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GITMO Registry Study on Allogeneic Transplantation in Patients Aged ≥60 Years from 2000 to 2017: Improvements and Criticisms

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A B S T R A C T

Today, allogeneic stem cell transplantation (allo-SCT) can be offered to patients up to age 70 to 72 years and represents one of the most effective curative treatments for many hematologic malignancies. The primary objective of the study was to collect data from the allo-SCTs performed in Italy between 2000 and 2017 in patients aged ≥60 years to evaluate the changes in safety and efficacy outcomes, as well as their distribution and characteristics over time. The Italian Group for Bone Marrow Transplantation, Hematopoietic Stem Cells and Cell Therapy (GITMO) AlloEld study (ClinicalTrials.gov identifier NCT04469985) is a retrospective analysis of allo-SCTs performed at 30 Italian transplantation centers in older patients (age ≥60 years) between 2000 and 2017 (n = 1996). For the purpose of this analysis, patients were grouped into 3 time periods: time A, 2000 to 2005 (n = 256; 12%); time B, 2006 to 2011 (n = 584; 29%); and time C, 2012 to 2017 (n = 1156; 59%). After a median follow-up of 5.6 years, the 5-year nonrelapse mortality (NRM) remained stable (time A, 32.8%; time B, 36.2%; and time C, 35.0%; $P = .5$), overall survival improved (time A, 28.4%; time B, 31.8%; and time C, 37.3%; $P = .012$), and the cumulative incidence of relapse was reduced (time A, 45.3%; time B, 38.2%; time C, 30.0%; $P < .0001$). The 2-year incidence of extensive chronic graft-versus-host disease was reduced significantly (time A, 17.2%; time B, 15.8%; time C, 12.2%; $P = .004$). Considering times A and B together (2000 to 2011), the 2-year NRM was positively correlated with the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) score; NRM was 25.2% in patients with an HCT-CI score of 0, 33.9% in those with a score of 1 or 2, and 36.1% in those with a score of 3 ($P < .001$). However, after 2012, the HCT-CI score was not significantly predictive of NRM. This study shows that the transplantation procedure in elderly patients became more effective over time. Relapse incidence remains the major problem, and strategies to prevent it are currently under investigation (eg, post-transplantation maintenance). The selection of patients aged ≥60 could be improved by combining HCT-CI and frailty assessment to better predict NRM.

INTRODUCTION

In this era of targeted therapies, the first-line treatment strategy for many hematologic malignancies still includes allogeneic stem cell transplantation (allo-SCT) [1], even in patients aged ≥60 years [2,3].

GITMO (Italian Group for Bone Marrow Transplantation, Haematopoietic Stem Cells and Cell Therapy) has reported that the number of patients aged ≥60 years who underwent transplantation increased from 9% in 2010 to 26% in 2020, and a progressive growth is expected in the coming years owing to the aging of the population [4,5]. Moreover, thanks to the introduction of reduced-intensity and reduced-toxicity conditioning regimens, allo-SCT now can be offered to patients up to age 75 years, and the clinical and biological tools used to select patients have improved significantly.

Numerous barriers to the referral of older patients for transplantation have been discussed in the literature. Most of these are related to patient age per se, nonwhite race, socioeconomic status, and insurance costs [6]. Overall, comorbidities and frailty are considered major obstacles to transplantation success in patients of advanced age. In an effort to improve the selection of patients for transplantation, several assessment scoring systems have been generated over the last 2 decades and are currently applied in this field, but none can be considered completely satisfactory [7-9]. The Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) score [7], based on patient comorbidity, and the European Society for Blood and Marrow Transplantation [8] or Shouval [9] scores, based on the characteristics of the patients and the disease, donor type, conditioning intensity, and transplantation center activity, are useful for stratifying patients with different risks of nonrelapse mortality (NRM), cumulative incidence of relapse (CIR), and overall survival (OS). However, these scores need to be integrated on a case-by-case basis, considering patient fitness or frailty, conditioning regimen intensity, graft-versus-host disease (GVHD), and infectious prophylaxis and therapy.

Here we report the results of a registry-based retrospective study on behalf of GITMO (GITMO AlloEld). The primary goal of the study was to evaluate the changes in safety and efficacy outcomes and in the distribution and characteristics of allo-SCTs performed in Italy in patients aged ≥60 years between 2000 and 2017.

METHODS

The GITMO AlloEld study (ClinicalTrials.gov identifier NCT04469985) is a retrospective nationwide analysis of allo-SCTs performed in patients aged ≥60 between 2000 and 2017. Among all the 50 Italian transplantation centers accredited to GITMO for adult allo-SCT, 30 (60%) provided consent to participate in the protocol. Following approval from the Ethics Committees of the participating centers, data from all allo-SCTs registered in the European PROMISE database (n = 2061) were extracted, and additional queries were then submitted to each center to minimize missing data. Finally, a total of 1996 allo-SCTs were included in this analysis, representing the first transplantation for each patient. All patients included in the registry provided informed consent for data registration in the PROMISE database. The study was conducted in compliance with current national and European legislation on clinical trials and in accordance with the Declaration of Helsinki and the principles of good clinical practice.

Statistical Analysis

Dichotomous variables were summarized as number and percentage and compared using the chi-square or Fisher exact test. Continuous variables were summarized as median and range and compared using the Wilcoxon rank-sum test. Median follow-up was determined using a reverse Kaplan-Meier method [10].

OS was calculated according to the Kaplan-Meier method from the date of transplantation to the date of death or last follow-up; the log-rank test was used to detect significant differences among subgroups. NRM, CIR, and cumulative incidence of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were calculated based on competing risk models, and Gray's test was used to assess statistical differences among subgroups. Death without the event of interest was considered the competing risk.

Cox and Fine-Gray proportional hazard regressions were used for univariate and multivariate analyses of OS and NRM, respectively.

