Biol Blood Marrow Transplant 22 (2016) 324–329

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Improved Outcome of Alternative Donor Transplantations in Patients with Myelofibrosis: From Unrelated to Haploidentical Family Donors

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Article history:
Received 29 July 2015
Accepted 28 September 2015

Key Words:
Unrelated donors
Haploidentical donors
Myelofibrosis

A B S T R A C T

This is a retrospective analysis of 95 patients with myelofibrosis who were allografted between 2001 and 2014. The aims of the study were to assess whether the outcome of alternative donor grafts has improved with time and how this compares with the outcome of identical sibling grafts. Patients were studied in 2 time intervals: 2000 to 2010 (n = 58) and 2011 to 2014 (n = 37). The Dynamic International Prognostic Scoring System score was comparable in the 2 time periods, but differences in the most recent group included older age (58 versus 53 years, $P = .004$), more family haploidentical donors (54% versus 5%, $P < .0001$), and the introduction of the thiotepa-fludarabine-busulfan conditioning regimen (70% of patients versus 2%, $P < .0001$). Acute and chronic graft-versus-host disease were comparable in the 2 time periods. The 3-year transplantation-related mortality (TRM) in the 2011 to 2014 period versus the 2000 to 2010 period is 16% versus 32% ($P = .10$), the relapse rate 16% versus 40% ($P = .06$), and actuarial survival 70% versus 39% ($P = .08$). Improved survival was most pronounced in alternative donor grafts (69% versus 21%, $P = .02$), compared with matched sibling grafts (72% versus 45%, $P = .40$). In conclusion, the outcome of allografts in patients with myelofibrosis has improved in recent years because of a reduction of both TRM and relapse. Improvement is most significant in alternative donor transplantations, with modifications in donor type and conditioning regimen.

INTRODUCTION

Patients with myelofibrosis undergoing an allogeneic stem cell transplantation (HSCT) have some specific problems: first, they usually have hypersplenism, which may be expected to remove significant numbers of infused donor stem cells from circulation and has been reported to delay engraftment up to 1 week in several studies [1-3]. Whether to remove a large spleen before transplantation remains a question of individual choice, as there are conflicting results on whether splenectomy is a risk factor for transplantation-related mortality (TRM) or relapse [1-3], and splenectomy itself is hazardous. An alternative option is ruxolitinib, which has been shown to reduce the spleen volume in a significant proportion of patients and may, therefore, be used for this purpose before an allogeneic HSCT [4].

Second, the marrow is, by definition, fibrotic to different degrees, and this may be considered an additional problem for engraftment and graft function. To this point, in a recent paper on the treatment of poor graft function with $CD34^+$-selected peripheral blood cells [5], 50% of the patients had myelofibrosis. Therefore, poor engraftment or poor graft function are problems for these patients either because of the large spleen, marrow fibrosis, or both. When, in addition, the donor is not an identical sibling or has some degree of HLA mismatch, infections and related complications can lead to a very high TRM [2,3,6]. In a recent paper by the

Financial disclosure: See Acknowledgments on page 329.

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http://dx.doi.org/10.1016/j.bbmt.2015.09.028
1083-8791/

International Consortium on Myeloproliferative Disorders, TRM was 22% in identical sibling transplantation, compared with 59% in unrelated donor (UD) grafts [6]. This was seen also in a Center for International Blood and Marrow Transplant Research study (50% TRM for UD compared with 35% for siblings) [3] and in a 2009 study by the European Society for Blood and Marrow Transplantation Research, with a 3-fold increased TRM for HLA-mismatched donor transplantations [2]. TRM is not the only problem in patients with myelofibrosis: relapse is seen in a significant number of cases, especially in patients with a high-risk score, as identified by Dupriez [7-9] or by the more recent Dynamic International Prognostic Scoring System (DIPSS) [10,11]; therefore, conditioning regimens capable of eradicating the disease but with low toxicity would be required in this difficult disease.

The aims of the present study were to assess whether the outcome of alternative donor grafts for MF has improved with time in our transplantation unit and how this currently compares with the outcome of identical sibling grafts.

