Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation

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ABSTRACT

Allogeneic hematopoietic cell transplantation is widely used to treat adults with high-risk acute lymphoblastic leukemia. The aim of this study was to analyze whether the results changed over time and to identify prognostic factors. Adult patients treated between 1993 and 2012 with myeloablative allogeneic hematopoietic cell transplantation from HLA matched sibling (n=2681) or unrelated (n=2178) donors in first complete remission were included. For transplantations from sibling donors performed between 2008 and 2012, 2-year probabilities of overall survival were: 76% (18-25 years old), 69% (26-35 and 36-45 years old) and 60% (46-55 years old). Among recipients of transplantations from unrelated donors, the respective survival rates were 66%, 70%, 61%, and 62%. In comparison with the 1993-2007 period, significant improvements were observed for all age groups except for the 26-35-year old patients. In a multivariate model, transplantations performed between 2008 and 2012, when compared to 1993-2007, were associated with significantly reduced risks of non-relapse mortality (Hazard Ratio 0.77, *P*=0.00006), relapse (Hazard Ratio 0.85, *P*=0.007), treatment failure (Hazard Ratio 0.81, *P*<0.00001), and overall mortality (Hazard Ratio 0.79, *P*<0.00001). In the analysis restricted to transplantations performed between 2008 and 2012, the use of total body irradiation-based conditioning was associated with reduced risk of relapse (Hazard Ratio 0.48, *P*=0.004) and treatment failure (Hazard Ratio 0.63, *P*=0.02). We conclude that results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia improved significantly over time. Total body irradiation should be considered as the preferable type of myeloablative conditioning.

Introduction

Allogeneic hematopoietic cell transplantation (alloHCT) is widely used for the treatment of adult patients with acute lymphoblastic leukemia (ALL) in first complete remission (CR1) with high risk of relapse. It allows for administration of high doses of total body irradiation (TBI) or myeloablative chemotherapy, which may contribute to eradication of residual disease. The effect may be further strengthened by graft-*versus*-leukemia reaction driven by lymphocytes of donor origin.[1] Unfortunately, alloHCT is also associated with high risk of early and late complications, including infections, graft-*versus*-host disease (GvHD) and secondary malignancies, which result in significant mortality and morbidity. Hence, the balance between potential advantages and disadvantages should be carefully considered in all clinical situations.[2]

Over the past two decades, advances have been made in the care of patients undergoing transplantation. Results of several studies indicated reduced risk of non-relapse mortality (NRM) after alloHCT, observed over the period 1990-2007, which could be a consequence of improved supportive care and more accurate donor selection.[3-5] Those studies, however, included heterogenous populations, most frequently patients with acute myeloid leukemia. Trends in outcome of alloHCT for patients with ALL are less well documented. In particular, no large scale analyses are available for patients treated after 2007. In addition, prognostic factors for alloHCT performed in recent years are still not known. Such data are essential for proper patient selection and optimization of the transplantation procedure.

The goal of this study was to analyze the results of myeloablative alloHCT for patients with ALL in various age groups and according to donor type, as well as to evaluate whether results changed over time during the 20-year period (1993-2012). In addition, we performed an analysis of prognostic factors for transplantations performed in more recent years (2008-2012).

Methods

Study design and data collection

This was a retrospective, multicenter analysis. Data were provided by the registry of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT). The EBMT is a non-profit, scientific society representing more than 600 transplant centers, mainly in Europe. Data are entered, managed, and maintained in a central database; each EBMT center is represented in this database. The validation and quality control program includes verification of the computer printout of the entered data, cross-checking with the national registries, and on-site visits of selected teams.

The study was approved by the ALWP of the EBMT. Patients provided informed consent authorizing the use of their personal information for research purposes.

Criteria of selection

Inclusion criteria were: 1) patients with ALL in CR1; 2) age 18-55 years; 3) alloHCT from either matched sibling donor (MSD-HCT) or unrelated donor (URD-HCT) performed between 1993 and 2012 in centers reporting to the EBMT; 4) T-replete bone marrow or peripheral blood used as a source of stem cells (cord blood transplantations were excluded); 5) myeloablative conditioning, i.e. regimen based on busulfan administered at the total dose of 8 mg/kg or more or total body irradiation (TBI) applied at 6 Gy or more.

For the analysis of prognostic factors, only transplantations performed between 2008 and 2012 were considered. The population was restricted to subjects with available data regarding initial disease characteristics (cytogenetics, immune subtype, white blood cell count).

Patients, donors, and HSCT procedure

Altogether data on 4859 patients treated in 203 transplant centers were included in the analysis. Median age was 33.3 years (range 18-55 years). Data on cytogenetics were available for 2577 patients among whom 1242 (50.1%) had Philadelphia (Ph)-positive ALL. Transplantations were performed from HLA identical sibling in 2681 patients (55%) and from unrelated volunteer in 2178 cases (45%). Peripheral blood was used as a source of stem cells in 3174 (65.8%) cases.

The analysis of prognostic factors included a subgroup of 562 patients treated with either MSD-HCT (n=252, 44.8%) or URD-HCT (n=310, 55.2%), between 2008-2012. Ph-positive ALL was reported in 225 cases (40%).

Detailed patients' and procedural characteristics are listed in Table 1.

Statistical analysis

Study end points were probabilities of NRM, relapse incidence (RI), leukemia-free survival (LFS), and overall survival (OS). The LFS was defined as time interval from alloHCT to either relapse or death in remission. Probabilities of OS and LFS were calculated using the Kaplan-Meier estimate. The RI and NRM were calculated using cumulative incidence curves in a competing risks setting, death in remission being treated as a competing event to relapse.[6,7] Univariate analyses were made with the use of log-rank test for LFS and OS, while Gray test was used to compare RI and NRM. In a univariate analysis we compared results of alloHCT performed in three periods: 1993-2002 (10 years), 2003-2007 (5 years), and 2008-2012 (5 years). The first period was longer than subsequent ones to ensure a representative number of observations. Multivariate analyses were performed with the use of Cox proportional hazard model, adjusted for potential risk factors. The effect of year of alloHCT (2008-2012 *vs.* 1993-2007) was analyzed in a model adjusted for donor type and recipient age. The analysis of prognostic factors was restricted to years 2008-2012.

Median follow up for survivors was 38 months. All *P*-values are two-sided with type 1 error rate fixed at 0.05. Statistical analyses were performed with SPSS 22.0 (IBM Corp., Armonk, NY, USA) and R 3.1.1 software packages (R Development Core Team, Vienna, Austria).

