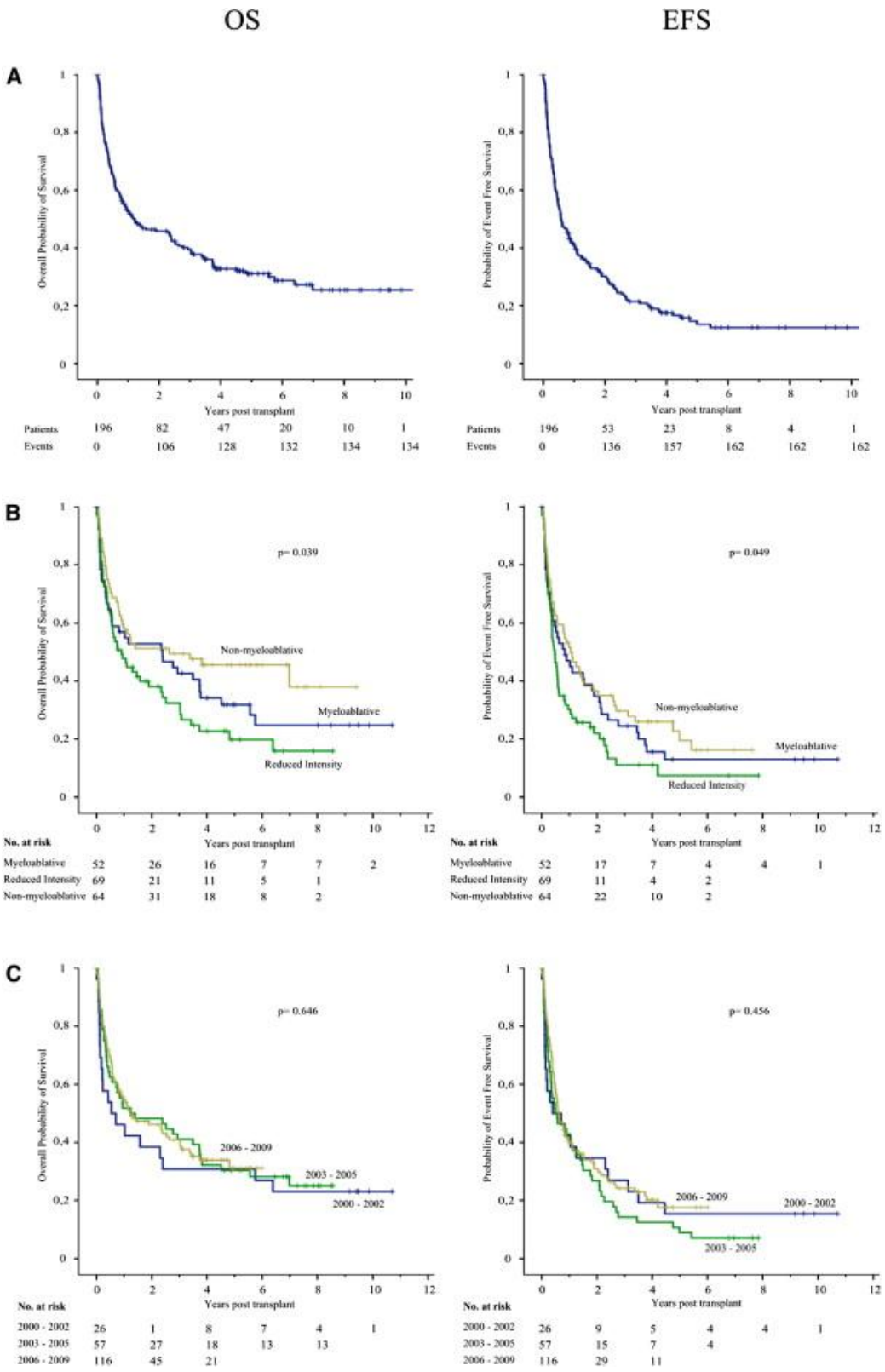


Figure 3.
(A) OS and EFS from the allograft of the entire study population. (B) OS and EFS of 3 patient cohorts defined by conditioning regimen. (C) OS and EFS of 3 patient cohorts defined by year of transplantation.