PATIENTS AND METHODS

Patients

This is a retrospective analysis of 95 patients with histologically proven myelofibrosis who were allografted in our center between January 26, 2001 and April 4, 2014; thus, with a minimum follow-up of 1 year. Primary myelofibrosis was diagnosed in 27 patients (64%) before and in 17 (49%) after 2010; the remaining patients had myelofibrosis secondary to polycytemia vera or thrombocythemia. Janus Kinase 2 (JAK2) mutation status was available in 80 patients: it was mutated in 20 (44%) before and in 18 (51%) after 2010. CD34 cell count in peripheral blood was available in 90 patients and was comparable in the 2 time periods (Table 1). Clinical characteristics of patients are outlined in Table 1. The donor was an HLA-identical sibling in 46 patients or an alternative donor in 49. Patients were scored for DIPSS at the time of transplantation [12] (Table 1) and classified as low risk (n = 1), intermediate 1 (n = 18), intermediate 2 (n = 36), and high risk (n = 40). DIPSS scores were comparable before and after 2010. Splenectomy was usually performed in patients with a large spleen (>22 cm); the spleen size was somewhat smaller after 2010 and splenectomy was less frequent, especially in the alternative donor group (Table 1). The median number of circulating CD34 cells/microliter was comparable in the 2 time periods (104 versus 120; $P = .90$).

Modified Transplantation Score

In a previous study, we published a transplantation score based on donor type (matched siblings or alternative donors), transfusion history (≤/>20 units), and spleen size (≤/>22 cm), which proved to be predictive of transplantation outcome [13]. In the present study, in which donor type was treated as a separate predictive variable, we used a modified version of our transplantation score (MTS), based on transfusion history (≤/>20 units) and spleen size (≤/>22 cm).

Table 1
Clinical Data of Patients with Myelofibrosis

Year of Transplantation	2000 to 2010	2011 to 2014	*P* Value
No. of patients	58	37	
Age, median (range), yr	53 (24-67)	58 (37-69)	.004
DIPSS low-int 1/int 2/high	11/24/23	8/12/17	.60
Spleen size, median (range), cm	23 (12-40)	20 (14-30)	.04
JAK2 mutated	20 (44%)	18 (51%)	.50
CD34 cells in PB/μL	104 (0-5280)	120 (2-354)	.90
Splenectomy	46 (79%)	9 (24%)	<.0001
Transfusions >20 units	33 (57%)	13 (35%)	.03
MTS: low, int, high	11/27/20	19/13/6	.006
Interval Dx-Tx, median, d	889	745	.40
Ruxolitinib	0 (0%)	6 (16%)	.001
Donors: SIBS/UD/Haplo	35/20/3	11/6/20	<.0001
Stem cell source BM/PB	50/8	32/5	.90
Myeloablative regimens	9 (15%)	26 (70%)	<.0001
TBF regimen, n (%)	1 (2%)	26 (70%)	<.0001

Int indicates intermediate; PB, peripheral blood; BM, bone marrow; Dx, diagnosis; Tx, treatment; SIBS, HLA-identical siblings.
Data presented are n (%), unless otherwise indicated.

Alternative Donors

In the period 2001 to 2010, UD (n = 20) prevailed over family mismatched donors (n = 3), and of these, 8 were 8/8 HLA–allelic matched and 12 were <8/8 matched. In the most recent period, there was a predominance of haploidentical (HAPLO) family donors (n = 20) over UD (n = 6), and of the latter, 5 were 8/8 matched and 1 was mismatched (Table 1).

Conditioning Regimens

In the first period, (2001 to 2010) reduced-intensity regimens (RIC), mainly thiotepa and cyclophosphamide (CY) [13], were predominantly used, both in sibling and alternative donor grafts; myeloablative regimens consisted of conventional CY and total body irradiation (Table 1). In the more recent period, (2011 to 2014) most patients (70%) received the combination of thiotepa, fludarabine, and busulfan (TBF). This regimen has been described in detail [14]: the original program called for thiotepa (5 mg/kg/day × 2), fludarabine (50 mg/m^2/day × 3), and 3 days of intravenous busulfan, 3.2 mg/kg/day; we reduced the busulfan dose to 2 days (6.4 mg/kg total dose) in patients over 60 years of age or patients with comorbidities; overall 15 patients received TBF-busulfan 2 and 12 TBF-busulfan 3.