The following variables were included in the regression models: age of donor (5-year interval), use of total body irradiation (TBI), in vivo T cell depletion, intensity of conditioning regimen, $CD34^+$ and $CD3^+$ cell doses (as continuous variables), disease status at transplantation (responsive versus nonresponsive disease), source of hematopoietic stem cells (umbilical cord blood [UCB] versus peripheral blood stem cells plus bone marrow [BM], peripheral blood stem cells versus BM plus UCB), donor type/stem cell source (sibling donor versus UCB, sibling versus haploidentical [Haplo] donor and sibling versus unrelated donor [UD]), diagnosis (acute leukemia versus other diseases), HCT-CI score (low risk versus intermediate to high risk), Karnofsky Performance Status (KPS) (≥90 versus <90), cytomegalovirus serostatus (negative donor and positive recipient versus other combinations), donor-recipient sex match(female donor to male recipient versus all other

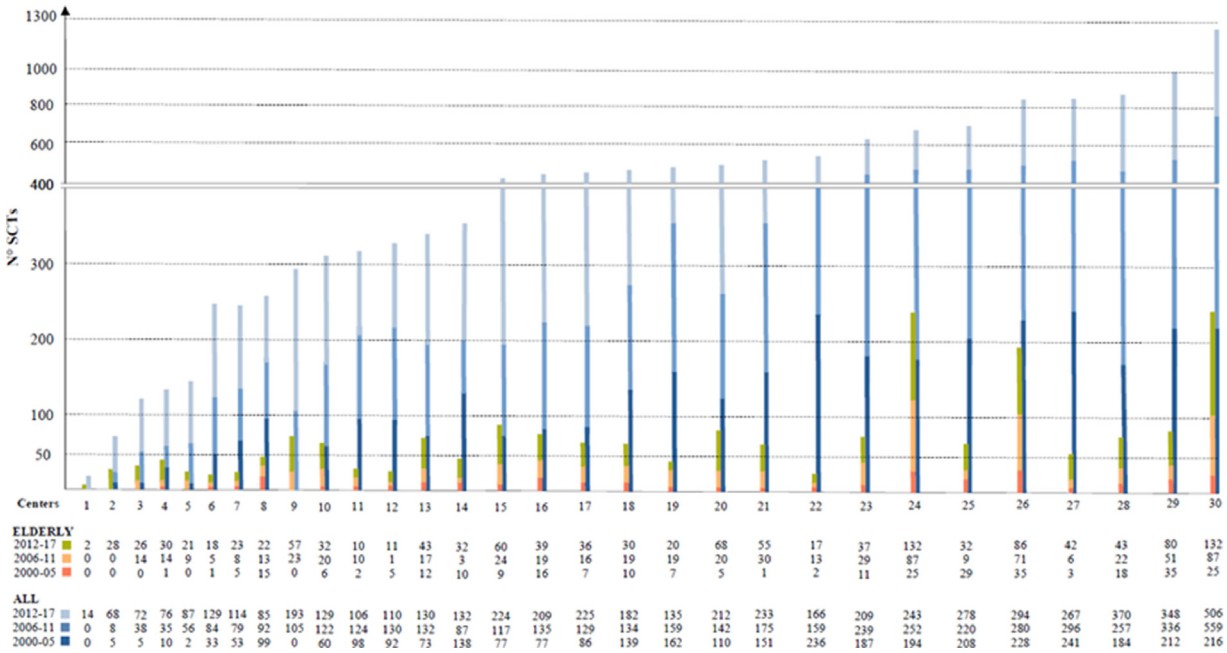


Figure 1. Distribution of allo-SCT according to time A (2000-2005), time B (2006-2011), and time C (2012-2017) in the 30 transplant Centers included in the study.

Table 1
Characteristics of the 1996 Allo-SCT Recipients Included in the Analysis

Characteristics	Total, 2000-2017 (N = 1996)	Time A, 2000-2005 (N = 256; 12%)	Time B, 2006-2011 (N = 584; 29%)	Time C, 2012-2017 (N = 1156; 58%)	*P* Value
Age, yr, median (range)	63.5 (60-77.8)	62.6 (60-74.5)	63.02 (60-76.4)	63.94 (60-77.8)	<.001
Males, n (%)	1229 (62)	161 (63)	367 (63)	701 (61)	.612
Females, n (%)	764 (38)	95 (37)	216 (37)	453 (39)	
Diagnosis, n (%)					<.001
Acute leukemias	1054 (53)	70 (27)	279 (48)	705 (61)	
Myelodysplastic syndrome	291 (15)	32 (12)	75 (13)	184 (16)	
Lymphomas	277 (14)	41 (16)	116 (20)	120 (11)	
MPNs	178 (9)	18 (7)	56 (10)	104 (9)	
Multiple myeloma	158 (8)	63 (24)	56 (10)	39 (3)	
Other	38 (1)	32 (13)	2 (0.5)	4 (0.5)	
Disease status at SCT, n (%)					<.001
CR	947 (49)	68 (29)	268 (47)	611 (54)	
PR	551 (28)	96 (42)	148 (26)	307 (27)	
NR	131 (7)	12 (5)	51 (9)	68 (6)	
Frontline	305 (16)	56 (24)	99 (18)	150 (13)	
Missing	62 (3)	24 (9)	18 (3)	20 (2)	
Lines of therapy, n (%)					.076
- 1	444 (37)	54 (42)	97 (29)	293 (40)	
- ≥ 2	709 (60)	70 (55)	226 (68)	413 (57)	
- Missing	807 (40)	128 (50)	251 (43)	428 (37)	
HCT-CI, n (%)					<.001
0	694 (45)	57 (70)	207 (46)	430 (42)	
1 or 2	435 (28)	16 (20)	123 (28)	296 (29)	
≥3	422 (27)	8 (10)	114 (26)	300 (29)	
Missing	445 (22)	175 (68)	140 (24)	130 (11)	
KPS, n (%)					<.001
100	479 (27)	10 (10)	123 (24)	346 (30)	
90	754 (43)	69 (72)	209 (40)	476 (42)	
80	388 (22)	15 (16)	120 (23)	253 (22)	
<80	138 (8)	2 (2)	65 (13)	71 (6)	
Missing	240 (12)	160 (62)	67 (13)	10 (1)	
Follow-up, yr, median (95% CI)	5.6 (5.2-6.0)	15 (14.0-15.8)	9.7 (9.2-10.2)	4 (3.8-4.2)	—

MPN indicates myeloprolipherative neoplasms; PR, partial remission; NR, nonresponse.