At a median follow-up of 120 months (range, 30 to 189), 76 months (range, 26 to 180), and 93 months (range, 25 to 183) from diagnosis, median OS was 71, 66, and 67 months for

myeloablative, reduced-intensity, and nonmyeloablative regimens, respectively (P = .362). At a median follow-up of 63 months (range, 3 to 128), 48 months (range, 10 to 103), and 58 months (range, 11 to 113) posttransplantation, median OS and EFS from the allograft were 29 and 10 months, 11 and 6 months, and 32 and 13 months in patients who underwent myeloablative, reduced-intensity, and nonmyeloablative transplants, respectively (P = .039 and P = .049; Figure 3B). OS (P = .646) and EFS (P = .456) from the allograft in the 3 patient cohorts defined by year of transplantation are reported in Figure 3C.

Factors Affecting OS and EFS

By univariate analyses, lower number of therapy lines before the allograft, disease status at transplantation, a fully matched (10/10 alleles) HLA-identical donor, the use of PBSCs rather than bone marrow, and a better response posttransplantation were statistically significant variables for OS, whereas disease status at transplant, limited chronic GVHD, and a better response posttransplantation were statistically significant variables for EFS.

However, by multivariate analyses, only the use of PBSCs (hazard ratio [HR], .55; P = .051) and the development of chronic GVHD (HR, .51; P = .009) were significant predictors for longer OS, whereas acute GVHD (HR, 2.53; P = .001) was a significant predictor for poorer OS. Most important predictors for EFS were a better response posttransplantation (PR versus CR: HR, 2.13; SD-PD versus CR: HR, 4.25; P < .001) and the conditioning regimen (reduced intensity versus myeloablative: HR, 1.96; P = .001). Complete univariate and multivariate analyses are reported in Tables 3 and 4.

Table 3.
Univariate and Multivariate Analyses (Cox Models) for OS

Variable	Univariate Analyses			Multivariate Analyses		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Durie-Salmon stage (III vs. I-II)	1.27	.87-1.86	.218			
Previous therapy lines (>2 vs. ≤ 2)	1.54	1.09-2.17	.014	1.15	.71-1.88	.567
Disease status at transplant			.009			.747
PR vs. CR	1.51	.84-2.71	.170	1.20	.49-2.93	.696
SD-PD vs. CR	2.25	1.26-4.01	.006	.98	.40-2.42	.965
Recipient–donor HLA matched alleles			.010			.871
9/10 vs. 10/10	1.55	1.06-2.27	.025	1.14	.66-1.97	.642
≤8/10 vs. 10/10	1.91	1.20-3.03	.006	1.16	.54-2.50	.697
Recipient–donor gender combinations			.866			
f.f. vs. m.f.	1.26	.70-2.29	.441			
m.m. vs. m.f.	1.20	.74-1.93	.459			
f.m. vs. m.f.	1.16	.69-1.97	.571			
New drugs before allograft (yes vs. no)	.96	.65-1.41	.829			
Source (PBSC vs.BM)	.60	.41-.87	.007	.55	.30-1.00	.051
Conditioning			.042			.163
R vs M	1.26	.82-1.93	.293	1.46	.81-2.66	.211
NM vs. M	.72	.45-1.15	.173	.86	.43-1.69	.655
Acute GVHD∗	1.49	.96-2.31	.078	2.53	1.50-4.28	.001
Chronic GVHD∗	.67	.34-1.34	.258	.51	.31-.84	.009

Variable	Univariate Analyses			Multivariate Analyses		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Chronic GVHD∗			.467			
Limited vs. no GVHD	.66	.34-1.28	.220			
Extensive vs. no GVHD	.80	.36-1.80	.597			
Best response posttransplantation∗			.011			.349
PR vs. CR	.97	.53-1.80	.926	.82	.41-1.64	.580
SD-PD vs. CR	2.35	1.09-5.06	.030	1.35	.54-3.37	.520
Year of transplant			.647			
2003-2005 vs. 2000-2002	.82	.48-1.39	.453			
2006-2009 vs. *20*00-2002	.79	.48-1.30	.789			

f. indicates female; m., male; BM, bone marrow; R, reduced intensity; M, myeloablative; NM, nonmyeloablative, vs., versus.

∗

Treated as a time-dependent variable.