Stem Cell Source

Bone marrow was the predominant stem cell source for both alternative donors and matched siblings (Table 1).

Ruxolitinb

Only 6 patients in the recent cohort (16%) received ruxolitinib before transplantation (Table 1).

Graft-versus-host Disease Prophylaxis

HLA-identical siblings received cyclosporin (CyA) + short course methotrexate (MTX); patients grafted from UD received CyA + MTX + antithymocyte globulin (Thymoglobulin, Sanofi Aventis, France) (3.75 mg/kg) on days −3 and −2 before transplantation [14]; patients receiving a HAPLO transplant were given CyA from day 0, mycophenolate mofetil from day +1, and CY 50 mg/kg on days +3 and +5 [14].

Diagnosis and Treatment of Graft-versus-host Disease

The clinical diagnosis of acute and chronic graft-versus-host disease (GVHD) was made according to standard criteria and confirmed histologically by skin and/or rectal biopsies. First and second-line therapy of GVHD were given as per institutional protocols.

Supportive Care

Antimicrobial prophylaxis was started during conditioning regimen and consisted of standard-dose acyclovir, levofloxacine 500 mg a day, and fluconazole 400 mg per day until day +75. Cytomegalovirus monitoring, with pp65 antigenemia, was started on day −7 until day +100, twice weekly: preemptive therapy (ganciclovir or foscarnet) was given to patients with positive cytomegalovirus antigenemia. Weekly Epstein-Barr virus monitoring by PCR was started on day +15 and continued weekly until day +100: preemptive therapy with rituximab was given to patients with a viral load greater than 1000 copies/10^5 mononuclear cells. Weekly monitoring of galactomannan was started on day 0 until day +100 and patients with possible or probable invasive aspergillosis received antifungal therapy.

Relapse

Hematologic relapse was diagnosed when patients presented with abnormal peripheral blood counts, declining donor bone marrow chimerism, increasing peripheral blood CD34 counts or blasts, and/or mutated JAK2 (if present before transplantation).

Statistical Analysis

Comparison between groups was carried out using the chi-square test for categorical variables and the nonparametric Whitney test for continuous variables. Univariate and multivariate survival analyses on survival were carried out using the Cox proportional hazard model. Variable with *P* values ≤ .10 in univariate analysis were entered in the multivariate model. When calculating the cumulative incidence (CI) of TRM, the competing risk was relapse. When calculating the CI of relapse, the competing risk was TRM. The log-rank test was used for univariate comparison of survival curves, whereas the Fine and Gray test was used for univariate comparison of cumulative incidences.

Table 2
Outcome of Patients with Myelofibrosis

Year of Transplantation	2000 to 2010	2011 to 2014	*P* Value
No. of patients	58	37	
Patients engrafted	52 (90%)	35 (95%)	.30
Day to PMN .5 × 10^9/L, median (range)			
Matched siblings	18 (11-37)	21 (15-50)	.60
Alternative donors	20 (11-37)	21 (13-50)	.60
Full donor chimerism			
Matched siblings	26/29* (90%)	10/11 (91%)	.90
Alternative donors	11/16* (69%)	22/23* (95%)	.02
Death within 1 yr			
Matched siblings	11 (31%)	3 (27%)	.70
Alternative donors	13 (56%)	8 (31%)	.06

PMN indicates neutrophils.
Data presented are n (%), unless otherwise indicated.
* Evaluable patients.

RESULTS

Engraftment and GVHD

Engraftment, as identified by a neutrophil count of .5 × 10^9/L, was seen in 90% versus 95% in the 2 time periods (Table 2). When looking at alternative donor transplantations, engraftment was achieved in 83% up to the year 2010 and in 92% after 2010; time to engraftment was not different in the 2 time periods (Table 2).

