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# Outcome of HLA-matched related allogeneic hematopoietic stem cell transplantation for patients with acute leukemia in first complete remission treated in Eastern European centers. Better results in recent years

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**Abstract** The goal of this study was to analyze results and to determine factors affecting outcome of HLA-matched hematopoietic stem cells transplantation (MRD-HSCT) for patients with acute leukemia transplanted in first complete remission in Eastern European countries. Six hundred forty HSCT were performed between 1990 and 2006 for adults with acute myeloid ( $n=459$ ) and lymphoblastic ( $n=181$ ) leukemia. Two-year leukemia-free survival (LFS), nonrelapse mortality (NRM), and relapse incidence were  $58\pm 2\%$ ,  $19\pm 2\%$ , and  $23\pm 2\%$ , respectively. The cumulative incidence of NRM

decreased from  $22\pm 2\%$  for patients treated between 1990 and 2002 to  $15\pm 3\%$  for transplantations performed between 2003 and 2006 ( $p=0.02$ ), despite increasing recipient age. In a multivariate analysis, time of HSCT affected both NRM and LFS. Among other prognostic factors, the use of TBI decreased relapse incidence and increased the LFS rate. We conclude that results of MRD-HSCT for acute leukemia in Eastern Europe improved over time as a consequence of decreased NRM. The use of TBI containing regimens appears advantageous.

On behalf of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

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**Key words** Matched related donor HSCT · Acute leukemia · Prognostic factors · Leukemia-free survival · Nonrelapse mortality

## Introduction

Allogeneic hematopoietic stem cell transplantation from HLA-matched related donor (MRD-HSCT) is a well-recognized option for the treatment of patients with acute leukemia in first complete remission (CR). The benefit of MRD-HSCT over conventional-dose chemotherapy with regard to relapse rate has been demonstrated in a number of analyses for both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) [1–9]. The number of MRD-HSCT for acute leukemia in Europe has been continuously growing over the last decades [10]. However, as demonstrated by Gratwohl et al., transplantation rates varied strongly between countries, which in major part could be explained by different economical conditions defined by the gross national income (GNI) per capita [11]. In particular, the number of MRD-HSCT procedures performed per year per ten million inhabitants between year 1990 and 2003 in Eastern European countries, representing medium GNI per capita, was markedly lower compared to Western Europe [12]. This difference resulted initially from later introduction of MRD-HSCT in Eastern countries but has been maintained over years as a consequence of parallel increase in transplantation rates in both parts of the continent [12].

Among various factors influencing outcome of MRD-HSCT, the role of center effect has been highlighted in recent years. Frassoni et al. demonstrated that NRM varies strongly among transplant centers and that this phenome-

non can partially be explained by the differences regarding team experience [13]. Provided that the MRD-HSCT has been widely introduced in Eastern Europe in the 1990s, i.e., approximately a decade later than in Western countries, it may be hypothesized that results in Eastern Europe are inferior and are characterized by higher rate of NRM. This issue is of particular importance in acute leukemia where the expected incidence of transplantation-related deaths should be taken into account for treatment decisions.

The goal of this study was to evaluate results of MRD-HSCT for acute leukemia patients in Eastern Europe and to determine if the outcome changed over time. In addition, we searched for other prognostic factors related to donor, recipient, and procedure characteristics.

## Patients and methods

### Study design and data collection

This was a retrospective multicenter analysis. Data were provided by the registry of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Centers participating in the EBMT are annually requested to report all consecutive stem cell transplantations and follow-up. The validation and quality control program includes verification of the computer print-out of the entered data, cross-checking with the national registries, and on-site visits of selected teams.

### Criteria of selection

Inclusion criteria for the analysis were as follows: (1) Diagnosis of AML or ALL, (2) Age  $\geq 16$  years, (3) MRD-

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HSCT performed between 1990 and 2006 in Eastern European countries, including those that entered the European Union after 2003 and those not being member-states of the European Union, and (4) CR1 at transplantation.

