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Comparison of Outcomes of Allogeneic Hematopoietic Cell Transplantation for Multiple Myeloma Using Three Different Conditioning Regimens

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Allogeneic hematopoietic cell transplantation (allo-HCT) is a potentially curative therapy for patients with multiple myeloma, as it provides a graft-versus-myeloma effect alongside a myeloma-free graft. Although reduced-intensity conditioning regimens decrease nonrelapse mortality (NRM), there is a paucity of data with regard to the ideal conditioning regimen in myeloma. We conducted a retrospective comparison of 3 different preparative regimens used for allo-HCT for multiple myeloma at our institution in recent clinical trials: busulfan/fludarabine (BuFlu), fludarabine/melphalan 100 mg/m^2 (FM100), and fludarabine/melphalan 140 mg/m^2 (FM140). NRM, progression-free survival (PFS) at 3 years, and overall survival (OS) at 3 years were the primary endpoints. Secondary endpoints included time to engraftment, and the incidence of grades II through IV acute graft-versus-host disease and chronic graft-versus-host disease. A total of 73 patients received allo-HCT with these regimens. NRM at 3 years was seen in 3 (21%), 5 (28%), and 6 (24%) patients in the BuFlu, FM100, and FM140 groups, respectively. Three-year PFS in the BuFlu, FM100, and FM140 groups was 16% (hazard ratio [HR], 1.2; 95% confidence interval [CI], 0.6 to 2.1), 26% (HR, 0.6; 95% CI, 0.3 to 1.2), and 11% (reference), respectively. Three-year OS in the BuFlu, FM100, and FM140 groups was 39% (HR, 1.1; 95% CI, 0.5 to 2.2), 43% (HR, 0.7; 95% CI, 0.3 to 1.4), and 32% (reference), respectively. High-risk cytogenetics and relapsed disease prior to allo-HCT were found to be independent predictors of inferior OS on multivariate analysis, with a HR of 2.1 ($P = .02$) and 2.6 ($P = .004$), respectively. In contrast, the preparative regimen did not emerge as a predictor of PFS or OS. Durable clinical remission can be achieved in 11% to 25% of patients with multiple myeloma with the use of allo-HCT without any significant difference in the safety or efficacy of the conditioning regimen. High-risk cytogenetics and relapsed disease prior to transplant were associated with inferior PFS and OS.

INTRODUCTION

The treatment landscape for multiple myeloma has evolved rapidly in recent years. Introduction of proteasome inhibitors [1-4], immunomodulatory drugs [5,6], and antibody therapies [7,8] have significantly prolonged the life expectancy of patients with multiple myeloma, especially when combined with high-dose chemotherapy and autologous hematopoietic cell transplantation (auto-HCT) [9,10]. Unfortunately, even with newer agents and auto-HCT, patients still experience an eventual relapse [11].

Studies with myeloablative allogeneic hematopoietic cell transplantation (allo-HCT) have suggested that cure might be possible for a small subset of patients [12-14], which has been attributed to the graft-versus-myeloma effect [15,16]. Unfortunately, myeloablative allo-HCT has significant nonrelapse mortality (NRM), such as infections and graft-versus-host disease (GVHD) that can be as high as 53% at 100 days [17], which has limited its use despite improvements in survival with better supportive care [18]. Attempts to reduce the NRM have led to the use of reduced-intensity conditioning (RIC) regimen allo-HCT. Studies have shown that RIC has decreased NRM and improved overall survival (OS) when compared with myeloablative regimens [17], athough with higher relapse rates [19]. At this time, the optimal RIC regimen for multiple myeloma is still unknown. This article investigates 3 different RIC regimens in multiple myeloma patients who underwent allo-HCT at our single institution.

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METHODS

We conducted a retrospective comparison of 3 different preparative regimens used for allo-HCT for multiple myeloma at the MD Anderson Cancer Center in recent clinical trials. The 3 regimens used at our institution were busulfan/fludarabine (BuFlu), fludarabine/melphalan 100 mg/m^2 (FM100), and fludarabine/melphalan 140 mg/m^2 (FM140). Data regarding FM100 and FM140 were obtained from a prospective Phase II randomized clinical trial comparing the 2 regimens, whereas data for the BuFlu regimen were extracted from a separate single-arm prospective study. Eligibility for both clinical trials included age older than 18 years, Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function. Both clinical trials were approved by the institutional review board and were conducted according to the Declaration of Helsinki.