Table 2
Characteristics of the 1996 Allo-SCTs Included in the Analysis

Characteristics	Total, 2000-2017, (N = 1996)	Time A, 2000-2005 (N = 256; 12%)	Time B, 2006-2011 (N = 584; 29%)	Time C, 2012-2017 (N = 1156; 58%)	*P* Value
SC source, n (%)					<.001
PBSC	1489 (75)	217 (86)	467 (80)	805 (70)	
BM	469 (23)	34 (13)	105 (18)	330 (29)	
UCB	34 (2)	2 (1)	12 (2)	20 (1)	
Missing	4 (<1)	3 (1)	0	1 (<1)	
Conditioning, n (%)					<.001
Alkylator-based	1566 (83)	86 (49)	431 (77)	1049 (91)	
Treosulfan-based	237 (15)	2 (2)	91 (21)	144 (14)	
Busulfan-based	422 (27)	6 (5)	107 (25)	309 (29)	
Thiotepa-based	858 (55)	71 (82)	210 (48)	577 (55)	
Melfalan-based	49 (3)	7 (8)	23 (5)	19 (2)	
TBI-based	255 (13)	76 (43)	99 (18)	80 (7)	
Other	63 (4)	15 (8)	26 (5)	22 (2)	
Missing	112 (6)	79 (31)	28 (5)	5 (<1)	
Conditioning intensity, n (%)					<.001
MAC	638 (32)	34 (14)	121 (21)	483 (42)	
Reduced intensity	1340 (68)	209 (86)	461 (79)	670 (58)	
Missing	18 (<1)	13 (5)	2 (<1)	3 (<1)	
GVHD prophylaxis, n (%)					<.001
CnI ± MMF	775 (42)	134 (83)	295 (54)	346 (30)	
In vivo T cell depletion	745 (40)	27 (16.5)	229 (42)	277 (43)	
EDX post-SCT	286 (15)	0 (0)	9 (2)	490 (24)	
Other	45 (3)	1 (0.5)	10 (2)	34 (3)	
Missing	145 (7)	94 (37)	41 (7)	9 (<1)	
Donor, n (%)					<.001
Sibling	791 (40)	216 (86)	263 (46)	312 (27)	
UD	738 (37)	16 (6)	226 (39)	495 (43)	
Haplo	419 (21)	18 (7)	76 (13)	325 (28)	
UCB	31 (2)	2 (1)	12 (2)	20 (2)	
Missing	14 (<1)	4 (2)	7 (1)	4 (<1)	
Donor age, yr, median (range)	42.6 (0-77.8)	59.5 (0-75)	51.5 (0-76)	38.5 (0-77.8)	<.001
Female donor-male recipient, n (%)	462 (24)	78 (31)	128 (23)	256 (22)	.007
CMV serostatus, n (%)					
Donor negative/recipient positive	513 (29)	7 (7)	145 (28)	361 (32)	<.001
Missing	252 (13)	158 (62)	69 (12)	25 (2)	

PBSCs indicates peripheral blood stem cells; CnI, calcineurin inhibitors; MMF, mycophenolate mofetil; EDX, endoxan; MUD, matched unrelated honor.

combinations), patient age (5-year intervals), and era of transplantation (2012 to 2017 versus earlier period). All resulting variables associated with OS and NRM with $P < .05$ in univariate analysis were subjected to multivariate analysis. In vivo T cell depletion was found to be correlated with donor type (chi-square test, $P < .0001$), and thus the latter was excluded from the multivariate analysis.

All P values $< .05$ were considered statistically significant. Statistical analysis was performed with EZR version 1.54) [11].

RESULTS

Clinical and Transplantation Characteristics of the Study Population

For analysis purposes, the patients were grouped into 3 time periods: time A, 2000 to 2005 (n = 256; 12%); time B, 2006 to 2011 (n = 584; 29%); and time C, 2012 to 2017 (n = 1156; 58%). The median follow-up of the 3 time periods was 15 years (95% confidence interval [CI], 14.0 to 15.8 years) for time A, 9.7 years (95% CI, 9.2 to 102 years) for time B, and 4 years (95% CI, 3.8-4.2 years) for time C. The total number of transplantations performed at the 30 adult centers independent of patient age was 3376 in time A, 4681 in time B, and 5546 in time C. Of note, the proportion of elderly patients increased over time, from 256 of 3376 (8%) in time A to 584 of 4681 (12.5%) in time B to 1156 of 5546 (21%) in time C ($P < .0001$). Figure 1 shows the distribution of transplantations in the 3 time periods across the 30 GITMO centers. In 5 of the 30 centers (17%), transplantation was performed in only times B and C, and all 30 centers performed more than 50% of their transplantations in times B and C. Moreover, in 22 of the 30 centers (73%), more than 50% of the transplants were performed in time C.

Patient characteristics are reported in Table 1. We observed several significant differences when comparing times A, B, and C. Over time, the median patient age increased (from 62.6 years to 63.02 years to 63.94 years; $P< .001$), the proportion of allo-SCTs to treat acute leukemias increased (from 27% to 48% to 61%; $P < .001$), the rate of complete remission (CR) at allo-SCT increased (from 29% to 47% to 54%; $P < .001$), the proportion of patients with a HCT-CI >3 at transplantation increased (from 10% to 26% to 29%; $P < .001$), and the percentage of patients with KPS 100 increased (from 10% in time A to 30% in time C; $P < .001$).

Table 2 reports the characteristics of the 1996 allo-SCTs. The most important differences across the 3 time periods were a progressive increase in the use of BM as the graft source (from 13% to 18% to 29%; $P < .001$), a reduction in TBI-based regimens (from 43% to 18% to 7%; $P < .001$), and an increase in myeloablative conditioning (MAC) regimens (from 14% to 21% to 42%; $P < .001$). The distribution of the different alkylators was comparable across the 3 time periods, and none of them was associated with a different transplantation outcome, according to both conditioning intensity (MAC versus reduced intensity) and disease phase at transplantation (CR versus no CR) (data not shown). Moreover, increased use of in vivo T cell depletion (from 16.5% to 42% to 43%; $P < .001$), post-transplantation cyclophosphamide (PT-Cy; from 0% to 2% to 24%; $P < .0001$), and UD and Haplo transplants (from 6% to 39% to 43%

for UD and from 7% to 13% to 28% for Haplo; $P < .0001$) was observed. Finally, there was a significant reduction in the median age of donors (from 59.5 years to 51.5 years to 38.5 years; $P < .001$). In the cohort of 419 Haplo transplants, GVHD prophylaxis was PT-Cy in 269 (64%; 0 in time A, 6 in time B, and 263 in time C), ATG/Campath-based in 112 (27%; 8 in time A, 50 in time B, and 54 in time C), and cyclosporine/tacrolimus with or without methotrexate or mycophenolate in 38 (9%; 3 in time A, 6 in time B, and 29 in time C). Interestingly, the use of UD declined with increasing recipient age: 538 transplantations in patients age <65 years (40%) versus 196 (34%) in those age 65 to 70 years and only 4 (5%) in those age >70 years ($P < .001$).