Full donor chimerism in matched siblings was 90% in both periods (Table 2). However, in alternative donor grafts, full chimerism was documented in 69% of evaluable patients in 2000 to 2010 (Table 2), with 3 patients with autologous reconstitutions and 2 patients with less than 50% donor chimerism; in the 2010 to 2014 period, 22 of 23 evaluable patients (95%) achieved full donor chimerism (P = .02) (Table 2).

On day +100 after transplantation, more patients in the 2011 to 2014 period had an absolute lymphocyte count >.5 × 10^9/L (63% versus 25% P = .01); platelet and hemoglobin levels were comparable.

The CIs of acute GVHD grades II to IV were comparable in the 2 periods: 34% versus 27% (P = .40) as well as grades III and IV GVHD (7% versus 10%, P = .50). Moderate/severe chronic GVHD was also comparable: 19% versus 21% (P = .70).

TRM, Relapse, and Survival

The 3-year TRM in the 2011 to 2014 period versus the 2000 to 2010 period was 16% versus 32% (P = .10) (Figure 1A), the relapse rate was 16% versus 40% (P = .06) (Figure 1B), and actuarial survival was 70% versus 39% (P = .08) (Figure 2).

Deaths within 1 year from transplantation remained stable in sibling transplantations (31% versus 27%) but have been almost halved in alternative donor transplantations (56% versus 31%) (Table 2). When looking at alternative donor transplantations only, in the 2000 to 2010 period, the TRM for patients aged ≤/>55 years was 41% versus 66%; in the 2011 to 2014 period, TRM for patients aged ≤/>55 years was 22% versus 23%. In the 2011 to 2014 period, we provided transplantation to 13 patients ages 61 to 69 from alternative donors, and their TRM is 15%.

Causes of death are shown in Table 3. A trend for a reduction of all causes is seen, particularly for multiorgan failure, infections, and relapse.

Comparison of Transplantations from Alternative Donors and HLA Identical Siblings

Figure 3 shows the actuarial survival of patients who received transplants from identical siblings compared with that for those who received alternative donor grafts in the 2 periods: actuarial survival in the 2000 to 2010 period was 45% versus 21% (P = .02) (Figure 3A) and it is currently (2011 to 2014) 72% versus 69% (P = .60) (Figure 3B).

Survival and DIPSS Score

When stratifying patients, regardless of donor type, by DIPPS, the actuarial survival in the 2000 to 2010 period was as follows: DIPSS low/intermediate 1/intermediate 2 (n = 35), 57% and high risk (n = 23) (8%) (P < .01) (Figure 4A). In the 2011 to 2014 period, survival was as follows: DIPSS low/intermediate 1/intermediate 2 risk (n = 20) 80% and high risk (n = 17) 57% (P = .20).

UD Matching and Outcome

In the 2000 to 2010 period, there were 8 matched (8/8) and 12 mismatched UD graft recipients (<8/8): TRM was 50% in both groups. Two of 8 matched and 2 of 12 mismatched