PREPARATIVE REGIMENS AND SUPPORTIVE CARE

The BuFlu regimen consisted of busulfan 80 mg/m^2 per day on days −13 and −12 in the outpatient clinic. Busulfan was subsequently dosed to achieve a target area under the curve of 16k or 20k on days −6, −5, −4, and −3 based on pharmacokinetic studies. Fludarabine was given 40 mg/m^2 i.v. on days −6, −5, −4, and −3. The FM100 and FM140 regimens consisted of the same dose of fludarabine 30 mg/m^2 given i.v. on days −4, −3, −2, and −1. Melphalan was dosed at 100 mg/m^2 or 140 mg/m2 given i.v. on day −1. Patients receiving grafts from matched unrelated donors (MUDs) all received antithymocyte globulin 1.5 mg/kg infused over 6 hours for 3 days (days −3, −2, and −1). All patients received similar infectious prophylaxis with standard antimicrobials. Filgastrim 5 μg/kg was started 7 days following allo-HCT until ANC $> 0.5 \times 10$ [9] /L for 3 consecutive days. GVHD prophylaxis was given similarly in all 3 groups, which consisted of tacrolimus day −2 or −1 alongside methotrexate 5 mg/m^2 on days 1, 3, 6, and 11. Rituximab was administered weekly for 4 doses on days −5, +2, +9, and +16 in the last 23 patients treated with FM-based regimens to reduce the risk of GVHD. Donor lymphocyte infusion (DLI) was given at the discretion of the treating physician at time of relapse. Maintenance chemotherapy following transplant was allowed at the discretion of the treating physician.

International Myeloma Working Group uniform response criteria were used to assess response before and after transplantation. Primary endpoints were NRM, progression-free survival (PFS) at 3 years, and OS at 3 years. Survival at 3 years was chosen because it reflects the length of follow-up in the most recent of the 2 clinical trials. Secondary endpoints included time to engraftment, grades II through IV acute graft-versus-host disease (aGVHD), and chronic graft-versus-host disease (cGVHD). PFS was defined as the time from the day of allo-HCT to progression or death. OS was defined as the time from the day of allo-HCT to death. Observations were censored at the time the patient was last known to be alive without disease progression for PFS and the time last known to be alive for OS. NRM was defined as death in the absence of relapse or persistence of disease. High-risk cytogenetic abnormalities were defined as del (17p), t(4;14), t(14;16), del(1p), amp(1q), and del 13 by (conventional karyotyping only), and plasma cell leukemia. Categorical variables were compared using the chi-square test or Fisher exact test. The Kaplan-Meier method was used to estimate the probability of OS and PFS. The cumulative incidence method accounting for competing risks was used to estimate the incidence of NRM and GVHD. Predictors of OS and PFS were evaluated on univariate and multivariate analysis using Cox proportional hazards regression analysis. Statistical significance was defined at the 0.05 level. Analyses were primarily conducted using STATA 14.0 (StataCorp, College Station, TX).

RESULTS

Among 73 patients who received allo-HCT from 2005 to 2015 with these regimens, there were 22, 23, and 28 patients who received BuFlu, FM100, and FM140 conditioning, respectively. Median follow-up in the BuFlu group was 31 months compared with 93 months for FM100 and 75 months for FM140.

Baseline Characteristics

The median age at transplant was 53 years, which was similar among all 3 regimens (Table 1). Patients receiving BuFlu were more likely to harbor high-risk cytogenetic abnormalities (82%) than those receiving FM100 (30%) and FM140 (43%) (Table 1). The Durie-Salmon stage and the percentage of patients achieving a very good partial response (VGPR) or greater prior to transplant were also similar across the 3 regimens (Table 1). Sixty-seven patients (92%) received prior auto-HCT. Most patients received allo-HCT at disease relapse (62%) as opposed to consolidation following auto-HCT in first remission (38%), which was similar among all 3 groups (Table 1). Most patients received a matched related donor (MRD) transplant as opposed to a MUD transplant. The FM100 arm had a higher rate of MRD transplants (91%) than the FM140 (57%) and BuFlu (73%) arms (Table 1). Thirteen patients received post-transplant maintenance therapy (6 in the BuFlu group, 2 in the FM100 group, and 5 in the FM140 group). The maintenance regimens consisted of lenalidomide (6), bortezomib (4), carfilzomib (1), carfilzomib/pomalidomide (1), and dexamethasone (1). Six patients received DLI.