NRM, CIR, and OS

After a median follow-up of 5.6 years (95% CI, 5.2 to 6.0 years) for the whole patient cohort, the cumulative incidence of NRM at 1, 2, and 5 years was 26.3%, 30.6%, and 35.2%, respectively; the CIR was 24.4%, 30.0%, and 34.9%; and the probability of OS was 57.4%, 46.1%, and 34.5%. Over the course of the study period, there was a significant improvement in 5-year OS (time A, 28.4%; time B, 31.8%; time C, 37.3%; $P = .012$; Figure 2A) and a significant reduction in 5-year CIR (from 45.3% to 38.2% to 30.0%; $P < 0.0001$; Figure 2B). No significant changes in 5-year NRM were seen (32.8%, 36.2%, and 35.0%, respectively; $P = .5$; Figure 2C). Table 3 reports the distribution of causes of NRM over time. Notably, there was a reduction in 5-year NRM due to GVHD (from 47% to 45% to 32%; $P = .006$) and, in parallel, an increase in 5-year NRM due to infections (from 32% to 40% to 45%; $P = .003$).

Data and onset time of aGVHD and cGVHD were available for 1779 patients (89%) and 1993 patients (99%), respectively. The cumulative incidence of aGVHD of any grade was 15.8% at 30 days and 29.2% at 100 days, whereas that of grade II-IV aGVHD was 11.1% at 30 days and 20.1% at 100 days. At 100 days, the overall incidence of aGVHD did not change significantly from time A to time B to time C (any grade: from 25.6% to 31.4% to 29.2%; $P = .106$; grade II-IV: from 16.8% to 21.3% to 20.1%; $P = .289$; Supplementary Figure S1A and B). Focusing on cGVHD, the cumulative incidence at 2 years was 27.6% for cGVHD of any grade and 13.9% for extensive cGVHD. The incidence of cGVHD of any grade at 2 years was 31.6% for time A, 29.9% for time B, and 25.6% for time C ($P = .0181$; Supplementary Figure S2A). Similarly, the incidence of extensive cGVHD was 17.2% for time A, 15.8% for time B, and 12.2% for time C ($P = .004$) (Supplementary Figure S2B).

Considering the whole cohort of patients, the 1-year NRM was positively correlated with the HCT-CI score: 21.8% for HCT-CI of 0, 28.4% for HCT-CI 1 or 2, and 31.9% for HCT-CI ≥3 ($P < .001$; Figure 3A). When times A and B were grouped together because of the relatively small number of patients, NRM was significantly correlated with the HCT-CI (Figure 3A; $P < .02$). However, this phenomenon had borderline significance among patients who underwent transplantation after 2011 (time C; $P = .052$; Figure 3A). Moreover, the NRM for each HCT-CI category (0, 1 to 2, and ≥3) remained stable between 2000 to 2011 (time A + B) and 2012 to 2017 (time C) (data not shown). Furthermore, HCT-CI was significantly correlated with OS (Figure 3B); for the whole cohort at 5-year follow-up, OS was 40.2% in patients with an HCT-CI of 0, 33.6% in those with an HCT-CI of 1 to 2, and 31.4% in those with an HCT-CI of ≥3 ($P < .001$). When the patients in

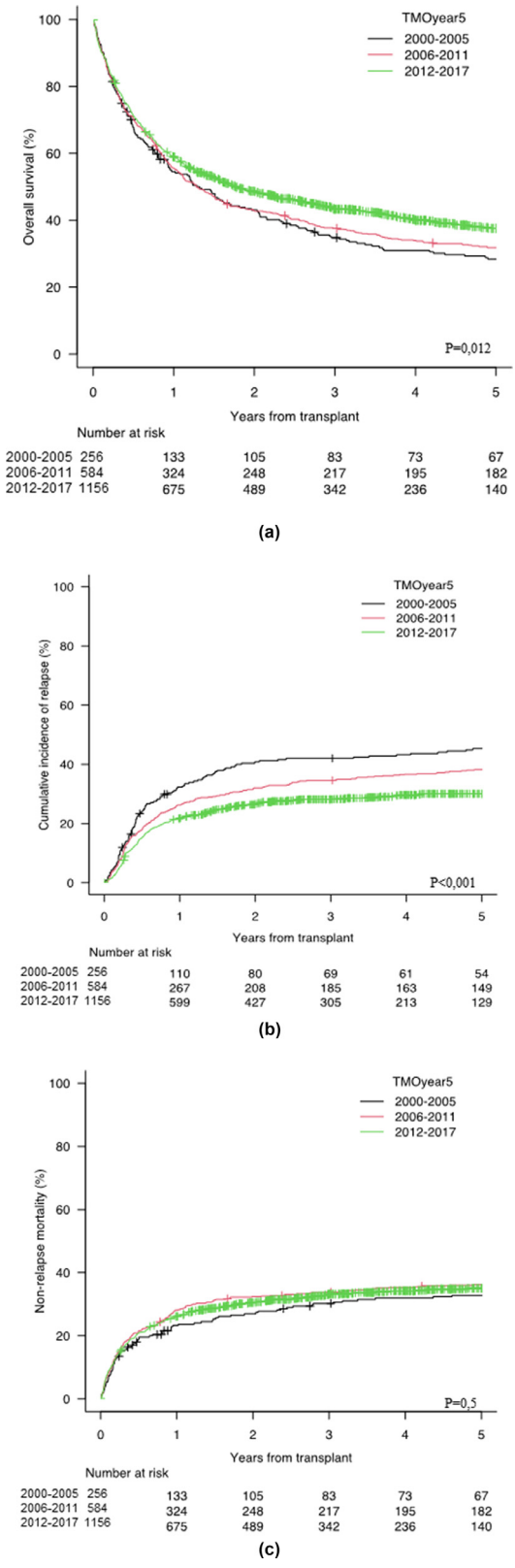


Figure 2. OS, CIR, and NRM according to time of allo-SCT. (A) Probability of OS at 5 years: 28.4% in time A versus 31.8% in time B versus 37.3% in time C ($P = .012$). (B) CIR at 5 years: 45.3% in time A versus 38.2% in time B versus 30.0% in time C ($P < .0001$). (C) Cumulative incidence of NRM at 5 years: 32.8% in time A versus 36.2% in time B versus 35.0% in time C ($P = .5$).