Results

Outcome of MDS-HCT: changes over time according to recipient age

Results of alloHCT were analyzed separately for MSD-HCT and URD-HCT in four age groups: 18-25 years, 26-35 years, 36-45 years, and 46-55 years. Outcome of alloHCT performed in three study periods was compared. Detailed results are presented in Table 2.

The cumulative incidence of NRM at two years after MSD-HCT decreased over time for all age groups; however, the differences reached statistical significance only among patients aged 36-45 years. In this age category, the

incidence of NRM decreased from 21% and 23.3% in years 1993-2002 and 2003-2007, respectively, to 14.7% in the period 2008-2012 (P=0.02). No significant changes over time could be demonstrated for the incidence of relapse after MSD-HCT; however, there was significant improvement of LFS in all age groups except for patients

Table 1. Patients and donors: transplantation procedure.

	Whole group (years 1993-2012)	Subgroup analyzed for prognostic factors (years 2008-2012)
N	4859	562
Median patient age, range (years)	33.3 (18-55)	34.9 (18-55)
Median year of transplantation, (range)	2007 (1993-2012)	2010 (2008-2012)
Median WBC at diagnosis, range (x10⁹/L)	21 (0.1-829)**	21.2 (0.3-775)
High WBC at diagnosis*	722 (37.7%)***	215 (38.3%)
Philadelphia chromosome Positive Negative Unknown	1337 (48.5%) 1419 (51.5%) 2103	219 (39%) 343 (61%) –
Immune subtype		
B-cell	2846 (71.4%)	430 (76.5%)
T-cell	1140 (28.6%)	132 (23.5%)
Unknown	873	–
Median interval from diagnosis to transplantation, range (days)	166 (40-364)	160 (70-361)
Donor type		
Matched sibling donor	2681 (55%)	252 (44.8%)
Unrelated donor	2178 (45%)	310 (55.2%)
10/10 HLA matched	918 (69%)	191 (71.0%)
9/10 HLA matched	318 (23.9%)	60 (22.3%)
8/10 HLA matched	94 (7.1%)	18 (6.7%)
Unknown HLA compatibility	848	41
Donor/recipient sex Female/male Other combinations	997 (20.8%) 3794 (79.2%)	106 (18.9%) 456 (81.1%)
Donor/recipient CMV serological status		
Negative/negative	1194 (31.3%)	207 (36.8%)
Negative/positive	802 (21.0%)	117 (20.8%)
Positive/negative	420 (11.0%)	79 (14.1%)
Positive/positive	1399 (36.7%)	159 (28.3%)
Unknown	1044	–
Type of conditioning Busulfan + cyclophosphamide Busulfan + fludarabine Melphalan-based Other chemotherapy-based TBI-based	433 (8.9%) 78 (1.6%) 49 (1%) 247 (5.1%) 4052 (83.4%)	35 (6.2%) 16 (2.8%) – 7 (1.2%) 504 (89.7%)
Source of stem cells		
Bone marrow	1660 (34.2%)	216 (38.4%)
Peripheral blood	3174 (65.8%)	346 (61.6%)

*High white blood cell (WBC) count was defined as more than 30x10⁹/L for B-precursor acute lymphoblastic leukemia (ALL) and more than 100x10⁹/L for T-precursor ALL. **Data available for 2011 patients. ***Data available for 1914 patients. N: number; HLA: human leukocyte antigen; CMV: cytomegalovirus; TBI: total body irradiation.

aged 26-35 years. Among the youngest patients (18-25 years old) LFS rates increased from 53.5% between 1993-2002 to 66.2% between 2003 and 2007 and 65.4% between 2008 and 2012 (P=0.05). Respective LFS rates for patients aged 36-45 years were 47.7%, 58.7%, and 62.7% (P=0.002), while in the oldest group (46-55 years old) they equaled 33%, 45.5%, and 52.8% (P=0.03). In parallel, significant improvement could be demonstrated for the probabilities of OS. The 2-year OS rates for MSD-HCT performed between 2008-2012 in various age groups reached 76.3% (18-25 years), 69.3% (26-35 years), 68.6% (36-45 years), and 59.7% (46-55 years).

Outcome of URD-HCT: changes over time according to recipient age

In a univariate analysis, NRM after URD-HCT did not change significantly over time; however, a tendency was observed in the youngest study group. For patients aged 18-25 years the 2-year NRM rates decreased from 32.1% between 1993 and 2002 to 15.6% between 2003 and 2007 and 17.9% between 2008 and 2012 (P=0.08) (Table 2). Significant reduction of the incidence of RI after URD-HCT could be demonstrated for older adults. For patients aged 36-45 years, the 2-year RI rates decreased from 39.8% between 1993 and 2002 to 20.9% between 2003 and 2007 and 18.6% between 2008 and 2012 (P=0.02). In the oldest study groups (46-55 years), respective RI rates were 34.6%, 22%, and 13.9% (P=0.0002).

Although the probabilities of LFS and OS increased over time in all age groups, significant differences could be demonstrated only for older adults. For patients aged 36-45 years, the 2-year LFS rates in subsequent study periods were 23.5%, 50%, and 55% (P<0.0001) while OS was 37.5%, 57.3% and 60.9%, respectively (P=0.005). Among those aged 46-55 years, the probabilities of LFS increased from 30.8% between 1993 and 2002 to 39.8% between 2003 and 2007 and 57.7% between 2008 and 2012 (P<0.0001) while OS rates were 34.6%, 44.5%, and 61.8%, respectively (P=0.0007).

Outcome of alloHCT: general trends

Univariate and multivariate analyses were performed for MSD-HCT and URD-HCT, including all age groups to see if outcome changed over time for a general population of adults aged 18-55 years (Tables 2 and 3).

In a univariate model, improvement regarding LFS and OS rates could be demonstrated for both types of transplantations (Table 2 and Figures 1 and 2). As for NRM, a significant reduction could be demonstrated after MSD-HSCT (18.8%, 20%, and 14.7% in subsequent study periods; P=0.003) while the differences after URD-HCT were not statistically significant (Table 2). In contrast, significant reduction of RI rates was observed after URD-HCT (28.5%, 22%, and 18.5%, respectively, P=0.006), while not after MSD-HCT. In a multivariate analysis adjusted for recipient age and donor type significant effects of the treatment period were observed with regard to all study end points (Table 3). AlloHCT procedures performed between 2008-2012 were associated with reduced risk of NRM [Hazard Ratio (HR) 0.77, P=0.00006], relapse (HR 0.85, P=0.007), treatment failure (either relapse or NRM; HR 0.81, P<0.00001), and overall mortality (HR 0.79, P<0.00001).