#### Patients, donors, and procedure

Six hundred forty patients with the diagnosis of AML ( $n=459$ ) or ALL ( $n=181$ ) were included in the analysis. Transplantations were performed in 32 centers representing 10 countries (Poland,  $n=178$ ; Czech Republic,  $n=133$ ; Croatia,  $n=60$ ; Hungary,  $n=52$ ; Slovakia,  $n=40$ ; Slovenia,  $n=29$ ; Serbia,  $n=17$ ; Estonia,  $n=7$ ; Romania,  $n=6$ ; Lithuania,  $n=1$ ). Median age of the recipients equaled 35 years (range, 16–69 years). Selection of donors was based either on serological or molecular methods at low resolution level.

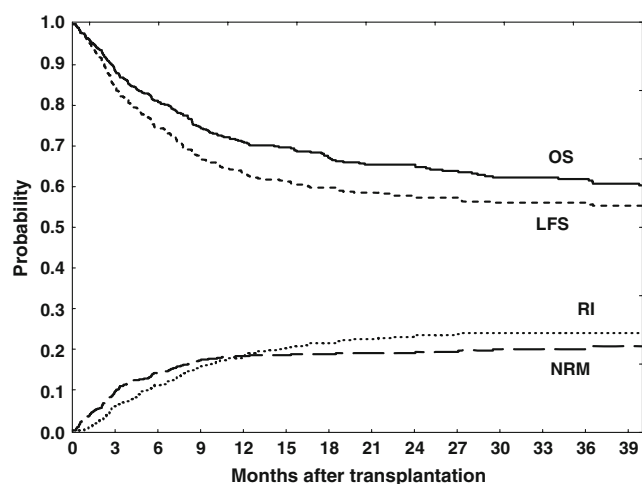
All patients and donors were fully matched for HLA-A, HLA-B, and HLA-DR. The data on pre-transplant CMV serological status were available in 201 patient/donor pairs. CMV positivity was established in 63% of patients and 62% of donors. The conditioning regimen was myeloablative in 90% of cases and was based on either total body irradiation (TBI, mainly for ALL) or chemotherapy alone (predominantly for AML). Definition of reduced intensity conditioning regimen was considered lower dose of busulfan (less than 8 mg/kg total dose) or TBI (less than 6 Gy). The transplantations were performed using bone marrow (BMT) and peripheral blood (PBSCT) as a sources of stem cells in similar proportions. Ex vivo T-depletion was applied in seven cases (1%). After transplantation patients were monitored CMV antigenemia or CMV-DNA. Detailed characteristics of patients, donors, and MRD-HSCT procedure are listed in Table 1.

**Table 1** Patients and donors: transplantation procedure

	AML	ALL	Total
<i>N</i>	459	181	640
Median patient age, range (years)	39 (16–68)	25 (16–58)	35 (16–69)
Recipient gender			
Male	212 (46%)	112 (92%)	324 (51%)
Female	244 (54%)	68 (8%)	312 (49%)
Unknown	3	1	4
Donor gender			
Male	236 (52%)	102 (57%)	338 (53%)
Female	216 (48%)	78 (43%)	294 (47%)
Unknown	7	1	8
Donor/recipient gender			
Female/male	102 (23%)	44 (24%)	146 (23%)
Other combinations	350 (77%)	136 (76%)	486 (77%)
Unknown	7	1	8
Median interval from diagnosis to transplantation, range (days)	187 (23–933)	196 (55–668)	190 (23–933)
Median year of transplantation, range	2001 (1990–2006)	2002 (1992–2006)	2002 (1990–2006)
Conditioning intensity			
Myeloablative <sup>a</sup>	404 (88%)	174 (96%)	578 (90%)
Reduced <sup>b</sup>	55 (12%)	7 (4%)	62 (10%)
Type of conditioning			
Chemotherapy-based	381 (85%)	69 (39%)	450 (66%)
TBI-based	68 (15%)	109 (61%)	177 (34%)
Unknown	10	3	13
Source of stem cells			
Bone marrow	240 (52%)	106 (59%)	346 (54%)
Peripheral blood	219 (48%)	75 (41%)	294 (46%)
Ex vivo T-depletion			
No	431 (99%)	173 (98%)	604 (99%)
Yes	4 (1%)	3 (2%)	7 (1%)

<sup>a</sup>Details on conditioning were available in 31% of patients among whom 54% received TBI-based regimen while 46%, busulfan-based one

<sup>b</sup>Details on conditioning were available in 54% of patients among whom 84% received fludarabine-based regimen while 16%, TBI-based one



**Fig. 1** Outcome of acute leukemia patients treated with MRD-HSCT in CR1 in Eastern Europe between 1990 and 2006

### Statistical analysis

The following factors were analyzed for their prognostic value on each of the outcomes: year of MRD-HSCT, the diagnosis, interval from diagnosis to MRD-HSCT, recipient and donor characteristics (age, sex), and transplantation procedure (regimen intensity, use of TBI, stem cell source).