Table 1
Baseline Characteristics of Patients Receiving Three Conditioning Regimens: BuFlu, FM100, and FM140

Characteristic	BuFlu (N = 22)	FM100 (N = 3)	FM140 (N = 28)	*P* Value
Median age, year (range)	54.5	53	52	.20
Sex (%)				.20
Male	14 (64)	11 (48)	16 (57)	
Female	8 (36)	12 (52)	12 (43)	
Donor type (%)				.03
MRD	16 (73)	21 (91)	16 (57)	
MUD	6 (27)	2 (9)	12 (43)	
Cytogenetics (%)				.001
Standard risk	4 (18)	16 (70)	16 (57)	
High risk	18 (82)	7 (30)	12 (43)	
Disease status at transplant (%)				.70
1st remission	7 (32)	10 (43)	11 (39)	
Relapsed	15 (68)	13 (57)	17 (61)	
≥PR prior to transplant (%)	17 (77)	16 (69)	19 (68)	.70

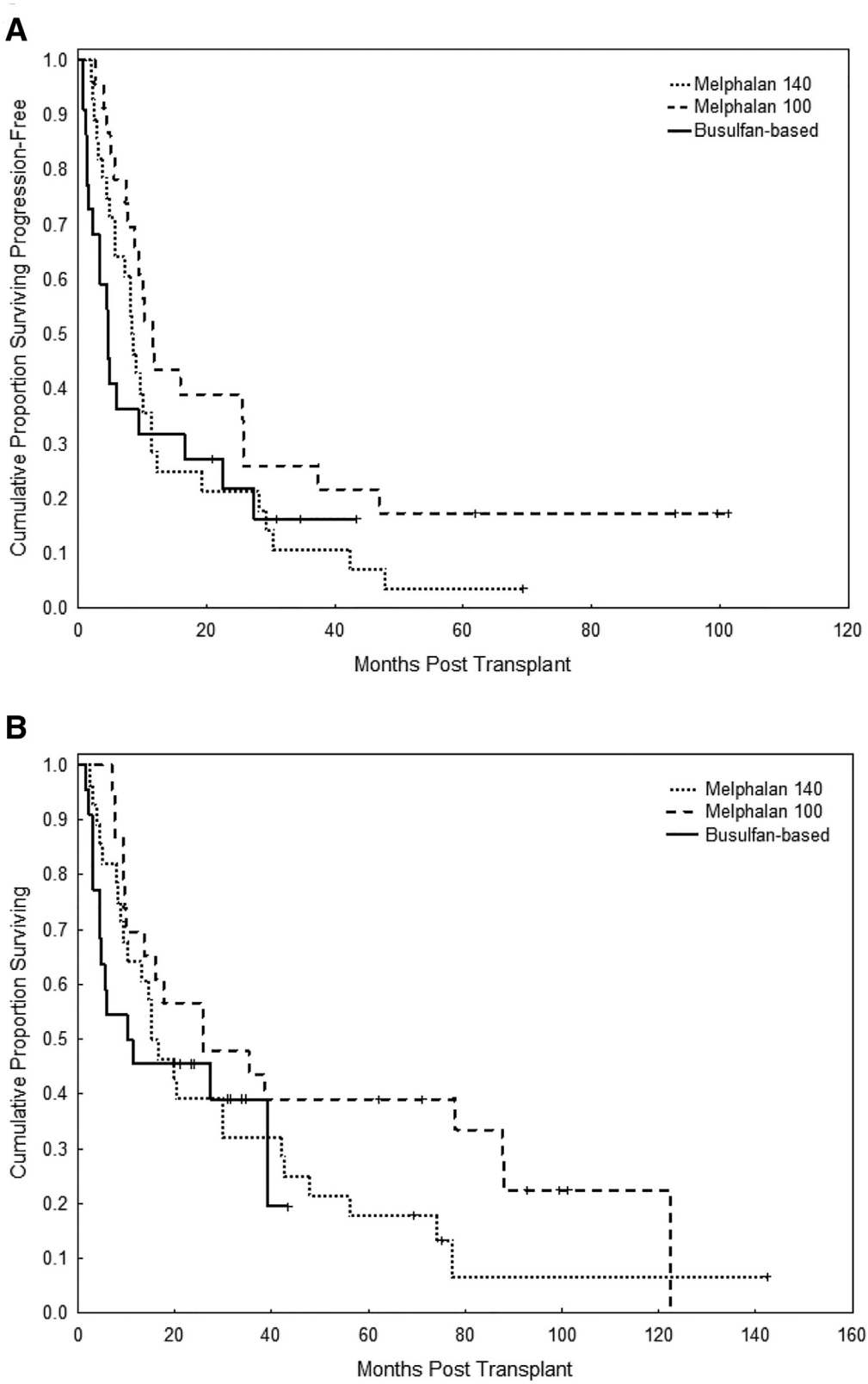

Figure 1. The PFS (A) and OS (B) by conditioning regimen.