Table 3
Causes of Transplantation-Related Mortality by Period

Causes	Total (N = 1996), n (%)	2000 to 2005 (N = 256), n (%)	2006 to 2011 (N = 584), n (%)	2012 to 2017 (N = 1156), n (%)	*P* Value
NRM available	547 (77)	53 (58)	171 (75)	323 (83)	—
GVHD	206 (38)	25 (47)	77 (45)	104 (32)	.006
Infection	260 (47)	17 (32)	69 (40)	174 (54)	.003
Type of infection missing	151 (58)	11 (65)	53 (77)	86 (49)	—
Bacterial	84 (62)	4 (67)	8 (50)	72 (82)	—*
Fungal	29 (21)	1 (17)	2 (12)	12 (14)	—*
Viral	22 (16)	1 (17)	6 (37)	4 (4)	—*
Organ toxicity	81 (15)	11 (21)	25 (15)	45 (14)	.4
NRM missing	162 (23)	39 (42)	58 (25)	65 (17)	—
NRM total	709 (35)	92 (36)	229 (39)	388 (34)	—

* *P* value was not calculated because of the high percentage of missing data.

times A and B were grouped together, the predictive value of HCT-CI was present (OS at 5 years: 40.7% for HCT-CI of 0, 29.8% for 1 to 2, and 20.4% for ≥3; $P < .001$), whereas it lost its impact in time C (OS at 5 years: 39.5%, 36.3%, and 35.7%, respectively; $P = .074$).

Figure 4 shows long-term outcomes according to patient age (60 to 65 years, 66 to 70 years, and >70 years) in time A + B (n = 627, 197, and 16, respectively) versus time C (n = 714, 384, and 58, respectively). The 3 age groups had significantly different OS only in time A + B (at 5 years: 33.7% versus 22.7% versus 18.8%; $P = .003$; Figure 4A). On the other hand, NRM and CIR did not differ significantly according to age in the 2 time periods (Figure 4B and C).

We performed univariate and multivariate analysis on NRM and OS.

Considering the multivariate analysis on NRM (Figure 5A), the use of UCB (hazard ratio [HR], 4.19; 95% CI, 1.74 to 10.1; $P = .001$), a Haplo donor (HR, 2.00; 95% CI, 1.37 to 2.90;

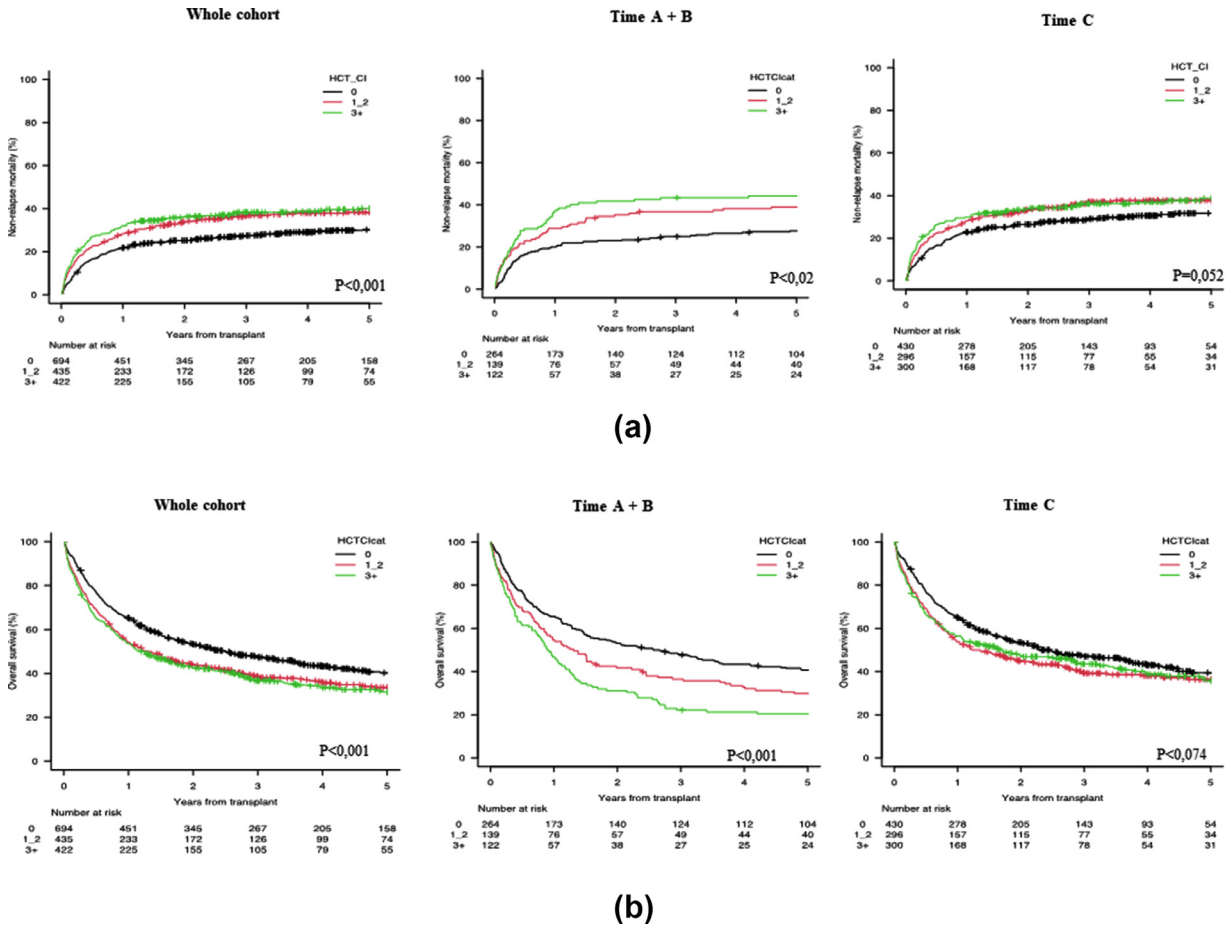


Figure 3. NRM and OS according to HCT-CI. (A) Cumulative incidence of NRM at HCT-CI scores of 0, 1 to 2, and >3: 21.8% versus 28.4% versus 31.9% at 1 year, 25.2% versus 33.9% versus 36.1% at 2 years, 30.2% versus 38.3% versus 40.2% at 5 years ($P < .001$; significance in times A and B only). (B) Probability of OS for HCT-CI 0 versus 1 to 2 versus >3 in time A + B: 65.5% versus 54.7% versus 46.7% at 1 year, 53% versus 41.7% versus 31.1% at 2 years, 40.7% versus 29.8% versus 20.4% at 5 years ($P < .001$). Probability of OS for HCT-CI 0 versus 1 to 2 versus >3 in time C: 65.1% versus 53.8% versus 56.4% at 1 year, 53.5% versus 44.9% versus 47.3% at 2 years, 39.5% versus 36.3% versus 35.7% at 5 years ($P = .074$).