The probabilities of leukemia-free survival (LFS), relapse incidence (RI), and nonrelapse mortality (NRM) were the primary study endpoints. The LFS was defined as time interval from MRD-HSCT to either relapse or death in remission and was 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 [14, 15]. Univariate analyses were done with the use of log-rank test for LFS while Grey's test was applied for RI and NRM. Continuous variables were first categorized to divide the study group in five equal cohorts. Based on results of initial analysis, the final cutoff points were selected to be used in multivariate models. All potential prognostic factors with a  $p$  value less than 0.20 in univariate analyses were included in the Cox proportional hazard model, together with year of transplantation, diagnosis, and recipient age.

Additional study endpoints included engraftment and acute graft-versus-host disease (GVHD), which were reported as proportions, the probability of the overall survival (OS) estimated using the Kaplan-Meier method, and chronic graft-vs.-host, analyzed as cumulative incidence, relapse and death in remission being considered as competing. For the comparisons of transplant characteristics in various periods, Mann-Whitney  $U$  test and  $\chi^2$  test were used, as appropriate. All  $p$  values are two-sided with type 1 error rate fixed at 0.05. Statistical analyses were

performed with SPSS (Inc., Chicago) and S-Plus (Math-Soft, Inc, Seattle) software packages.

## Results

### Engraftment and GVHD

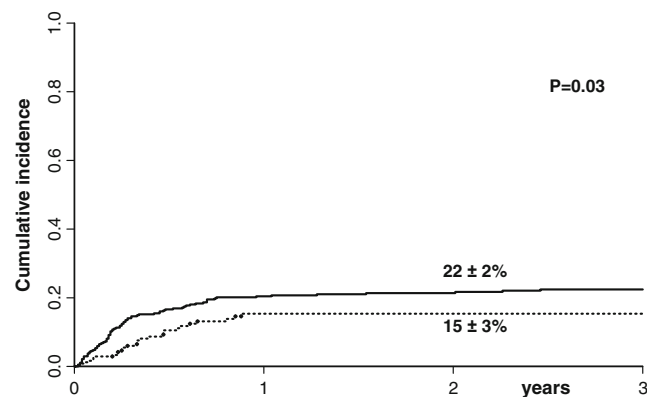
Six hundred thirteen out of 632 evaluable patients (97%) engrafted with the median time to neutrophil  $>0.5 \times 10^9/L$  recovery of 18 days (range, 5–60 days). The incidence of primary graft failure was 3% while secondary graft loss was diagnosed in 0.5% cases. One hundred fifty-seven out of 615 eligible patients (26%) experienced grade II–IV acute GVHD, whereas the 2-year probability of chronic GVHD was  $29 \pm 2\%$ .

### Nonrelapse mortality

With the median follow-up of 21 months (range, 1–157 months), the cumulative incidence of NRM was 19 (standard error (SE)  $\pm 2\%$ ; Fig. 1). For MRD-HSCT performed between years 1990 and 2002, the rates of NRM did not change significantly while the outcome for transplantations performed after 2002 improved in comparison with the preceding period ( $22 \pm 2\%$  vs.  $15 \pm 3\%$ ,  $p = 0.02$ ; Fig. 2). In a multivariate analysis, the only factors affecting the risk of NRM were the year of transplantation (HR=0.58 for MRD-HSCT performed after year 2002) and the recipient age  $\geq 40$  years (HR=1.48; Table 2).

### Relapse incidence

The cumulative incidence of RI was  $23 \pm 2\%$  for all patients (Fig. 1),  $22 \pm 3\%$  for AML, and  $25 \pm 3\%$  for ALL. No changes of RI rates were observed over time. In both



**Fig. 2** Cumulative incidence of Non Relapse Mortality (NRM) in patients receiving MRD-HSCT between 1990 and 2002 (solid line) or in 2003–2006 (dotted line)

univariate and multivariate analysis the use of peripheral blood resulted in increased risk of RI (HR=1.63) whereas female donor gender (HR=0.63), interval from diagnosis to MRD-HSCT $\geq$ 9 months (HR=0.44), and TBI-based conditioning (HR=0.52) were associated with reduced incidence of relapse (Table 2).