Outcomes

All patients achieved neutrophil engraftment, with the median time to engraftment being 12 days (range, 10 to 24), which was similar across all 3 groups. At day 100, the cumulative incidence of grades II through IV aGVHD was 4 of 22 patients (18%) in the BuFlu group, 5 of 23 (22%) in the FM100 group, and 6 of 28 (21%) in the FM140 group. The 3-year risk of cGVHD was also similar among the 3 groups: 6 of

Table 2
Multivariate Analysis for PFS and OS

	PFS			OS		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Cytogenetics						
Standard risk	Reference			Reference		
High risk	2.3	1.3-4.1	.004	2.1	1.1-4.1	.02
Disease status at HCT						
1st remission	Reference			Reference		
Relapsed	2.5	1.5-4.4	.001	2.6	1.3-5.1	.004

22 (27%) with BuFlu, 9 of 23 (39%) with FM100, and 8 of 28 (29%) with FM140. A 100-day NRM was seen in 0, 0, and 1 (4%) patients in the BuFlu, FM100, and FM140 groups, respectively ($P = .50$). A 1-year NRM was seen in 2 (9%), 2 (9%), and 4 (14%) patients in the BuFlu, FM100, and FM140 groups, respectively ($P = .70$). The most common cause of NRM was GVHD. There were 4 deaths from aGVHD: 2 each in the BuFlu and FM140 groups. There were 4 deaths from cGVHD: 2 each in the FM100 and FM140 groups.

In terms of post-allo-HCT response, 5 (23%), 4 (18%), and 8 (36%) patients achieved near complete response/complete response/stringent complete response, VGPR, and partial response (PR) with BuFlu; 10 (43%), 4 (17%), and 7 (30%) with FM100; and 9 (32%), 6 (21%), and 9 (32%) with FM140. The overall response rates (complete response + VGPR + PR) were 17 (77%) with BuFlu, 21 (91%) with FM100, and 24 (86%) with FM140. The 3-year PFS in the BuFlu, FM100, and FM140 groups was 16% (hazard ratio [HR], 1.2; 95% confidence interval (CI), 0.6 to 2.1), 26% (HR, 0.6; 95% CI, 0.3 to 1.2), and 11% (reference), respectively ($P = .20$; Figure 1A). The 3-year OS in the BuFlu, FM100, and FM140 groups was 39% (HR, 1.1; 95% CI, 0.5 to 2.2), 43% (HR, 0.7; 95% CI, 0.3 to 1.4), and 32%, respectively ($P = .50$; Figure 1B).

Among the 13 patients who received post-transplant maintenance, 9 (69%) patients progressed while on maintenance therapy with no significant differences in median time to progression among the treatment groups. At the time of analysis, 2 patients were still receiving maintenance with lenalidomide with an ongoing stringent complete response at 43 and 99 months post-allo-HCT.

Six patients received DLI: 4 after disease progression and 2 for persistent disease after transplant. Of the 4 given DLI after disease progression, 3 failed to respond and died within 2 months. One patient achieved a VGPR and progressed after 23 months. Of the 2 patients who received DLI for persistent disease, one with high-risk cytogenetics progressed after 4.7 months, whereas the other with standard-risk cytogenetics progressed 31.8 months after DLI.

We evaluated the role of preparative regimen, donor type, Durie-Salmon stage, cytogenetics, response to pretransplant therapy, and disease status at transplant on PFS and OS in univariate analyses. On univariate analysis for PFS, high-risk cytogenetics, less than VGPR to pretransplant therapy, and relapsed disease at allo-HCT were significant predictors for worse PFS. Of these factors, high-risk cytogenetics and relapse disease remained significant predictors for worse PFS in a multivariate analysis (Table 2). Similarly, for OS, both high-risk cytogenetics and relapsed disease at allo-HCT remained significant predictors on both univariate and multivariate analyses (Table 2). Preparative regimen was not associated with PFS or OS when added to the multivariate analysis.