Additional analyses were performed for patients with known Ph-status. Survival improvement was observed for

patients with Ph-positive ALL and Ph-negative ALL (*Online Supplementary Tables S1 and S2*).

Prognostic factors for alloHCT performed between 2008-2012

Results of univariate and multivariate analyses restricted to transplantations performed in the most recent era are reported in Tables 4 and 5.

Among disease-related factors, increased risk of relapse was observed for patients with high leukocyte count at diagnosis (HR 1.89, *P*=0.001) and the presence of Philadelphia chromosome (HR 1.61, *P*=0.02). High initial

Table 2. Results of transplantation from matched sibling donors and unrelated donors in various different age groups and time periods.

MSD-HCT Age	Period	N	NRM % (95%CI)	RI % (95%CI)	LFS % (95%CI)	OS % (95%CI)
18-25 years	1993-2002	126	18.5 (13.7-24)	28 (20.3-36.2)	53.5 (44.6-62.4)	60.5 (51.8-69.2)
	2003-2007	278	10.9 (7.3-15.3)	22.9 (18-28.3)	66.2 (60.4-72)	73 (67.5-78.5)
	2008-2012	298	11.7 (8-16.3)	22.9 (17.5-28.7)	65.4 (58.9-71.8)	76.3 (70.5-82.2)
	P		0.47	0.34	0.05	0.04
26-35 years	1993-2002	167	14 (10-18.7)	25.8 (19.3-32.7)	60.2 (52.7-67.7)	68.1 (60.9-75.2)
	2003-2007	279	17.3 (12.8-22.4)	24 (19-29.5)	58.7 (52.6-64.7)	68.2 (62.4-74)
	2008-2012	318	11.2 (7.7-15.5)	32.4 (26.7-38.3)	56.1 (49.9-62.4)	69.3 (63.1-75.5)
	P		0.06	0.08	0.68	0.63
36-45 years	1993-2002	139	21 (15.8-26.7)	31.4 (23.8-39.3)	47.7 (39.3-56)	58.2 (49.8-66.5)
	2003-2007	303	23.3 (17.9-29.1)	27 (21.9-32.2)	49.4 (43.5-55.2)	58.6 (52.8-64.4)
	2008-2012	283	14.7 (10.4-19.8)	22.2 (16.9-28)	62.7 (56.2-69.2)	68.6 (62.2-75)
	P		0.02	0.19	0.002	0.002
46-55 years	1993-2002	74	26.1 (19.7-32.9)	40.9 (29.3-52.2)	33 (22-44)	41.2 (29.6-52.7)
	2003-2007	207	31.1 (24.4-38)	23.4 (17.7-29.6)	45.5 (38.5-52.5)	53.3 (46.3-60.3)
	2008-2012	209	23.5 (17.4-30.1)	23.7 (17.6-30.4)	52.8 (45.1-60.6)	59.7 (52-67.4)
	P		0.20	0.09	0.03	0.02
18-55 years	1993-2002	506	18.8 (16.2-21.5)	30 (26-34.1)	51.2 (46.7-55.6)	59.6 (55.2-63.9)
	2003-2007	1067	20 (17.4-22.8)	24.5 (21.9-27.2)	55.4 (52.3-58.5)	63.8 (60.7-66.8)
	2008-2012	1108	14.7 (12.4-17.1)	25.7 (22.8-28.7)	59.5 (56.2-62.9)	69.1 (65.8-72.3)
	P		0.003	0.07	0.009	0.00006

URD-HCT Age	Period	N	NRM % (95%CI)	RI % (95%CI)	LFS % (95%CI)	OS % (95%CI)
18-25 years	1993-2002	44	32.1 (26.6-37.7)	21 (10.2-34.3)	46.9 (32-61.8)	53.9 (39-68.8)
	2003-2007	207	15.6 (11.5-20.3)	22.9 (17.3-29.1)	61.5 (54.7-68.3)	72 (65.7-78.3)
	2008-2012	312	17.9 (13.5-22.8)	20.5 (15.7-25.6)	61.7 (55.7-67.7)	65.8 (59.7-71.8)
	P		0.08	0.99	0.11	0.08
26-35 years	1993-2002	69	17.7 (13.4-22.4)	23.8 (14.4-34.6)	58.5 (46.7-70.3)	64.4 (53-75.9)
	2003-2007	240	20.2 (15.6-25.2)	22.2 (17.1-27.8)	57.6 (51.2-64)	63.9 (57.7-70.1)
	2008-2012	313	18.1 (13.8-23)	19.7 (15.2-24.6)	62.2 (56.4-68)	70 (64.4-75.5)
	P		0.53	0.68	0.30	0.49
36-45 years	1993-2002	44	36.7 (31.3-42.1)	39.8 (25-54.3)	23.5 (10.8-36.2)	37.5 (23.1-52)
	2003-2007	223	28.9 (23.7-34.2)	20.9 (15.8-26.5)	50 (43.4-56.6)	57.3 (50.7-63.9)
	2008-2012	334	26.4 (21.3-31.7)	18.6 (14.3-23.4)	55 (49.2-60.9)	60.9 (55.1-66.6)
	P		0.24	0.02	<0.0001	0.005
46-55 years	1993-2002	26	34.6 (28-41.3)	34.6 (16.9-53.1)	30.8 (13-48.5)	34.6 (16.3-52.9)
	2003-2007	132	38.2 (31.6-44.9)	22 (15.1-29.7)	39.8 (31.1-48.4)	44.5 (35.7-53.3)
	2008-2012	234	28.5 (22.2-35.1)	13.9 (9.4-19.2)	57.7 (50.6-64.7)	61.8 (54.9-68.8)
	P		0.19	0.0002	<0.0001	0.0007
18-55 years	1993-2002	183	28.2 (22-35.2)	28.5 (25.4-31)	43.4 (36.1-50.6)	51.2 (43.8-58.5)
	2003-2007	802	24.4 (21.7-27.1)	22 (19.1-25)	53.6 (50-57.1)	61 (57.5-64.5)
	2008-2012	1193	22.4 (19.8-25)	18.5 (16.1-21)	59.1 (56-62.2)	64.8 (61.7-67.8)
	P		0.27	0.006	0.0001	0.003

Probabilities are reported at two years after transplantation. MSD-HCT: matched sibling donor-hematopoietic cell transplantation; N: number; NRM: non-relapse mortality; RI: relapse incidence; LFS: leukemia-free survival; OS: overall survival; CI: confidence interval; URD-HCT: unrelated donor hematopoietic cell transplantation.

leukocyte count was also associated with increased risk of treatment failure (HR 1.45, *P*=0.01) and overall mortality (HR 1.5, *P*=0.01). The effect of Ph-status on LFS was significant in a univariate analysis (*P*=0.007) (*Online Supplementary Figure S1*), but not in a multivariate model.

