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Continuous Reduced Nonrelapse Mortality after Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Institution's Three Decade Experience

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This study analyzed changes in patients, transplantation, graft characteristics, and outcome among 827 patients who received their first allo-SCT in a single center between 1983 and 2010. In the 2001 to 2010 decade, compared with the 1983 to 1990 and 1991 to 2000 decades, patients were significantly older and presented with higher risk diseases, reduced intensity conditioning and alternative donors were used more often, and stem cell sources changed from bone marrow to peripheral blood stem cells and cord blood. In the 2001 to 2010 decade, we observed a significant decrease in nonrelapse mortality (NRM) ($P = .0007$ and $P < .0001$, respectively) and an increase in relapse incidence ($P = .04$ and $P = .009$, respectively), but overall survival (OS) was increased ($P = .11$ and $P = .009$, respectively), and there was a trend towards an increased progression-free survival ($P = .30$ and $P = .09$, respectively), as compared with the 1983 to 1990 and 1991 to 2000 decades. Chronic graft-versus-host disease (GVHD) was significantly increased, whereas grades III to IV acute GVHD remained stable. These data suggest that, despite the fact that older and higher risk patients with more comorbidities underwent transplantation in the last 10 years, NRM decreased while the incidence of relapse increased and the OS improved.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-SCT) is an effective therapy for different life-threatening malignant and nonmalignant diseases. However, this treatment is limited by high morbidity and mortality, mainly related to infection, graft-versus-host disease (GVHD), and conditioning-related toxicity. Fortunately, since its introduction in the early 70s [1], important progress has been made in allo-SCT, leading to a reduced nonrelapse mortality (NRM). Indeed, significant innovations have emerged in supportive care for prevention or treatment of GVHD, fungal infections, and viral reactivations. Further advances in allo-SCT were represented by the development of new types of grafts [2,3] and the use of alternative donors [4]. Finally, the advent of reduced-intensity conditioning (RIC) regimens [5,6] has led to a significant development of various indications, especially in patients who were usually considered not eligible for allo-SCT because of their age or their comorbidities. Our hypothesis was that all these changes in the care of allo-SCT patients, implemented in our center over the past 3 decades, have improved outcome. We, therefore, compared the cumulative incidence of NRM, relapse, acute and chronic GVHD, overall survival (OS), and progression-free survival (PFS) in 3 successive cohorts of patients who underwent transplantation in a single-center academic transplantation program from 1983 through 1990, from 1991 through 2000, and from 2001 through 2010.

PATIENTS AND METHODS

Patients and Study Design

This retrospective single-center study included patients who underwent their first allo-SCT at the University Hospital of Nantes (Nantes, France) between 1983 and 2010. For the purpose of this study, only patients aged over 18 years at time of transplantation were included. As part of standard practice, patients and donors gave their approval for use of their data for research purposes. The study was approved by the local institutional review board.

Transplantation Techniques

All patients received a preparative regimen followed by the infusion of donor cells as inpatients in private rooms, and they remained hospitalized until hematopoietic and clinical recovery. The myeloablative conditioning (MAC) regimens generally contained high-dose cyclophosphamide and either 12 Gy of total body irradiation (TBI) or busulfan. Reduced-intensity

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conditioning (RIC) regimens usually contained fludarabine with 2 Gy of TBI or fludarabine, low-dose busulfan, and antithymocyte globulin (ATG). In our transplantation program, eligibility criteria for RIC allo-SCT included the following: (1) patient age older than 50 years, (2) patients who were heavily pretreated and who received auto-SCT or more than 2 lines of chemotherapy before allo-SCT, and (3) patients with poor performance status because of significant medical comorbidities, as confirmed in 2007 by Sorror et al. [7]. For GVHD prophylaxis, patients received cyclosporine A (CsA) alone until 1986 and then in association with methotrexate for MAC [8]. For RIC, GVHD prophylaxis consisted of CsA alone in the case of a matched sibling donor or CsA and mycophenolate mofetil in the case of an alternative donor [9]. CsA was administered at a dose of 3 mg/kg/day by continuous intravenous infusion starting from day −3 or −2, and changed to twice daily oral dosing as soon as tolerated [10]. Prophylaxis against infection included acyclovir or valacyclovir for Herpes simplex virus [11,12], trimethoprim and/or sulfamethoxazole for *Pneumocystis jirovecii*, and oral penicillin against encapsulated bacteria [13]. In patients with neutropenia, empiric broad-spectrum antibiotics were begun for a temperature greater than 38.3°C or clinical signs of infection. Patients with cytomegalovirus infection received preemptive therapy with ganciclovir from 1989 or valganciclovir from 2002 [14,15]. Patients with Epstein-Barr virus DNA levels exceeding 1000 copies/10^5 cells on 2 or more occasions were preemptively treated with rituximab to prevent Epstein-Barr virus–related lymphoproliferative diseases from 2004 [16,17]. For fungal infections, patients received prophylactic therapy with fluconazole from 1992 [18]; in RIC regimens, fluconazole was discontinued after 2007. The majority of patients received intravenous heparin (100 UI/kg/day) until the absolute neutrophil count reached 500/μL to prevent veno-occlusive disease [19].