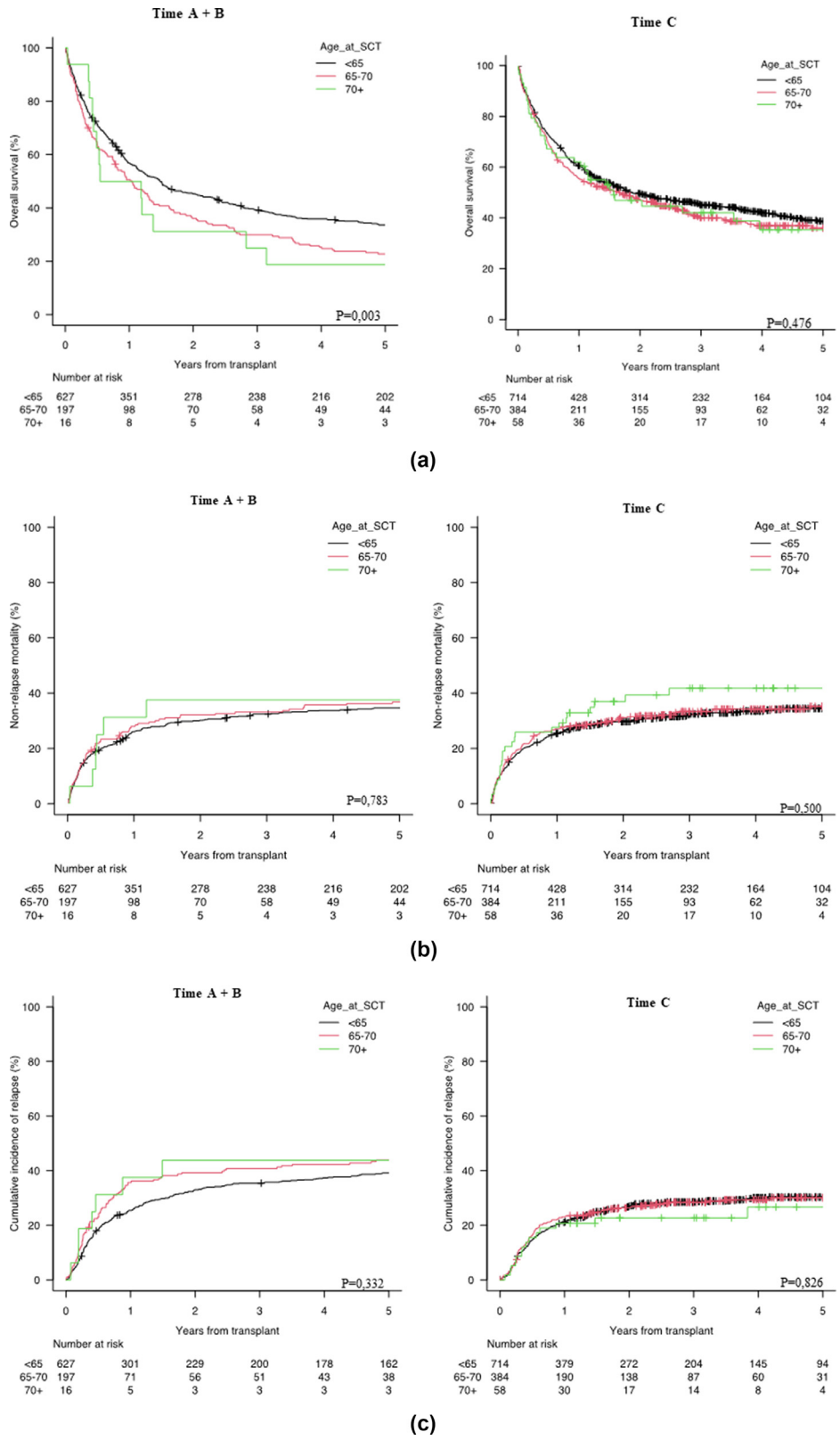


Figure 4. OS, CIR, and NRM according to patient age. (A) Probability of OS at 5 years according to patient age; time A + B: 33.7% versus 22.7% versus 18.8% ($P = .003$); time C: 38.7% versus 35.9% versus 35.3% ($P = .476$). (B) CIR at 5 years: time A + B: 39.2% versus 49.7% versus 49.3% ($P = .332$); time C: 30.3% versus 30.1% versus 26.6% ($P = .826$). (C) NRM at 5 years: time A + B: 34.6% versus 36.7% versus 37.5% ($P = .783$); time C: 34.4% versus 35.2% versus 41.7% ($P = .500$).

$P < .001$), or a UD (HR, 1.77; 95% CI, 1.20 to 2.62; $P = .004$) significantly increased NRM, whereas an acute leukemia diagnosis (HR, 0.64; 95% CI, 0.53 to 0.79; $P < .001$), low-risk HCT-CI (<1) (HR, 0.74; 95% CI, 0.60 to 0.90; $P = .003$), and KPS 90 to 100 (HR, 0.68; 95% CI, 0.55 to 0.84; $P < .001$) significantly reduced NRM.

According to the multivariate analysis (Figure 5B), the factors that significantly impaired OS were use of UCB (HR, 2.07; 95% CI, 1.33 to 3.23; $P = .001$), a Haplo donor (HR, 1.22; 95% CI, 1.02 to 1.47; $P = ,031$), nonresponse (ie, no remission) at the time of allo-SCT (HR, 1.68; 95% CI, 1.46 to 1.94; $P < .001$), and male recipient (HR, 1.15; 95% CI, 1.01 to 1.32; $P = .04$). On the other hand, HCT-CI <1 (HR, 0.81; 95% CI, 0.71 to 0.93; $P = .002$), KPS of 90 to 100 (HR, 0.65; 95% CI, 0.57 to 0.75; $P < .001$) and transplantation between 2011 and 2017 (HR, 0.86; 95% CI, 0.74 to 0.99; $P = .03$) significantly improved OS.