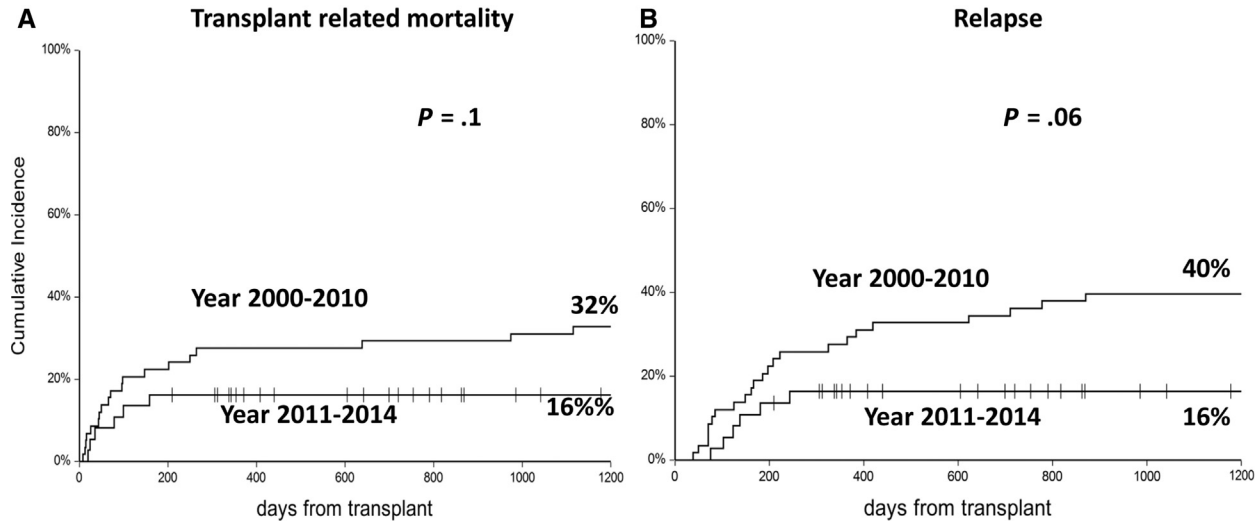

Figure 1. (A) Cumulative incidence of transplantation-related mortality (TRM) stratified by transplantation period (2000 to 2010 and 2011 to 2014). (B) Cumulative incidence of relapse stratified by transplantation period (2000 to 2010 and 2011 to 2014).

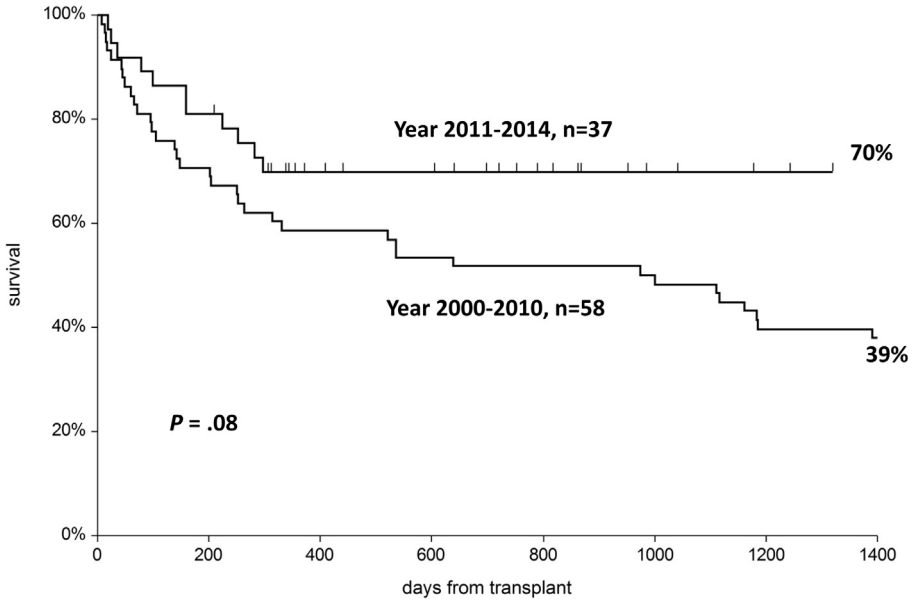

Figure 2. Overall survival, stratified by transplantation period.

UD graft recipients are alive. In the 2011 to 2014 period, there were 5 matched and 1 mismatched UD grafts recipients: all 6 are surviving.

Univariate and Multivariate Cox Analysis

Donor recipient gender combination, JAK2 mutational state, interval from diagnosis to transplantation, patient age, and diagnosis (primary myelofibrosis or myelofibrosis secondary to polycythemia vera or thrombocythemia), a CD34 count greater than 100/μL (yes or no), and TBF (yes or no) were not significant predictors in univariate analysis (Table 4). DIPSS, MTS, transplantation era (</≥2010), and donor type were selected from the univariate analysis to enter the multivariate model (Table 4). DIPSS and MTS proved to be independent predictors in multivariate analysis, with a higher risk of mortality for patients with high-risk DIPSS and MTS (Table 4). Patients who underwent transplantation in the most recent era had one half the risk of death compared with those in the previous era ($P = .09$), and donor type was not predictive of mortality, with a 1.5 hazard ratio for alternative donors ($P = .10$) (Table 4).