Table 4.
Univariate and Multivariate Analyses (Cox Models) for EFS

Variable	Univariate Analyses			Multivariate Analyses		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Durie-Salmon stage (III vs. I-II)	1.31	.93-1.85	.126			
Previous therapy lines (>2 vs. ≤ 2)	1.28	.94-1.75	.115	.97	.63-1.50	.895
Disease status at transplant			.009			.605
PR vs. CR	1.83	1.08-3.11	.025	1.06	.49-2.30	.879
SD-PD vs. CR	2.28	1.34-3.89	.002	.85	.39-1.84	.674
Recipient–donor HLA matched alleles			.095			.886
9/10 vs. 10/10	1.31	.92-1.86	.132	.92	.57-1.48	.731
≤8/10 vs. 10/10	1.53	1.00-2.35	.050	1.08	.56-2.09	.820
Recipient–donor gender combinations			.901			
f.f. vs. m.f.	1.16	.67-1.99	.598			
m.m. vs. m.f.	1.16	.76-1.78	.503			
f.m. vs. m.f.	1.18	.74-1.89	.492			
New drugs before allograft (yes vs. no)	.99	.70-1.41	.961			
Source (PBSC vs.BM)	.75	.53-1.06	.098	1.02	.54-1.92	.951
Conditioning			.052			.025
R vs. M	1.34	.90-2.00	.145	1.96	1.16-3.33	.001
NM vs. M	.84	.56-1.27	.405	1.22	.71-2.08	.478
ATG (yes vs. no)	1.08	.79-1.47	.645			
Acute GVHD∗	1.12	.74-1.68	.593	1.15	.62-2.15	.658

Variable	Univariate Analyses			Multivariate Analyses		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Chronic GVHD∗	.54	.31-.97	.040	.82	.45-1.50	.516
Chronic GVHD∗			.047			
Limited vs. no GVHD	.51	.29-.89	.017			
Extensive vs. no GVHD	.55	.28-1.08	.082			
Best response posttransplantation∗			<.001			<.001
PR vs. CR	1.98	1.07-3.67	.029	2.13	1.34-3.41	.002
SD-PD vs. CR	4.85	2.29-1.29	<.001	4.25	2.41-7.50	<.001
Year of transplant			.459			
2003-2005 vs. 2000-2002	1.14	.69-1.89	.599			
2006-2009 vs. 2000-2002	.92	.57-1.47	.722			

f. indicates female; m., male; BM, bone marrow; R, reduced intensity; M, myeloablative; NM, nonmyeloablative; vs., versus.

∗

Treated as a time-dependent variable.

By omitting “disease status at transplantation” and “best response posttransplantation” in the Cox multivariate models, major predictors for shorter OS remained acute GVHD (HR, 2.10; 95% CI, 1.29 to 3.41; $P = .003$) and for longer OS chronic GVHD (HR, .42; 95% CI, .26 to .69; $P = .001$). Conditioning regimen (reduced intensity versus myeloablative: HR, 1.72; 95% CI, 1.04 to 2.84; $P = .035$) and chronic GVHD (HR, .48; 95% CI, .31 to .72; $P < .001$) were major predictors for EFS.

Discussion

The current role of allografting in multiple myeloma is controversial 9 and 10. The most recently published prospective studies were designed before new drugs with potent antimyeloma activity became readily available 11 and 12, enrolled newly diagnosed patients, used reduced-intensity or nonmyeloablative conditionings and donors were most frequently HLA-identical siblings 13, 14, 15, 16, 17, 18, 19, 20, 21, 22 and 23. Conflicting results were reported. Only a few published reports focused on allografting from unrelated donors 24, 25, 26, 27 and 28. Our retrospective analysis through the IBMDR was intended to evaluate trends in allografting from unrelated donors over the past decade, with the ultimate goal of possibly offering recommendations to our centers on timing and type of allograft and on donor selection.

In our experience, the number of allografts gradually increased over the study period. Overall, TRM at 1 year and 5 years was 25.8% and 33.2%, respectively. There was no significant difference in TRM ($P = .745$) between conditioning regimens. Incidence of acute GVHD was not significantly different among the 3 cohorts, whereas that of chronic GVHD was borderline significantly different ($P = .052$). Nonmyeloablative regimens showed a higher cumulative incidence of chronic GVHD, presumably related to the use of PBSCs. Patients conditioned with reduced-intensity or nonmyeloablative regimens were significantly older than those conditioned with a myeloablative regimen ($P < .001$). This is not irrelevant given that the median age of newly diagnosed myeloma patients is 67 to 68 years. Median OS and EFS of the entire study population were 15 and 7 months, respectively, and a subset have become long-term disease-free survivors (Figure 3A). Even though