DISCUSSION

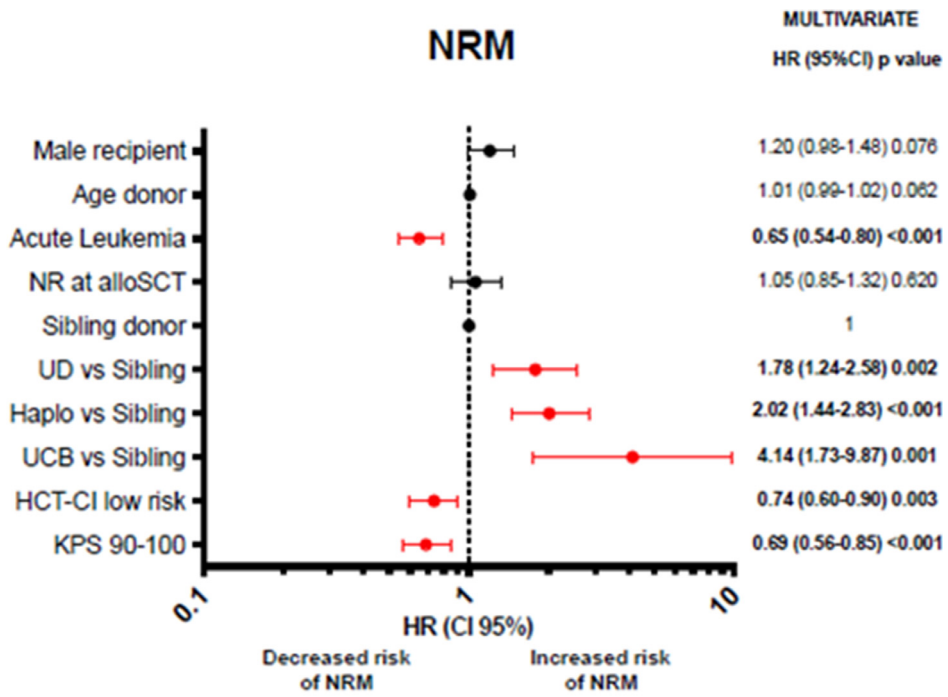
Given the significant increase in age of transplant recipients reported in all transplantation registries [4], and considering that elderly persons are expected to exceed one-third of the global population in the near future [5], we conducted this retrospective registry-based study to evaluate the safety, efficacy, and outcomes of allo-SCT performed in 1996 patients aged ≥60 years at 30 GITMO centers over the last 2 decades (2000 to 2017). The participating centers represent 60% (30 of 50) of the allogeneic adult transplantation programs accredited in Italy. We are aware that this percentage does not fully covers all the Italian activity, but these were the centers that consented to participate to the study.

One major strength of this analysis is represented by the number of transplants included (1996 first transplants) and the long median follow-up (5.6 years), which make the value and interpretation of our results quite reliable. Moreover, to the best of our knowledge, although some recently published studies cover the topics of outcomes and toxicity of allo-SCT in the elderly with specific hematologic malignancies [12-15], this is the first registry study that includes a comprehensive analysis of consecutive allo-SCTs performed in Italy, reflecting the trends in transplantation over the last 17 years. Nonetheless, some limitations of this study should be acknowledged, including its retrospective design. In particular, the lack of missing values for HCT-CI (22%) as well as cause of death (23%) limits the strength of the results and suggests that caution should be maintained when drawing final conclusions. Moreover, roughly one-quarter of the centers performed nearly 50% of the 1996 transplantations. This center effect should be considered, as a learning curve is inevitably present when performing transplantations in elderly patients.

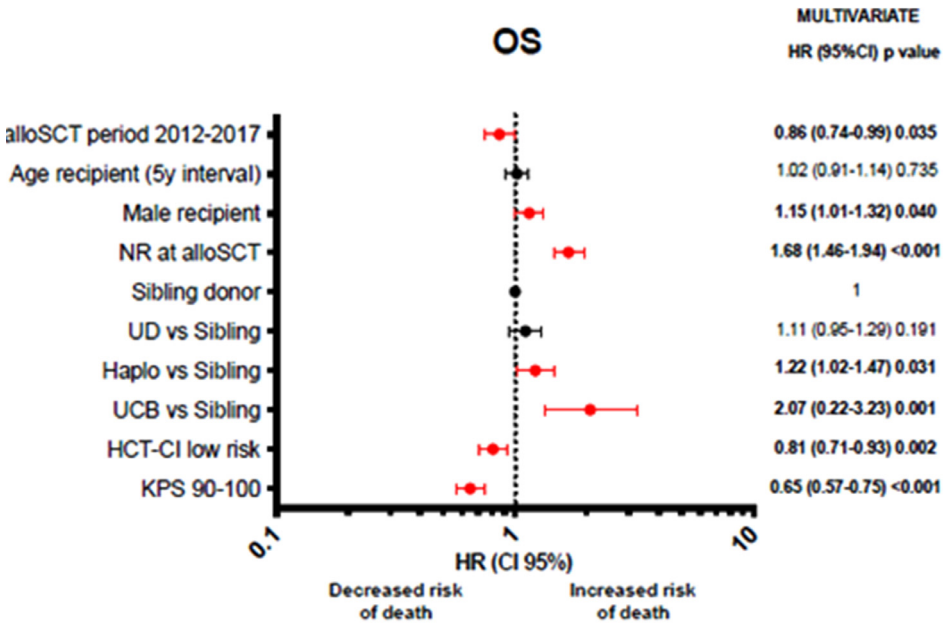
The significant increase in the number of transplantations in patients aged ≥60 years during this time frame (Figure 1) was due not only to the aging of the population and the increased prevalence of hematologic malignancies among the elderly, but also to clinicians' greater propensity to use allo-SCT to cure rather than to control these diseases, as confirmed by the progressive increase in the proportion of elderly patients who undergo allo-SCT over time. Notably, >50% of the registered transplantations were performed between 2012 and 2017, by 73% of the participating centers. This means that although allo-SCT has been performed in elderly persons in Italy since 2000, the transplantation procedure has evolved so much over time that by 2017, the percentage of transplantations in patients aged ≥60 years had nearly doubled in most of the centers (Figure 1). In fact, there was a significant change in most allo-SCT procedures worldwide, starting from the HLA typing [16] and the selection of patients and extending to the evolution of conditioning platforms [17-19], moving from standard MAC to reduced-toxicity regimens. Consequently, the characteristics of the patients undergoing allo-SCT have changed significantly over time (Table 1). More patients with acute leukemia in CR have undergone all-SCT in the most recent years. This reflects the improvement in the biological characterization of these diseases to rapidly identify patients at high risk of relapse who should be treated with allo-SCT in CR [20,21]. In parallel, transplantation platforms also have changed significantly, with modification of conditioning regimens and increasing use of MAC regimens, in vivo T cell depletion, and PT-Cy (Table 2). Focusing on the conditioning regimen, TBI has been progressively abandoned in favor of alkylators, namely busulfan (switching from oral around 2000 to i.v. thereafter), thiotepa, and, more recently, treosulfan, often included in reduced-toxicity conditioning regimens (total dose >10 g/m^2). This is relevant, considering that the balance between the antileukemic activity and toxicity of these conditioning regimens has become progressively more favorable [19,22,23]. In other words, the extensive use of MAC regimens in recent years reflects the importance of the chemotherapy dose in conditioning in determining the final cure of the disease.