DISCUSSION

In this study, we show that the outcome of transplantation in patients with myelofibrosis has significantly improved over the past years as a consequence of reduced TRM and reduced early relapse of the original disease. This is particularly true for alternative donor transplantations. The most significant predictor of survival remains the DIPSS score, followed by our MT, although patients who underwent transplantation after 2010 had a comparable risk profile as patients who underwent transplantation earlier. In addition, patients who underwent transplantation after 2010 were significantly older than patients who underwent transplantation before 2010, and age is a negative prognostic factor [15]. Therefore, patient selection is probably not the reason for improved outcome. There have been major changes in the period 2011 to 2014 compared with the 2000 to 2010 era: conditioning regimen, donor type, and GVHD prophylaxis.

Table 3
Causes of Death

Year of Transplantation	2000 to 2010	2011 to 2014	*P* Value
No. of patients	58	37	
Rejection	2	1	
GVHD	3	1	
Infections	6	2	
Interstitial pneumonia	2	1	
Multiorgan failure	7	1	
Second tumor	2	0	
Relapse	18	5	.05

As with many other disorders, but perhaps more so in myelofibrosis, there is no standard conditioning regimen: conventional myeloablative regimens, with full-dose total body irradiation, have been largely abandoned because of the high risk of TRM [8] and have been substituted with so called RIC or reduced-toxicity regimens [10,16]. The latter usually include fludarabine with low-dose busulfan [2], low-dose thiotepa [17], or melphalan [8]; nevertheless, TRM remains high for alternative donor grafts and those with RIC regimens [8]. An alternative approach is to maintain a myeloablative dose of busulfan preceded, rather than followed, by CY [18]: with this approach the incidence of severe liver complications has been significantly diminished and the eradicating effect of busulfan maintained [18]. In the present study, we modified our conditioning regimen such that in the period 2011 to 2014, the majority of patients received the combination of TBF, as originally described for cord blood transplantations [19]: TBF was well tolerated in both sibling and alternative donor transplantations, and, in the latter, it has significantly improved the proportion of patients engrafting and with full donor chimerism. In other words, the intensification of the conditioning regimen, with the combination of 2 alkylating agents such as busulfan and thiotepa, has increased the percentage of patients with strong functioning grafts, and not at the cost of increased toxicity. In particular, we have seen fewer infections and less multiorgan failure, also in older patients: In the 2000 to 2010 period, TRM for patients over 55 years of age was 63% and it is currently 23%. With more robust engraftment, higher lymphocyte counts on day +100, and greater proportion of full donor chimerism, we have seen less relapse (from 40% to 16%), and overall

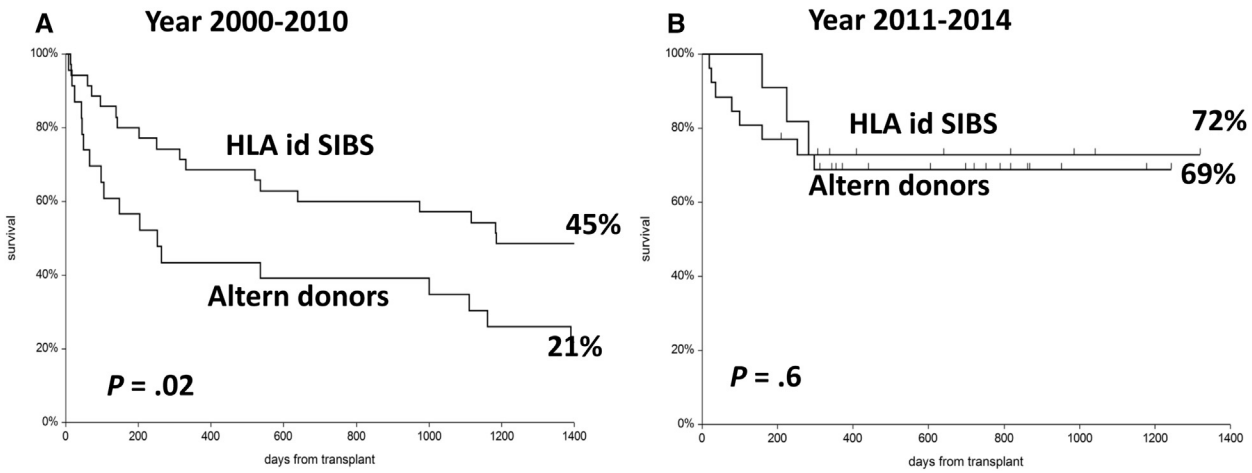

Figure 3. Comparison of outcomes between HLA identical sibling and alternative donor grafts. In the 2000 to 2010 period (A) a significant advantage is seen for siblings (n = 35) over alternative donor grafts (n = 23). In the 2011 to 2014 period, the outcomes of siblings (n = 11) and alternative donor grafts (n = 26) are comparable (B).