Outcome Measurements

Outcome measurements included OS, PFS, NRM, relapse, and the frequency and severity of acute and chronic GVHD. The database was locked on January 31, 2013. For NRM, we considered all deaths occurring after allo-SCT that were not caused by relapse or progression of the underlying disease. The severity of acute GVHD was graded according to the Glucksberg classification [20,21]. The severity of chronic GVHD was graded as limited or extensive, according to the historical classification [22]; because of the retrospective nature of our study and its spread over time, we were not able to apply the National Institutes of Health revised criteria [23].

Table 1
Study Population Characteristics

Characteristic (%)	All (N = 827)	1983-1990 (n = 103)	1991-2000 (n = 221)	*P* Value (1991-2000 versus 1983-1990)	2001-2010 (n = 503)	*P* Value (2001-2010 versus 1983-1990)	*P* Value (2001-2010 versus 1991-2000)
Patient age, median (range)	45.0 (18.0-70.7)	32.2 (18.5-62.6)	38.8 (18.0-63.7)	<.0001	52.0 (18.2-70.7)	<.0001	<.0001
Patient gender				.49		.21	.52
Male	484 (58.5)	55 (52.8)	127 (57.0)		302 (60.4)		
Female	343 (41.5)	48 (47.2)	94 (43.0)		201 (39.6)		
Diagnosis				.03		<.0001	.07
Myeloid malignancies	421 (50.9)	70 (69.4)	120 (55.3)		231 (46.5)		
AML	249 (30.1)	39 (39.8)	67 (31.6)		143 (28.6)		
MDS	53 (6.4)	3 (2.8)	9 (3.8)		41 (8.7)		
MPN	31 (3.7)	2 (1.9)	4 (1.7)		25 (4.8)		
CML	83 (10.0)	26 (25.0)	40 (18.1)		17 (3.3)		
CMML	5 (0.6)	0	0		5 (1.0)		
Lymphoid malignancies	386 (46.7)	29 (26.9)	95 (42.2)		262 (51.4)		
NHL	143 (17.3)	7 (6.5)	23 (10.1)		113 (21.8)		
HD	29 (3.5)	1 (0.9)	2 (0.8)		26 (5.2)		
CLL	36 (4.4)	2 (1.9)	7 (3.0)		27 (5.4)		
MM	68 (8.2)	5 (4.6)	18 (7.6)		45 (8.7)		
ALL	110 (13.3)	14 (13.0)	45 (20.7)		51 (10.2)		
Aplastic anemia	20 (2.4)	4 (3.7)	6 (2.5)		10 (2.1)		
Disease status				.62		<.0001	<.0001
Standard risk	226 (27.3)	42 (38.9)	82 (35.5)		102 (19.9)		
High risk	581 (70.3)	57 (57.4)	133 (62.0)		391 (71.0)		
NA	20 (2.4)	4 (3.7)	6 (2.5)		10 (2.4)		
HLA matching				.10		<.0001	<.0001
Matched related donor	527 (64.1)	92 (89.8)	181 (83.1)		254 (50)		
Alternative donor	300 (35.9)	11 (10.2)	40 (16.9)		249 (50)		
Stem cell source				<.0001		<.0001	<.0001
Bone marrow	403 (49.4)	103 (100)	195 (86.9)		105 (21.6)		
PBSC	368 (43.9)	0	26 (13.1)		342 (67.2)*		
CB	54 (6.7)	0	0		54 (11.2)		
Conditioning regimen				.0006		<.0001	<.0001
Myeloablative	465 (56.0)	103 (100)	207 (92.4)		155 (30.1)		
Reduced-intensity conditioning	362 (44.0)	0	14 (7.6)		348 (69.9)		
High-dose TBI-based conditioning regimen				.29		<.0001	<.0001
Yes	394 (45.5)	86 (78.7)	195 (83.1)		113 (21.4)		
No	433 (54.5)	17 (21.3)	26 (16.9)		390 (78.6)		
ATG-based conditioning regimen				.02		<.0001	<.0001
Yes	296 (35.6)	2 (1.9)	20 (9.3)		274 (54.6)		
No	531 (64.4)	101 (98.1)	201 (90.7)		229 (45.4)		
GVHD prophylaxis				<.0001		<.0001	<.0001
CsA alone (+/−CS)	238 (28.8)	35/2 (35.2)	14 (5.9)		189/3 (38.0)		
CsA + MMF (+/−CS)	187 (22.4)	0	0		187/3 (37.3)		
CsA + MTX	402 (48.8)	68/7 (64.8)	207 (94.1)		127/1 (24.7)		

AML indicates acute myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CML, chronic myeloid leukemia; CMML, chronic myelo monocytic leukemia; NHL, non-Hodgkin lymphoma; HD, hodgkin disease; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; ALL, acute lymphoblastic leukemia; NA, not applicable; PBSC, peripheral blood stem cells; CB, cord blood; TBI, total body irradiation; ATG, antithymocyte globulin; CsA, cyclosporine A; CS, corticosteroids; MMF, mycophenolate mofetil; MTX, methotrexate.

* Four patients from this cohort received both PBSC and bone marrow.