Neither immune subgroups (B- *vs.* T-ALL) nor time to achieve CR were associated with outcome.

The risk of NRM was increased for URD-HCT compared to MSD-HCT (HR 2.11, *P*=0.002) (*Online Supplementary Figure S1*), and in the case of female
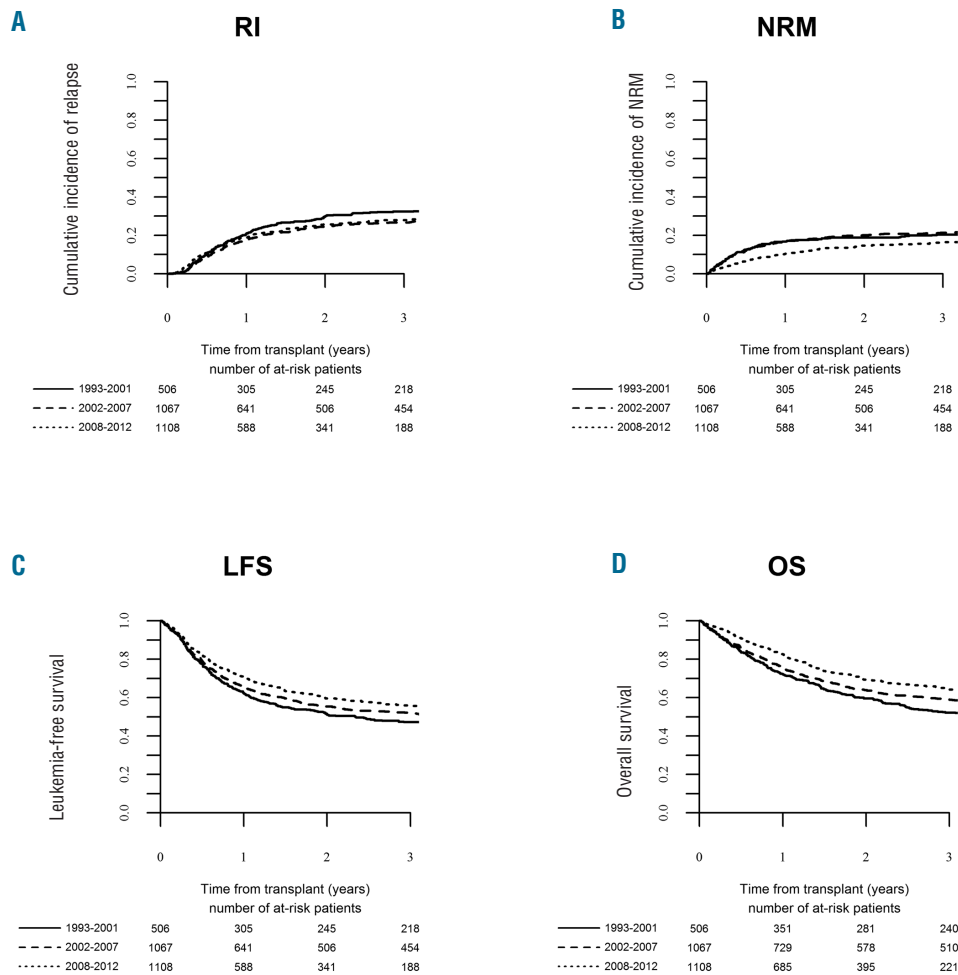
Figure 1. Outcome of matched sibling donor – hematopoietic cell transplantation for adults with acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Changes over time in the period 1993-2012. (A) Relapse incidence (RI), (B) non-relapse mortality (NRM), (C) leukemia-free survival (LFS), (D) overall survival (OS).

Table 3. Effect of the year of allogeneic HCT on outcome adjusted for recipient age and type of donor.

	Factor	HR (95% CI)	P
NRM	Year of alloHCT 2008-2012 *vs.* 1993-2007	0.77 (0.68-0.87)	0.00006
	Recipient age (*per* 10 years)	1.38 (1.31-1.47)	<0.00001
	MSD *vs.* URD	0.71 (0.62-0.8)	<0.00001
Relapse	Year of alloHCT 2008-2012 *vs.* 1993-2007	0.85 (0.75-0.96)	0.007
	Recipient age (*per* 10 years)	1.07 (1.01-1.13)	0.01
	MSD *vs.* URD	1.15 (1.02-1.29)	0.02
Treatment failure	Year of alloHCT 2008-2012 *vs.* 1993-2007	0.81 (0.74-0.88)	<0.00001
	Recipient age (*per* 10 years)	1.21 (1.16-1.26)	<0.00001
	MSD *vs.* URD	0.91 (0.84-0.99)	0.04
Overall mortality	Year of alloHCT 2008-2012 *vs.* 1993-2007	0.79 (0.72-0.87)	<0.00001
	Recipient age (*per* 10 years)	1.24 (1.19-1.3)	<0.00001
	MSD *vs.* URD	0.85 (0.78-0.93)	0.0005

HCT: hematopoietic cell transplantation; HR: hazard ratio; CI: confidence interval; NRM: non-relapse mortality; alloHCT: allogeneic hematopoietic cell transplantation; MSD: matched sibling donor; URD: unrelated donor.

donor/male recipient sex combination (HR 1.85, *P*=0.02). Both these factors were also associated with increased risk of the overall mortality (HR 1.52, *P*=0.01 and HR 1.59, *P*=0.02, respectively). In addition, the risk of mortality was increased for patients with CMV-positive serological status receiving transplantation from CMV-negative donors (HR 1.53, *P*=0.04).

Among procedure-related variables, decreased risk of relapse was demonstrated for transplantations preceded by total body irradiation (TBI)-based preparative regimens (HR=0.48, *P*=0.001). The use of TBI was also associated with reduced risk of treatment failure (HR=0.63, *P*=0.02) (Figure 3). The choice of stem cell source did not significantly affect outcome; however, there was a trend to reduced risk of relapse after peripheral blood compared to bone marrow transplantations (*P*=0.06).