actuarial survival has improved from 39% to 70%. TBF is the only regimen we are currently using in patients with myelofibrosis.

There has been another major change in alternative donor selection, with a predominance (77%) of family HAPLO in the 2011 to 2014 period compared with 13% family mismatched donors in the 2000 to 2010 period. The reason for this change is the poor results of UD transplantations, especially if <8/8 matched: of the 12 mismatched UD grafts performed before 2011, only 2 survived. We have, therefore, restricted UD search to 8/8 matched and this has reduced the number of patients with a suitable donor. The use of HAPLO donors has come with a change in GVHD prophylaxis; namely, high-dose post-transplantation CY plus CyA and mycophenolate, modified from the Baltimore program [14,20]. Therefore, we have moved from a standard UD transplantation, with CyA + MTX + antithymocyte globulin for GVHD prophylaxis, to HAPLO transplantation with post-transplantation CY + CyA + mycophenolate mofetil. It is impossible, at present, to assess whether the improved engraftment, reduced TRM, and reduced relapse in the alternative donor grafts are the consequences of the TBF conditioning, the use of HAPLO family donors, post-transplantation CY, or a combination of these 3 factors. What seems to be clear is that the outlook for a patients with myelofibrosis referred for an alternative donor transplantation in our unit is currently much better than it was 10 years ago.

When we compared the outcomes for recipients of HLA-identical sibling and alternative donor grafts, in the 2000 to 2010 period our results matched those reported by the International Consortium [8] and also by the largest registry-based study [11]; namely, poor survival for transplantations from unrelated donor grafts, significantly worse than identical siblings grafts.

Things changed in the 2011 to 2014 period and we now see overlapping survival of siblings and alternative donors, mainly HAPLO family donors. The most significant predictor for survival from Cox multivariate analysis is DIPSS, followed by our MTS that is based on pretransplantation transfusion history and spleen size. The transplantation era has a borderline positive effect, whereas patients age, gender, interval from diagnosis to transplantation, JAK2 mutational state, a