## Survival

The 2-year probabilities of OS and LFS for the whole group equaled 65 $\pm$ 2% and 58 $\pm$ 2%, respectively (Fig. 1). The LFS rates were 59 $\pm$ 3% for AML patients, and 55 $\pm$ 4% for ALL.

**Table 2** Factors affecting outcome after MRD-HSCT for acute leukemia in first complete remission

	Univariate analysis						Multivariate analysis						
	N	Leukemia-free survival		Relapse incidence		Nonrelapse mortality		Leukemia-free survival		Relapse incidence		Nonrelapse mortality	
		2-year KM	P value	2-year CI	P value	2-year CI	P value	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Patient age			.015		.15		.09		.03		NS		.045
<40 years	393	61 $\pm$ 3		21 $\pm$ 2		17 $\pm$ 2		1.0		–		1.0	
$\geq$ 40 years	247	53 $\pm$ 4		25 $\pm$ 3		22 $\pm$ 3		1.33 (0.97–1.03)		–		1.48 (1.01–2.16)	
Diagnosis			.45		.73		.73		.02		NS		NS
AML	459	59 $\pm$ 3		22 $\pm$ 3		18 $\pm$ 2		1.0		–		–	
ALL	181	55 $\pm$ 4		25 $\pm$ 3		20 $\pm$ 3		1.43 (1.05–1.96)		–		–	
Donor gender			.33		.016		.23		NS		.01		NS
Male	338	54 $\pm$ 3		28 $\pm$ 3		18 $\pm$ 2		–		1.0		–	
Female	294	62 $\pm$ 3		18 $\pm$ 3		20 $\pm$ 2		–		0.63 (0.43–0.9)		–	
Interval diagnosis-transplantation			.03		.0005		.48		.04		.003		NS
<9 months	501	56 $\pm$ 3		26 $\pm$ 2		19 $\pm$ 2		1.0		1.0		–	
$\geq$ 9 months	139	66 $\pm$ 4		13 $\pm$ 2		21 $\pm$ 3		0.69 (0.49–0.97)		0.44 (0.26–0.75)		–	
Conditioning intensity			.02		.005		.95						
Myeloablative	578	59 $\pm$ 2		22 $\pm$ 2		19 $\pm$ 2							
Reduced	62	44 $\pm$ 8		37 $\pm$ 7		19 $\pm$ 5							
Type of conditioning			.03		.03		.59		.007		.01		NS
Chemotherapy-based	450	55 $\pm$ 3		25 $\pm$ 2		19 $\pm$ 2		1.0		1.0		–	
TBI-based	171	63 $\pm$ 4		18 $\pm$ 3		19 $\pm$ 3		0.64 (0.46–0.88)		0.52 (0.31–0.86)		–	
Source of stem cells			.015		.0008		.59		.01		.01		NS
Bone marrow	346	63 $\pm$ 3		17 $\pm$ 3		20 $\pm$ 3		1.0		1.0		–	
Peripheral blood	294	51 $\pm$ 3		30 $\pm$ 3		19 $\pm$ 2		1.33 (1.01–1.79)		1.63 (1.11–2.41)		–	
Year of transplantation			.49		.21		.02		.045		NS		.02
<2003	377	57 $\pm$ 3		22 $\pm$ 2		22 $\pm$ 2		1.0		–		1.0	
$\geq$ 2003	263	60 $\pm$ 4		24 $\pm$ 3		15 $\pm$ 3		0.71 (0.52–1)		–		0.58 (0.36–0.93)	

KM Kaplan–Meier estimate, CI cumulative incidence, HR hazard ratio

Results are presented as percent $\pm$ standard error

Although the probabilities of LFS did not change markedly over time, in a multivariate model adjusted for other potential prognostic factors, the risk of failure for transplantations performed after 2002 was significantly reduced in comparison with the preceding period (HR=0.71; Table 2). As shown in Table 3, patients treated with MRD-HSCT between 2003 and 2006 were characterized by higher age, shorter interval from diagnosis to transplantation as well as more frequent use of PBSCT and reduced intensity regimens, compared to years 1990–2002.