Data on minimal residual disease (MRD) status before transplantation were available for 716 patients, including 502 patients with Ph-positive ALL (MRD-positive, n=314; MRD-negative, n=188) and 214 subjects with Ph-negative disease (MRD-positive, n=162; MRD-negative, n=52) treated between 2008-2012. Methods for MRD assessment were not specified. In a univariate analysis, among patients with Ph-negative ALL, the positive MRD status was associated with increased incidence of relapse (36.5%

vs. 17.6%; *P*=0.0005) and decreased probability of LFS (54.3% *vs.* 65.9%; *P*=0.04), while no significant effect was observed with regard to OS and NRM. For patients with Ph-positive ALL, the MRD status did not significantly affect outcome.

Discussion

AlloHCT is used as part of consolidation treatment of adults with ALL with intention to reduce the risk of relapse. However, this benefit may be counterbalanced by NRM. Results of the UK ALL XII/ECOG 2993 trial revealed that, among standard-risk patients with a sibling donor, the cumulative incidence of NRM was 19.5%, compared with 35.8% in the high-risk group.[8] Consequently, survival advantage could be demonstrated for standard- but not high-risk ALL. In the HOVON studies, NRM among patients with a sibling donor was lower: 16% for standard-risk and 15% for high-risk ALL.[2] Collectively, it has been concluded that patients with an over 50% risk of relapse and a less than 20%-25% risk of NRM are most likely to benefit from alloHCT performed in CR1. Therefore, assessing the risk of transplantation-related mortality is imperative in the decision-making
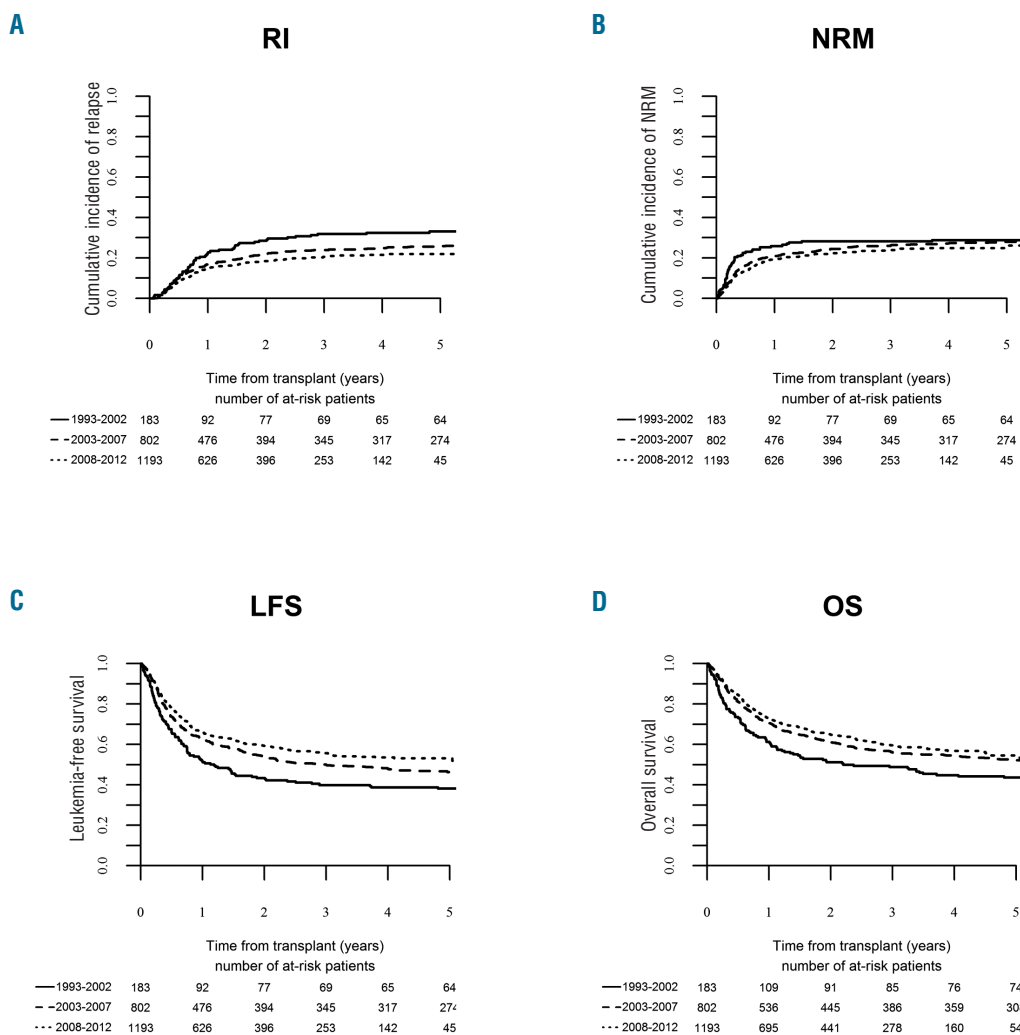

Figure 2. Outcome of unrelated donor – hematopoietic cell transplantation for adults with acute lymphoblastic leukemia (ALL) in first complete remission (CR1). Changes over time in the period 1993-2012.[2] (A) Relapse incidence (RI), (B) non-relapse mortality (NRM), (C) leukemia-free survival (LFS), (D) overall survival (OS).

process and there is a need for estimates related to procedures performed in the most recent era.[2]

In the current study, we focused on alloHCT performed in the period of 2008-2012, which reflected current clinical practice with regard to supportive care, HLA typing and other factors potentially influencing outcome. Results were compared with preceding periods. We were able to demonstrate a significant improvement in OS and LFS over time, which for the major part was related to reduced risk of NRM, and to a lesser extent the risk of relapse. For the entire population of adults between 18-55 years old treated between 2008 and 2012, the cumulative incidence of NRM at two years was 14.7% after MSD-HCT and 22.4% after URD-HCT.

The improvement over time has already been reported by Gooley et al. who compared results of transplantations performed between 2003 and 2007 with those performed between 1993 and 1997. In a heterogeneous population including 13% patients with ALL in various disease phases, the authors demonstrated reduction of the NRM rates from 41% to 26%.[4] Hahn et al. reported general survival improvement for patients with hematologic malignancies observed over the period 1994-2005; however, the analysis included children, and data on NRM were not reported.[5] In the previous analysis of the ALWP of the EBMT, we demonstrated that, for patients with acute leukemia treated with MSD-HCT in Eastern European countries, the rates of NRM decreased from 22% between 1990 and 2002 to 15% in the period 2002 and 2005.[3] Two studies were restricted to patients with ALL, transplanted

Table 4. Univariate analysis of factors affecting outcome after allogeneic HCT performed between 2008-2012.