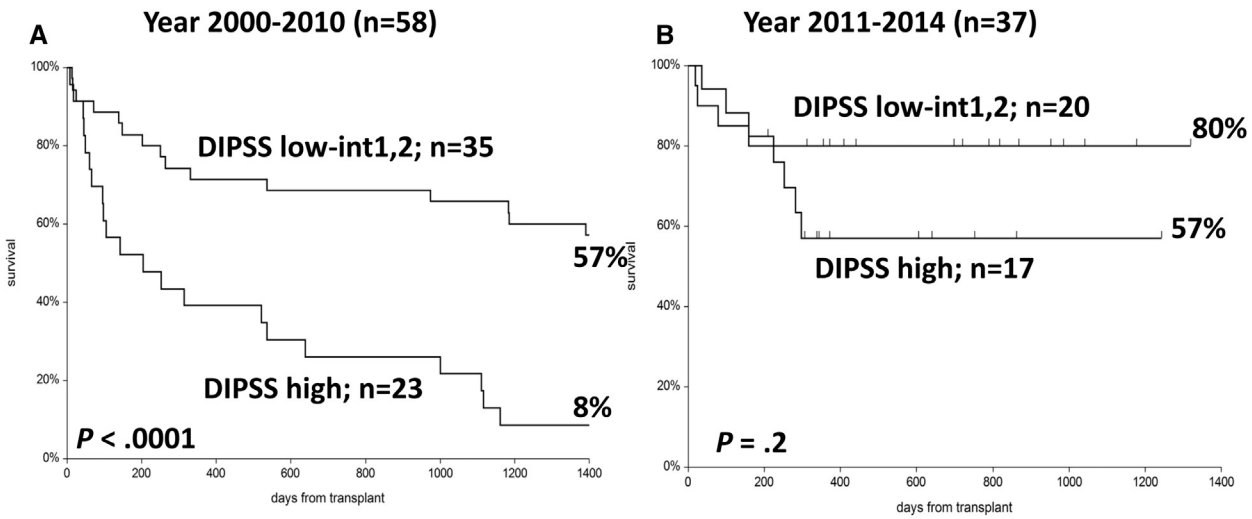

Figure 4. Shown is actuarial survival of MF patients stratified for transplantation period and DIPSS. In the 2000 to 2010 period (A) patients with DIPSS low, intermediate 1, and intermediate 2 risk scores have significantly superior survival compared with patients with DIPSS high-risk scores. In the 2011 to 2014 period, improved survival of high-risk patients can be seen, such that the difference with DIPSS low/intermediate 1/intermediate 2 is not statistically significant (B).

Table 4
Multivariate Cox Analysis

Variable	Baseline Value	Compared Value	Univariate	Multivariate		P Value
			P Value	HR	(95% CI)	
DIPSS	Low/int 1	Int 2/high	.0001	2.7	1.4-5.1	.001
MTS	Low	Int	.10	1.7	.7-4.0	.90
		High	.0006	2.5	1.0-6.1	.03
Year of Tx	2000-2010	2010-2014	.09	.5	.2-1.1	.09
Donor	Sibling	Alternative	.10	1.5	.8-2.7	.10
Patient age	Continuous		.70			
Gender	FD/MR	Other	.70			
JAK2	WT	Mutated	.40			
Interval Dx Tx	Continuous		.40			
PMF	Yes	No	.40			
PT-CY	No	Yes	.90			
CD34	≤100/μL	>100/μL	.30			
TBF	No	Yes	.50			
Donor	Sibling	UD	.50			
	Sibling	HAPLO	.30			

95% CI indicates 95% confidence interval; FD/MR, female donor in male recipient; WT, Janus Kinase 2 wild type; PMF, primary myelofibrosis (yes) versus no (secondary to thrombocythemia or polycythemia); PT-CY, post-transplantation cyclophosphamide.

diagnosis of primary or secondary myelofibrosis, donor type, and CD34 counts are not significant predictors of survival. Improved survival in the most recent era is best shown in high-risk DIPSS patients, those who most need the transplantation: survival for high-risk DIPPS patients was 8% before 2010 and it is currently 57%, independent of donor type.

A recent study compared the outcomes for patients with myelofibrosis undergoing or not undergoing an allogeneic HSCT in the pre-JAK2 inhibitor era [21]. Not unexpectedly, the risk of death for transplantation patients compared with no-transplantation patients was higher in low-risk patients (relative risk [RR], 5.6; $P = .005$), comparable in intermediate 1 patients (RR, 1.6; $P = .19$), and lower in intermediate 2 (RR, .55; $P = .005$) and high-risk cases (RR, .37; $P = .0007$) [20]. Our improved results in patients with high-risk DIPSS further confirm that intermediate 2 and high DIPSS, and possibly selected cases of intermediate 1 DIPPS, should be considered for an allogeneic transplantation.

In conclusion, we modified our conditioning regimen and all patients now receive the TBF conditioning. We are also using more HAPLO family donors with high-dose post-transplantation CY, and this has produced very encouraging outcomes, now comparable to identical sibling grafts. These data are now used in our unit for counseling patients with myelofibrosis; in particular, we no longer believe that high-risk DIPSS, lack of an identical sibling, and age above 60 are contraindications for an allogeneic transplantation.

ACKNOWLEDGMENTS

Financial disclosure: This work was partly supported by the “Associazione Italiana Ricerca contro il Cancro” (A.I.R.C.) Milano., Fondazione FARITMO Genova, Imm Stuarta Genova, Fondazione CARIGE Genova, and Compagnia di San Paolo, Torino, Italy.

Conflict of interest statement: There are no conflicts of interest to report.

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