Patients (n = 15) with standard risk cytogenetics who received allo-HCT while in first remission had a median PFS and OS of 28 and 78 months, respectively (Figure 2A,B). In contrast, patients (n = 24) with high-risk cytogenetics and relapsed disease status at allo-HCT had a median PFS and OS of 3 and 8 months, respectively (Figure 2A,B). The inferior OS and PFS in patients with high-risk cytogenetics and relapsed disease status prior to allo-HCT was seen across all 3 conditioning regimens.

DISCUSSION

In this retrospective analysis, we compared 3 preparative regimens used for allo-HCT for multiple myeloma. There were no significant differences in NRM, GVHD, or survival among the 3 regimens.

Several studies have shown a significant improvement in early treatment-related mortality after allo-HCT with RIC regimens and in patients who received allo-HCT in recent years [20,21]. Most of these regimens have used a combination of fludarabine or low-dose total body irradiation with an alkylating agent, either melphalan or busulfan [22-24]. Our results are consistent with outcomes reported in some of the recent allo-HCT studies that used similar conditioning, and reported a 1- to 3-year NRM of 22% to 27%, 2- to 3-year PFS of 18% to 34%, and 2- 3-year OS of 36% to 50% [20,21]. A recent single-center study from the University of Michigan reported on 22 patients with high-risk cytogenetics or early relapse who underwent an allo-HCT with a conditioning regimen of BuFlu. Their reported NRM at 3 years was 29%, PFS at 3 years was 15%, and OS at 3 years was 33% [25].

The regimens used in this report range from RIC (FM100) to myeloablative (BuFlu) as defined by Bacigalupo et al. [26]. However, NRM was comparable in the 3 groups, thereby confirming the relative safety of myeloablative regimens, such as BuFlu, in recent years perhaps due to better patient selection and supportive care.

In our study, patients who were transplanted after relapse, or had high-risk cytogenetics, had shorter PFS and OS than patients transplanted in first remission or with standard-risk cytogenetics. Several previous single-center and registry studies have shown that patients transplanted with relapsed or refractory disease had worse outcomes. Bashir et al. [27] from our group reported 5-year PFS and OS of 15% and 21% after allo-HCT for myeloma. They reported that patients receiving allo-HCT for relapsed disease had a significantly shorter PFS (HR, 0.35; 95% CI, 0.18 to 0.67; $P = .0016$) and OS (HR, 0.29; 95% CI, 0.15 to 0.55; $P = .0002$) than patients transplanted in first remission. Similarly, Freytes et al. [28], from the Center for International Blood and Marrow Transplant Research, reported 3-year PFS and OS of 6% and 20%, respectively, in patients who received an RIC allo-HCT in a salvage setting. Further, a recent meta-analysis that combined data from 7 clinical trials confirmed the favorable prognostic impact of remission status at transplantation on