Factor		N	NRM (%, 95%CI)	RI (%, 95%CI)	LFS (%, 95%CI)	OS (%, 95%CI)
Ph-status	Negative	337	17 (13.1 - 21.5)	18.9 (14.7 - 23.6)	64 (58.6 - 69.5)	69.8 (64.5 - 75)
	Positive	225	17.7 (13.7 - 22.2)	27.3 (21.3 - 33.5)	54.8 (48 - 61.7)	67.8 (61.3 - 74.3)
	P		0.48	0.01	0.007	0.53
Age at HSCT (years)	18-25	131	18.6 (12.6 - 25.6)	20.4 (13.6 - 28.2)	61 (52 - 70)	67.2 (58.5 - 75.9)
	26-35	152	13.5 (8.5 - 19.7)	24.1 (17.4 - 31.5)	62.2 (54.1 - 70.2)	76.2 (68.9 - 83.5)
	36-45	165	18.2 (12.3 - 25.1)	25.6 (18.7 - 33.1)	56.1 (48 - 64.3)	65.1 (57.3 - 72.9)
	46-55	114	19.3 (13.2 - 26.3)	17.7 (11.1 - 25.5)	63 (53.8 - 72.2)	66.9 (57.9 - 76)
	P		0.39	0.47	0.86	0.57
Initial WBC (x10⁹/L)	Low	347	17.7 (13.7 - 22)	16.6 (12.6 - 21)	65.6 (60.3 - 71)	73.7 (68.7 - 78.6)
	High*	215	16.6 (12.8 - 20.9)	31.5 (25.1 - 38.1)	51.9 (44.8 - 58.9)	61.7 (54.8 - 68.7)
	P		0.73	<0.0001	0.002	0.01
Subtype	B-cell	430	17.5 (14 - 21.5)	23.1 (19 - 27.5)	59.2 (54.3 - 64.2)	68.4 (63.7 - 73.2)
	T-cell	132	16.7 (13.2 - 20.5)	19.6 (13.1 - 27.1)	63.7 (55.2 - 72.2)	70.5 (62.3 - 78.6)
	P		0.52	0.39	0.24	0.41
Time to achieve CR (days)	< 42	320	16.4 (12.4 - 20.8)	23.1 (18.4 - 28.1)	60.5 (54.8 - 66.1)	70.8 (65.6 - 76.1)
	≥ 42	242	18.6 (14.4 - 23.2)	21.2 (16 - 27)	60.1 (53.5 - 66.6)	66.3 (59.9 - 72.8)
	P		0.55	0.49	0.97	0.28
Donor type	MSD	252	12.6 (8.7 - 17.3)	25.9 (20.4 - 31.8)	61.3 (54.9 - 67.7)	71.4 (65.4 - 77.5)
	URD	310	21.2 (16 - 26.8)	19.3 (14.9 - 24.2)	59.5 (53.7 - 65.3)	66.9 (61.4 - 72.5)
	P		0.002	0.08	0.35	0.04
Patient CMV status	Negative	286	16.3 (12.1 - 21)	18.6 (14 - 23.6)	65 (59.1 - 70.9)	73.9 (68.4 - 79.4)
	Positive	276	18.3 (13.9 - 23.3)	26.1 (20.8 - 31.6)	55.6 (49.4 - 61.8)	64.1 (58.1 - 70.1)
	P		0.48	0.06	0.03	0.03
Donor CMV status	Negative	324	17.1 (13.1 - 21.6)	22.5 (17.8 - 27.5)	60.4 (54.8 - 66.1)	69.6 (64.2 - 74.9)
	Positive	238	17.6 (13.5 - 22.1)	22.1 (16.8 - 27.8)	60.2 (53.6 - 66.7)	68.2 (61.9 - 74.6)
	P		0.87	0.44	0.44	0.96
Female donor/ male recipient	No	456	16.3 (12.9 - 19.9)	22.6 (18.6 - 26.7)	61.1 (56.4 - 65.8)	70.1 (65.6 - 74.5)
	Yes	106	22.4 (18.5 - 26.5)	20.9 (13.3 - 29.8)	56.7 (46.5 - 66.9)	63.7 (53.5 - 73.8)
	P		0.18	0.86	0.36	0.23
Conditioning	CHT	58	17.6 (9 - 28.6)	32.7 (20.6 - 45.5)	49.7 (36.3 - 63)	64 (51.2 - 76.7)
	TBI	504	17.3 (8.8 - 28.2)	21.1 (17.4 - 24.9)	61.6 (57.1 - 66.1)	69.5 (65.2 - 73.9)
	P		0.62	0.04	0.02	0.09
Stem cell source	BM	216	15.6 (11 - 21)	24.9 (19.1 - 31.2)	59.3 (52.4 - 66.2)	67.5 (60.9 - 74.2)
	PB	346	18.4 (13.4 - 24.1)	20.6 (16.3 - 25.3)	61 (55.5 - 66.5)	69.8 (64.6 - 75)
	P		0.18	0.18	0.83	0.68

Probabilities are reported at two years after transplantation. *High white blood cell (WBC) count was defined as more than 30x10⁹/L for B-precursor acute lymphoblastic leukemia (ALL) and more than 100x10⁹/L for T-precursor ALL. HCT: hematopoietic cell transplantation; N: number; NRM: non-relapse mortality; RI: relapse incidence; LFS: leukemia-free survival; OS: overall survival; CI: confidence interval; Ph: Philadelphia chromosome; WBC: white blood cell count; CR: complete remission; MSD: matched sibling; URD: unrelated donor; CMV: cytomegalovirus; CHT: chemotherapy; TBI: total body irradiation; BM: bone marrow; PB: peripheral blood.

in both CR1 and CR2. In a single center experience from the University of Minnesota, USA, alloHCT performed between 2000 and 2005 were associated with a significant reduction of NRM compared to preceding periods (1990-1994 and 1995-1999).[9] In a study by Wood *et al.*, reduction of NRM from 43% between 1990 and 1995 to 31% between 2002 and 2007 was reported among adolescents and young adults, i.e. patients 18-40 years old.[10]

In the current analysis, the estimated rates of NRM were lower compared to most previously reported results. This may reflect further improvement which occurred in the most recent time period. As suggested by Gooley *et al.*, reduction of NRM may be dependent on improving supportive care, but also on the reduction of the incidence of graft-*versus*-host disease.[4] The latter could be a consequence of more accurate HLA typing, and in particular, the introduction of high resolution techniques in the process of unrelated donor search.[11] On the other hand, it may be speculated that decreased NRM may be a consequence of more appropriate patient selection and that toxicity of conventional-dose chemotherapy decreased in parallel, positively affecting biological status of the transplant

Table 5. Multivariate analysis of factors affecting outcome after allogeneic HCT performed between 2008-2012.