In the whole study group, independently from the year of transplantation, the probability of LFS was adversely affected by the recipient age  $\geq 40$  years (HR=1.33), the diagnosis of ALL (HR=1.32) and the use of peripheral blood as a source of stem cells (HR=1.33), while the use of TBI (HR=0.64) and longer interval from diagnosis to transplantation (HR=0.69) were associated with better outcome (Table 2).

The univariate analysis revealed that the probability of LFS was significantly lower for patients treated with reduced-intensity regimens (RIC) compared to myeloablative conditioning (MAC;  $44\pm 8\%$  vs.  $59\pm 2\%$ ,  $p=0.02$ ), which resulted from increased RI ( $37\pm 2\%$  vs.  $22\pm 8\%$ ,  $p=0.02$ ). As all RIC transplantations were performed with the use of peripheral blood stem cells, the conditioning intensity and stem cell source could not be included together in the Cox model. However, in a subgroup analysis restricted to PBSCT, no significant difference could be demonstrated for RIC compared to MAC. Therefore, in contrast to stem cells source, the regimen intensity has not been considered for multivariate analyzes.

The effect of stem cell source was further analyzed in subgroups defined by the diagnosis as well as with restriction to MAC transplantations only. For AML patients receiving myeloablative conditioning the probability of LFS was higher after BMT compared to PBSCT ( $66\pm 3\%$  vs.  $54\pm 5\%$ ,  $p=0.025$ ), which was mainly a consequence of reduced RI ( $16\pm 3\%$  vs.  $27\pm 4\%$ ,  $p=0.01$ ). In contrast, in a cohort of ALL, no significant influence on outcome could be demonstrated for the stem cell source. The comparison of patients receiving BMT and PBSCT revealed that the use of peripheral blood was associated with significantly increased recipient age [41 years (range, 16–69 years) vs. 31 (16–58),  $p<0.0001$ ], and shorter interval from diagnosis to MRD-HSCT [200 days (range, 75–933 days) vs 178 (range, 50–798),  $p<0.0001$ ]. The association of source of stem cell was studied before 2003 and in years 2003–2006. Before 2003, LFS was  $45\pm 5\%$  for patients receiving PBSCT compared to  $63\pm 3\%$  for those receiving BMT ( $p=0.002$ ), while in the later period, LFS was  $59\pm 5\%$  and  $63\pm 8\%$ , respectively ( $p=0.52$ ).

The effect of conditioning regimen on outcome was observed for both AML and ALL subgroups. In AML patients, the use of TBI-based conditioning resulted in decreased incidence of NRM as compared to chemotherapy alone ( $11\pm 4\%$  vs.  $20\pm 2\%$ ,  $p=0.04$ ), which translated into higher LFS ( $70\pm 6\%$  vs.  $57\pm 3\%$ ,  $p=0.01$ ). ALL patients treated with TBI experienced significantly less relapses as compared to chemotherapy-based regimens ( $18\pm 4\%$  vs.  $34\pm 6\%$ ,  $p=0.009$ ), although the impact of conditioning on LFS was not significant.

**Table 3** Comparison of MRD-HSCT performed between 1990–2002 and 2003–2006

Year of transplantation	1990–2002	2003–2006	P value
N	377	263	
Median patient age, range (years)	33 (16–69)	38 (16–61)	.0003
Median interval from diagnosis to transplantation, range (days)	192 (62–933)	188 (50–601)	.007
Diagnosis			.95
AML	270 (72%)	189 (72%)	
ALL	107 (28%)	74 (28%)	
Conditioning intensity			<.0001
Myeloablative	354 (94%)	224 (85%)	
Reduced	23 (6%)	39 (15%)	
Type of conditioning			.85
Chemotherapy-based	263 (72%)	187 (71%)	
TBI-based	101 (28%)	75 (29%)	
Unknown	12	1	
Source of stem cells			<.0001
Bone marrow	262 (69%)	84 (32%)	
Peripheral blood	115 (31%)	179 (68%)	