this study cannot offer a formal comparison among conditionings, significant differences in both OS and EFS were observed among the 3 patient cohorts defined by conditioning (Figure 3B).
By multivariate analyses, acute and chronic GVHD were variables significantly associated with OS, whereas the use of a myeloablative conditioning and best response posttransplantation significantly correlated with EFS (Tables 3 and 4). The real impact of ATG on GVHD incidence could not formally be assessed because ATG was almost invariably associated with myeloablative and reduced-intensity conditionings. The impact of antileukemia effects associated with chronic GVHD was documented in many reports 29, 30 and 31.
With regard to the association between chronic GVHD and graft-versus-myeloma effects, reports are somewhat conflicting 17, 19, 32, 33 and 34. Ringdén et al. evaluated the impact of acute and chronic GVHD on relapse and survival in a cohort of 177 patients who received an allograft from HLA-identical siblings after nonmyeloablative or reduced-intensity conditionings [34]. Acute GVHD was significantly correlated with increased risk of TRM, whereas limited chronic GVHD significantly lowered the risk of myeloma recurrence. However, in their retrospective experience, the reduced relapse risk did not translate into better OS [34]. In contrast, another study by Crawley et al. reported that chronic GVHD was associated with better progression-free survival and OS after reduced-intensity conditioning [33]. In prospective studies, Björkstrand et al. did not report any difference in OS and EFS between patients with and without chronic GVHD after nonmyeloablative conditioning [20]. Similar findings were reported by others 17 and 19. Differences from study to study may be due to the design of the Cox multivariate models: By omitting “disease status at transplantation” and “best response post-transplant” in our multivariate analyses, acute GVHD was a major predictor of poorer OS (HR, 2.10; $P = .003$) and chronic GVHD of significantly better OS (HR, .42; $P = .001$) and EFS (HR, .48; $P < .001$).
Even though best response posttransplantation was the strongest predictor of better EFS but not of OS, this finding stresses the importance of depth of response 35 and 36. Consolidation and/or maintenance with new drugs may be a widely applicable option to explore. The efficacy of new drugs such as thalidomide and bortezomib in patients relapsed after an allograft has been reported in several studies 37 and 38. Furthermore, profound “immunomodulary effects” after allografting have already been observed. Higher response rates to salvage therapies, which translated into better OS, were reported in patients who had received a prior allograft rather than an autograft in a comparative study [19]. However, new drugs, such as lenalidomide, should be incorporated in clinical protocols as consolidation and/or maintenance with a degree of caution given that recently reported toxicity may be partly related to doses and treatment schedule [39]. Other strategies may include pre-emptive donor lymphocyte infusions with/without new drugs 40 and 41.
Our study did not allow for a comprehensive analysis of the impact of cytogenetic abnormalities because most patients were diagnosed when standard cytogenetic or FISH analyses had not yet become part of the diagnostic work-up. Research showed that abnormalities such as del(17p) are associated with shorter response duration and poor prognosis even after treatment with “new drugs” [42]. A retrospective analysis by the Société Francaise de Greffe de Moelle et de Thérapie Cellulaire showed that patients who carry these high-risk abnormalities may most benefit from an allograft [43]. With the introduction of new drugs, allografting has gradually become a less attractive treatment option. However, prospective studies may evaluate its current role in selected high-risk and/or refractory patients earlier in the course of the disease to limit the risk of cumulative toxicity and the potential emergence of plasma cell clones resistant to graft-versus-myeloma effects.
Before the introduction of reduced-intensity and/or nonmyeloablative conditioning, TRM was unacceptably high, up to 60% 44, 45 and 46. The wider use of reduced-intensity conditioning has recently shifted the burden of myeloma eradication and control from the pretransplantation intensive chemoradiotherapy of the conditioning to graft-versus-myeloma effects. A retrospective EBMT analysis showed that reduced-intensity conditioning was associated with less TRM but higher risk of relapse as compared with myeloablative conditioning [47]. It may be worth revisiting the role of more intense conditioning. Comorbidity scores, specifically designed for hematopoietic

cell transplantations, may help to choose the intensity of the conditioning and to better select patients 48 and 49. Moreover, high-resolution HLA typing at an allele level is currently more readily available for both class I and II MHC antigens in donor registries, and a fully matched HLA donor should be highly preferable. Unlike other reports, however, we did not find any correlation between donor gender and clinical outcomes [50].
In summary, younger medically fit patients, with high-risk cytogenetics, may be offered more intense conditionings to combine profound cytoreduction and potential graft-versus-myeloma effects, whereas older unfit patients, because of comorbidities, may best benefit from debulking therapies followed by a reduced-intensity and/or nonmyeloablative allograft to avoid unacceptably high TRM. This treatment plan may be explored in future prospective control studies through the IBMDR.

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