	Factor	HR (95% CI)	P
NRM	Age (years, continuous)	1.01 (0.99-1.03)	0.26
	High WBC at diagnosis*	1.02 (0.67-1.56)	0.91
	T-ALL *vs.* B-ALL	0.88 (0.52-1.51)	0.65
	Ph-positive *vs.* Ph-negative ALL	1.05 (0.66-1.65)	0.84
	Interval from diagnosis to CR1 >42 days	1.18 (0.79-1.76)	0.42
	URD-HCT *vs.* MSD-HCT	2.11 (1.33-3.34)	0.002
	CMV status D-neg/R-pos *vs.* D-neg/R-neg	1.29 (0.75-2.24)	0.36
	Female D to male R *vs.* other combinations	1.85 (1.12-3.05)	0.02
	TBI- *vs.* chemotherapy-based conditioning	0.90 (0.49-1.66)	0.73
	Peripheral blood *vs.* bone marrow transplantation	1.06 (0.68-1.64)	0.79
RI	Age (years, continuous)	0.99 (0.97-1.01)	0.34
	High WBC at diagnosis	1.89 (1.31-2.72)	0.001
	T-ALL vs B-ALL	1.14 (0.71-1.84)	0.59
	Ph-positive *vs.* Ph-negative ALL	1.61 (1.08-2.4)	0.02
	Interval from diagnosis to CR1 >42 days	0.92 (0.64-1.32)	0.64
	URD-HCT *vs.* MSD-HCT	0.76 (0.52-1.11)	0.16
	CMV status D-neg/R-pos *vs.* D-neg/R-neg	1.55 (0.95-2.55)	0.08
	Female D to male R *vs.* other combinations	1.05 (0.65-1.7)	0.85
	TBI- *vs.* chemotherapy-based conditioning	0.48 (0.3-0.79)	0.004
	Peripheral blood *vs.* bone marrow transplantation	0.69 (0.48-1.01)	0.06
LFS	Age (years, continuous)	1 (0.99-1.01)	0.99
	High WBC at diagnosis	1.45 (1.1-1.9)	0.01
	T-ALL *vs.* B-ALL	1.03 (0.72-1.47)	0.87
	Ph-positive *vs.* Ph-negative ALL	1.33 (0.98-1.79)	0.07
	Interval from diagnosis to CR1 >42 days	1.03 (0.79-1.34)	0.84
	URD-HCT *vs.* MSD-HCT	1.16 (0.87-1.55)	0.30
	CMV status D-neg/R-pos *vs.* D-neg/R-neg	1.41 (0.98-2.04)	0.06
	Female D to male R *vs.* other combinations	1.33 (0.94-1.88)	0.11
	TBI- *vs.* chemotherapy-based conditioning	0.63 (0.43-0.92)	0.02
	Peripheral blood *vs.* bone marrow transplantation	0.83 (0.62-1.1)	0.19
OS	Age (years, continuous)	1.01 (0.99-1.02)	0.31
	High WBC at diagnosis	1.5 (1.11-2.04)	0.01
	T-ALL *vs.* B-ALL	0.9 (0.61-1.33)	0.59
	Ph-positive *vs.* Ph-negative ALL	0.93 (0.67-1.3)	0.67
	Interval from diagnosis to CR1 >42 days	1.20 (0.89-1.62)	0.22
	URD-HCT *vs.* MSD-HCT	1.52 (1.1-2.1)	0.01
	CMV status D-neg/R-pos *vs.* D-neg/R-neg	1.53 (1.02-2.28)	0.04
	Female D to male R *vs.* other combinations	1.59 (1.08-2.32)	0.02
	TBI- *vs.* chemotherapy-based conditioning	0.72 (0.47-1.11)	0.14
	Peripheral blood *vs.* bone marrow transplantation	0.8 (0.58-1.09)	0.15

*High white blood cell (WBC) count was defined as more than 30x10⁹/L for B-precursor acute lymphoblastic leukemia (B-ALL) and more than 100x10⁹/L for T-precursor ALL (T-ALL). HCT: hematopoietic cell transplantation; HR: hazard ratio; CI: confidence interval; NRM: non-relapse mortality; PB: peripheral blood; BM: bone marrow; Ph: Philadelphia chromosome; CR1: complete first remission; URD: unrelated donor; MSD: matched sibling donor; CMV: cytomegalovirus; pos: positive; neg: negative; D: donor; R: recipient; TBI: total body irradiation; RI: relapse incidence; LFS: leukemia-free survival; OS: overall survival.

recipients. Results of our study indicate survival improvement after MSD-HCT for all age groups except for patients 26-35 years old. A trend towards reduction of NRM in this age category was counterbalanced by a tendency to increased RI. It may be speculated that selection criteria for alloHCT changed over time, and patients with higher risk of relapse were referred for transplantation in recent years. Among recipients of URD-HCT, the most prominent improvement could be shown in older age groups (36-55 years old), which, however, was mainly attributed to reduced RI.

Identification of prognostic factors in the most recent time period was a secondary goal of our study. Among donor/recipient-related variables, the use of unrelated donor and female donor to male recipient sex combination had the strongest impact, negatively affecting both the risk of NRM and survival. Several previous reports had suggested that results of MSD-HSCT and URD-HCT for patients with ALL may be comparable. In an analysis by Tomblyn *et al.*, the use of well-matched or partially matched unrelated donor was not associated with inferior outcome compared to MSD.[9] In a Japanese study, the OS rates after URD-HCT and MSD-HCT for patients in CR1 were superimposable; however, HLA disparities were associated with increased risk of NRM.[12] In the present analysis, 29% of URD-HCT were performed across single or double HLA mismatch. However, in a univariate analysis this factor did not influence significantly any of the study outcomes (*data not shown*). Female donor to male

recipient sex combination is a well-recognized risk factor associated with increased risk of graft-*versus*-host disease and NRM.[13] Results of our study confirm that, whenever possible, this combination should be avoided.