## Discussion

The outcome of patients treated with MRD-HSCT depends on a number of factors associated with the recipient, donor, and graft characteristics making direct comparisons between various study populations difficult. It may be hypothesized that in the early period transplant centers tend to select patients with favorable characteristics and low risk of NRM. With growing experience and increasing number of transplantations, this preselection should become less evident. In our study group including 640 MRD-HSCT performed in Eastern Europe for CR1 acute leukemia patients, between 1990 and 2006, 41% of procedures were done within last 4 years of this period, which reflects growing transplant activity in the region. The procedure characteristics have been changing with increasing recipient age, shorter interval from diagnosis to HSCT, and more frequent use of RIC and PBSCT between 2003 and 2006. Despite these features, which in multivariate models were found to adversely affect outcome, the 2-year probability of LFS increased and reached the level of 60%. The major improvement was observed in terms of the NRM, which in recent years decreased to 15%. Reasons of this phenomenon may only be a subject of speculation, but probably better control of infections and GVHD should be considered. On the other hand, it may be speculated that in recent years, transplant centers preferred to use conditioning regimens with partially reduced intensity not fulfilling, however, the arbitrary criteria of RIC. Unfortunately, in this registry-based analysis, we were unable to evaluate this factor in the multivariate models due to insufficient data.

Our findings regarding NRM are of particular importance as high mortality rates have been raised a major counterargument to use MRD-HSCT in frontline therapy of adults with acute leukemia, especially in ALL. In a recently published study on a large population of patients, Goldstone *et al.* failed to demonstrate advantage of MRD-HSCT over conventional-dose chemotherapy in a setting of high-risk ALL; however, the 2 years NRM rate for patients having an HLA-identical sibling was as high as 36% [3]. In the largest so far retrospective analysis including 2234 AML and ALL patients treated with MRD-HSCT in CR1 between 1994 and 2000, the NRM rate equaled 23% [16]. With all the limitations regarding potential selection bias, the results obtained in Eastern Europe seem encouraging. As analyses similar to our one have not been published in recent years, it may only be speculated that our findings reflect a global trend for reduction of NRM in acute leukemia patients. From the reasons given before, confirmation of such a trend seems essential to facilitate treatment decisions in this group of patients.

The univariate and multivariate analysis of prognostic factors revealed several unexpected findings. In particular,

the effects of stem cell source and type of conditioning appear intriguing. Comparison of bone marrow and peripheral blood MRD-HSCT was a subject of several randomized studies, all including heterogeneous populations with regard to both the diagnosis and the disease status at transplantation [17–22]. Recently updated results of the IBMTR/EBMT study revealed that for CR1 acute leukemia patients both sources of stem cells are equivalent with regard to all LFS, RI, and NRM [23]. In a metaanalysis performed for nine randomized trials, no difference was found for early stage leukemia, while patients with advanced AML benefited from the use of PBSCT [24]. On the other hand, in a retrospective study, based on the EBMT registry, Ringden *et al.* demonstrated higher RI for ALL CR1 patients receiving PBSCT compared to BMT, whereas no differences were found for AML [16]. In our study, the use PBSCT adversely affected LFS as a consequence of increased RI, which however, was observed only before 2003 and not in more recent period. Reliable interpretation of our results would require more detailed information on disease-related risk factors, particularly cytogenetic and molecular features that were unavailable in the current analysis.

TBI-based conditioning is widely accepted for ALL patients undergoing MRD-HSCT although until now, there is no direct evidence for its advantage over chemotherapy-based regimens [25]. In case of AML, the issue is even more controversial as some studies demonstrated better LFS after TBI compared to busulfan in combination with cyclophosphamide, while in other ones, such effect could not be confirmed [26–28]. A long-term follow-up of four randomized trials revealed a tendency for increased LFS and OS after TBI-based compared to busulfan-based conditioning [29]. In our analysis, the use of TBI was associated with improved LFS. In a cohort of ALL, TBI-based conditioning resulted in decreased risk of relapse, while in AML, with reduced NRM. These findings seem to support the use of TBI in acute leukemia patients, which, however, should be interpreted with caution taking into account the retrospective nature of our study.

We conclude that results of MRD-HSCT for acute leukemia in Eastern Europe improved over time, as a consequence of decreased NRM, despite increasing recipient age. Our results should enhance extended use of this procedure to be offered to a larger number of acute leukemia patients. This is of particular importance in countries where the transplant program is still in the early phase of development, as a consequence of insufficient financial support or unfavorable regulations. Further analyses are required to determine association of MRD-HSCT outcome with country- and center-specific socioeconomic factors.



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