The direct consequence of all these changes is that the NRM remained stable over time (Figure 2A), whereas the CIR was significantly reduced (Figure 2B). Notably, we should remember that with increasing of age, death is an expected event that might be not related to transplantation or disease recurrence. Interestingly, the stability of NRM over time was due to a balance between an increase in NRM owing to infections (mainly bacterial) and a reduction in NRM owing to GVHD (Table 3), even though caution in data interpretation is mandatory because of the high amount of missing data. A possible explanation for the increase in infective NRM could be that from 2000 to 2017, we performed allo-SCT in older patients, more often selected a matched UD or Haplo donor, and provided more intensive conditioning regimens. These latter 2 aspects could be at least partially explained by the idea that, particularly in acute leukemias, the timing of transplantation is more important than HLA matching, and that chemotherapy dose matters in determining the cure of the disease. Moreover, increased use of both in vivo T cell depletion and PT-Cy was observed (Tables 1 and 2). Notably, these 2 latter platforms for GVHD prophylaxis are associated with a reduction in GVHD incidence, [24-27] which explains the reduction in GVHD-related NRM. The consequence of NRM stability and CIR reduction over time was significantly improved OS (Figure 2C).

The improvement in OS would be expected to be related to the reduction in NRM, considering that NRM was once identified as the major limitation to allo-SCT success in elderly recipients [28]. Interestingly, focusing on the years 2000 to 2011 (time A + B), NRM was significantly lower in patients with an HCT-CI of 0 compared with those with an HCT-CI of 1 to 2 or ≥3, while it remained stable across all the HCT-CI groups in time C (Figure 3A). This may be related to the changes in patient characteristics and transplantation platforms over time, particularly in conditioning and GVHD prophylaxis regimens. Notably, conditioning regimens became progressively more intensive (Table 2) and in parallel, the proportion of patients with higher comorbidity increased and their KPS increased significantly (Table 1). Moreover, from 2000 to 2017, there was a significant reduction in extensive cGVHD cumulative incidence, associated with the use of in vivo T cell depletion, namely with antithymocyte globulin (ATG) (Supplementary Figure S2B). Interestingly, this did not increase the CIR, which is in line with prospective published data on the use of ATG or T antilymphocyte globulin in allo-SCT [24,29]. Overall, these data suggest that the selection of patients improved progressively over time, favoring fitter patients in CR, regardless of their HCT-CI score, conditioned



(a)



(b)

Figure 5. (A) Multivariate analysis of NRM. The use of UCB ($P = .001$), a haploidentical donor ($P < .001$), or a matched unrelated donor ($P = .004$) significantly increased NRM, whereas an acute leukemia diagnosis ($P < .001$), low-risk HCT-CI (<1) ($P = .003$), and KPS 90 to 100 ($P < .001$) significantly reduced NRM. (B) Multivariate analysis of OS. Use of an alternative donor ($P = .001$), nonresponse at the time of SCT ($P < .001$), and male recipient ($P = .04$) impaired OS, whereas HCT-CI <1 ($P = .002$), KPS 90 to 100 ($P < .001$), and transplantation between 2011 and 2017 ($P = .03$) significantly improved OS.

with more intensive regimens and treated with a more active anti-GVHD prophylaxis. Nevertheless, efforts to improve the CIR are urgently needed, and several preemptive strategies, such as the use of post-transplantation maintenance with hypomethylating agents (eg, azacitidine) or antiapoptotic drugs (eg, venetoclax) or molecular target drugs (eg, Flt3 inhibitors) in cases of targetable genetic lesions [30,31] are currently under active clinical and experimental research.

Another interesting result is that increasing age was associated with worse outcomes between 2000 and 2011 but not

between 2012 and 2017 (Figure 4A), whereas CIR and NRM remained stable across all the time periods. Once again, this suggests that age alone does not fully reflect the frailty and vulnerability of a patient ageìd ≥60. In this regard, other frailty scores (eg, that from the Fondazione Italiana Linfomi) should be prospectively explored in the elderly, as they may better predict NRM and OS than the historical HCT-CI [7,32-35]. A challenge for the future may be to find a way to combine these clinical frailty scores with biomarkers of aging [36,37] to improve the selection of elderly patients eligible for allo-SCT. Currently, at least in Italy, there are no standardized methods for multidimensional geriatric assessment, and each transplantation center performs its own evaluation, according to local guidelines. This lack of homogeneity in exploring this aspect of senescence should be a stimulus for designing prospective, multicentric trials, including a comprehensive assessment of frailty before allo-SCT.

Finally, focusing on the multivariate analysis, it is noteworthy that in our study, the use of an alternative donor (particularly a matched UD or Haplo donor) was associated with impaired outcome for increase in NRM (Figure 5A and B). Although some data from the literature suggest that the long-term outcome following allo-SCT is not influenced by donor type, this topic remains a matter of debate among hematologists, especially in patients with acute leukemias [2].

In summary, the use of allo-SCT in elderly patients in Italy increased progressively over the years in question. Moreover, the clinical and transplantation characteristics of the patient population changed significantly over time, with the aim of increasing the curability of the underlying disease. This explains why long-term OS progressively improved, owing to reductions in the CIR and cGHVD, while NRM remained stable. In particular, the progressive increase in the use of more intensive conditioning regimens over time despite the increases in patient comorbidity suggests that the selection of patients based on HCT-CI alone has been abandoned in favor of paying closer attention to patient fitness, as reflected by the improvement in patient KPS.

Overall, our data strongly support the use of allo-SCT in elderly patients, in particular within clinical trials exploring different transplant platforms, in several disease groups. Moreover, age alone cannot be considered a factor limiting the access to allo-SCT, which remains the best postinduction therapy for several high-risk hematologic malignancies. Patient selection remains crucial, and further investigation is needed to identify the best tool for predicting NRM and OS. Future research in the field of allo-SCT, especially in older patients, should be addressed to the following objective: not one transplantation for all the elderly, but different transplantations based on the heterogeneity of older patients.

COLLABORATORS

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2021.11.006.

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