The definition of high risk in adult ALL varies among countries and study groups; however, most of the stratification systems include high initial leukocyte count. This factor influences the overall outcome but its impact on results of alloHCT has not been well recognized. In our study, high WBC at diagnosis was a strong predictor of risk of relapse, treatment failure and survival. Our findings suggest the need for additional intervention in this patient population, e.g. therapy oriented to eradicate MRD prior to alloHSCT, intensification of the conditioning regimen, and close monitoring of MRD after alloHSCT followed by pre-emptive donor lymphocyte infusions.

General outcome of Ph-positive ALL improved with the introduction of tyrosine kinase inhibitors (TKIs).[14] Results of a recent analysis by the ALWP of the EBMT indicate that using TKIs both pre- and post-transplant is associated with reduced risk of relapse and improved survival.[15] Both pre-emptive or prophylactic use of imatinib after alloHCT may be considered.[16] In the current analysis, the presence of t(9;22) was associated with increased risk of relapse but not overall mortality. As our study population was quite young, longer follow up may be needed in order to obtain a final evaluation of the effect on OS. On the other hand, it may be speculated that some patients with Ph-positive ALL who relapse after alloHCT may still be salvaged, pos-
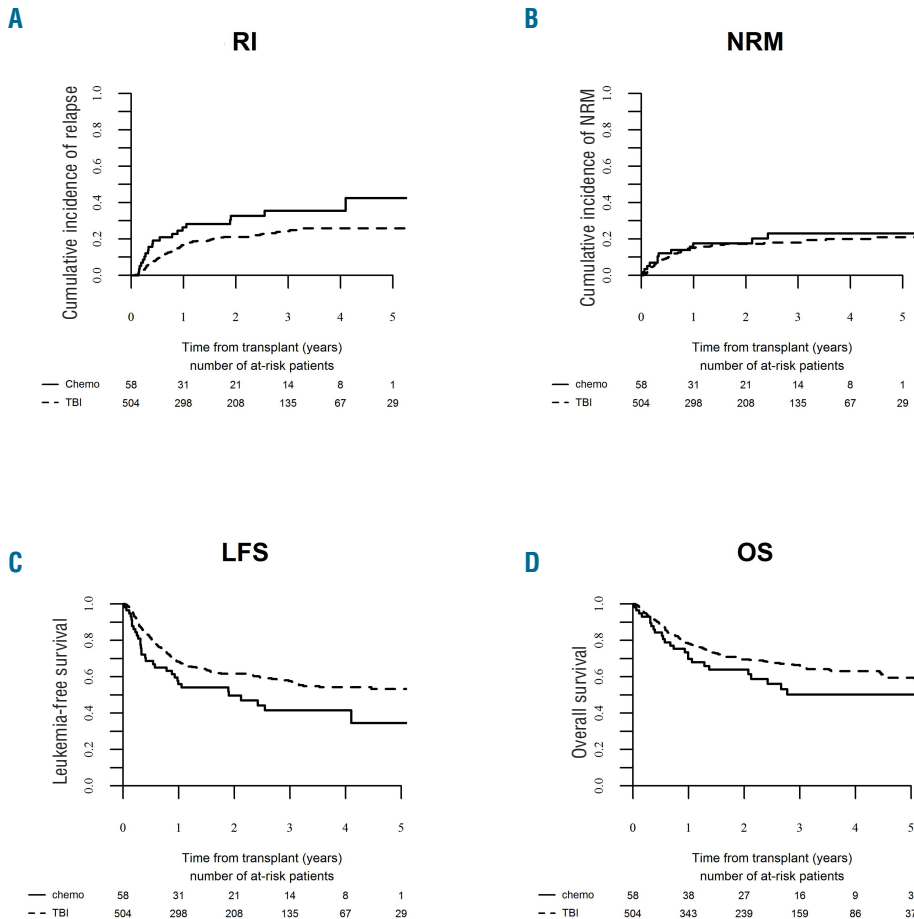

Figure 3. Outcome of allogeneic hematopoietic stem cell transplantation (alloHSCT) performed in the period 2008-2012 according to the type of conditioning (total body irradiation-based vs. chemotherapy-based). (A) Relapse incidence (RI), (B) non-relapse mortality (NRM), (C) leukemia-free survival (LFS), (D) overall survival (OS).

sibly with the use of 2nd- or 3rd-generation TKIs. Furthermore, the probabilities of LFS for Ph-positive ALL improved markedly between 2008 and 2012 compared to preceding periods as a consequence of reduced incidence of both relapse and NRM (*Online Supplementary Table S1 and Online Supplementary Figure S3*). It could be speculated that the introduction of TKIs not only increased the treatment efficacy but also, by allowing for a reduction in chemotherapy intensity, contributed to a reduction in the overall toxicity.

Among procedure-related factors, the use of TBI-based conditioning was the strongest predictor of relapse and was associated with an over 50% reduction of the risk of this event. Although comparison of TBI with myeloblative chemotherapy in a setting of ALL has never been a subject of a prospective trial, some retrospective analyses confirmed the advantage of TBI.[17,18] Results of the current study strongly support this statement. New, irradiation-free regimens based on the use of thiotepa are under development; however, their utility requires further evaluation.[19] Our study is the largest to focus on alloHCT performed in a very large cohort of adults with ALL in CR1. However, it does have several limitations related to its retrospective nature. We were unable to analyze the reasons of NRM after transplantation. In addition, some important variables related to the disease characteristics were unavailable. Among karyotype features we focused on the Ph-status, while the effect of other known high-risk abberrations, e.g. t(4;11) and molecular markers, could not be evaluated. Furthermore, for the majority of patients, we were unable to collect MRD data, which is a well-recognized risk factor in a setting of ALL.[20,21] Finally, selection procedures for patients to go forward to alloHCT could vary among centers and countries. The effect of center experience and national socio-economic status could have caused an additional bias.[22]

The role of alloHCT in first-line treatment of adults with ALL is a matter of debate in view of improving results of conventional-dose chemotherapy.[23] In this study, we demonstrate that results of alloHCT improved in parallel, due to the reduced risk of both NRM and relapse. The improvement is observed in most age categories after both MSD-HCT and URD-HCT. Therefore, we conclude that current estimates of NRM justify the use of alloHCT as consolidation in patients with a high risk of relapse. TBI-based regimens should still be considered the preferable type of conditioning for patients with ALL in CR1.

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