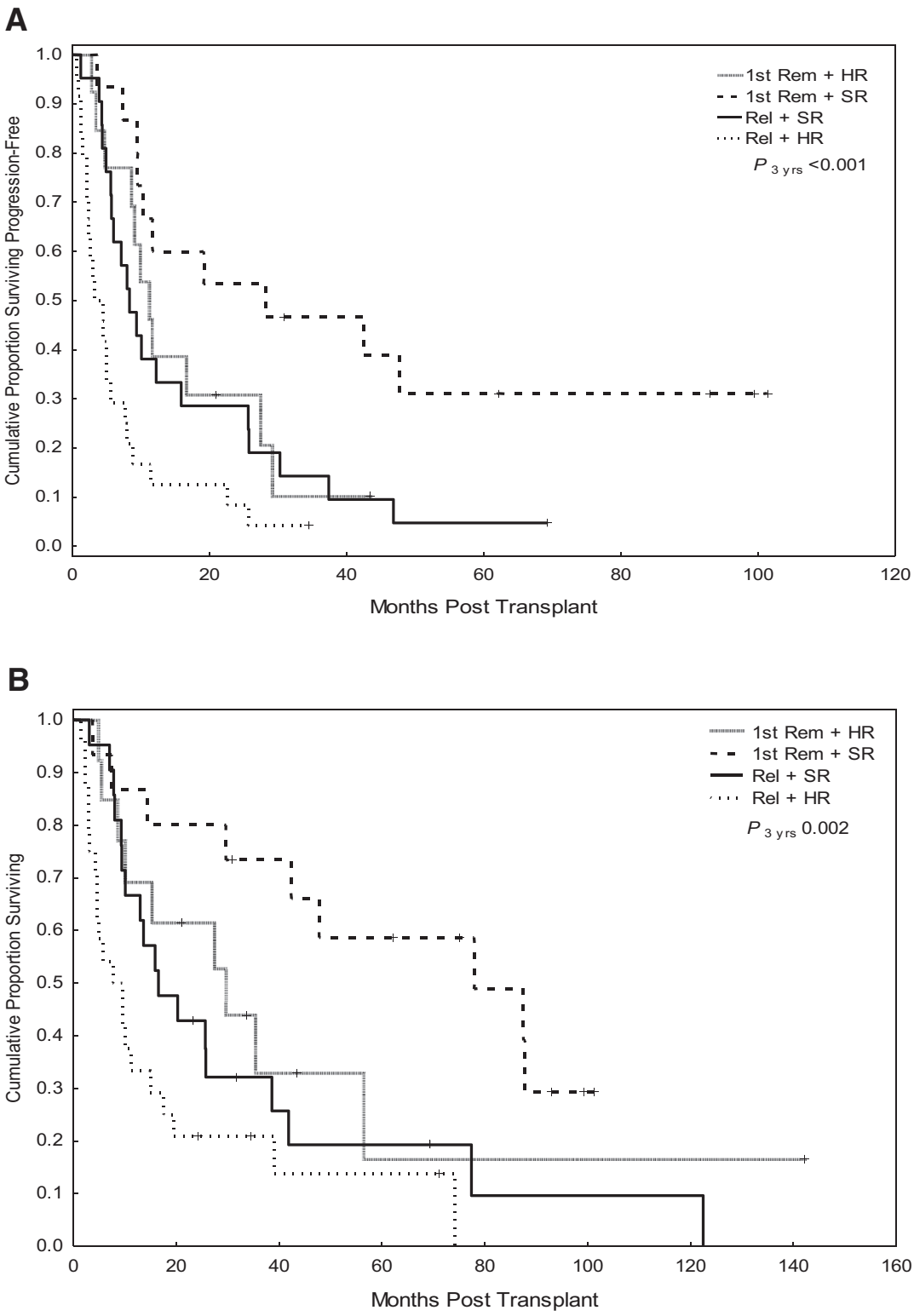

Figure 2. The PFS (A) and OS (B) categorized by cytogenetic risk and disease status (first remission versus relapse).

both PFS (HR, 0.59; 95% CI, 0.44 to 0.78) and OS (HR, 0.43; 95% CI, 0.29 to 0.63) [29].

Several studies have suggested that allo-HCT can overcome high-risk cytogenetic abnormalities [30,31]. Schilling et al. [30], in a multicenter analysis on 101 patients with advanced disease and multiple chromosomal abnormalities, showed that only del(17p13) was associated with a shorter event-free survival due to increased relapse incidence. Similarly, Roos-Weil et al. [31], from the French cooperative group Société Française de Greffe de Moelle et de Thérapie Cellulaire, reported the outcome of 143 myeloma who underwent an allo-HCT. They did not see any difference in PFS, OS, or progression rate between

patients with or without high-risk chromosomal abnormalities. In contrast, other studies showed a worse outcome in patients with high-risk cytogenetics after an allo-HCT [27]. Further, a recent meta-analysis by Yin el al. [29] showed no significant impact of genetic risk stratification on both PFS and OS. Our results, which included data from 3 prospective studies, showed significantly favorable outcomes for patients with standard-risk cytogenetics compared with those with high-risk cytogenetics after an allo-HCT. Other important issues related to allo-HCT are the role of DLI [32,33] and post-allo-HCT maintenance therapy [34,35], which could not be adequately addressed in our study due to the small number patients receiving these interventions.

Some of the limitations of our study include a small sample size, variable follow-up, heterogeneous patient population treated for more than a decade, and lack of data on minimal residual disease, as the test had not been standardized until recently.

In conclusion, BuFlu, FM100, and FM140 demonstrated similar outcomes and toxicity when used as conditioning regimens for multiple myeloma. High-risk cytogenetics and disease relapse were independent predictors of a worse outcome in allo-HCT. Patients with complete remission at transplantation and those with standard-risk cytogenetics had the best long-term outcomes regardless of the preparative regimen used.

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