Association of Human Development Index with rates and outcomes of hematopoietic stem cell transplantation for patients with acute leukemia

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Human Development Index (HDI) is used by the United Nations Organization to measure socioeconomic achievements of countries. We evaluated the association of HDI with rates and outcomes of hematopoietic stem cell transplantation (HSCT) for patients with acute leukemia. For the analysis of HSCT rates, all adults with acute leukemia (n = 16 403) treated in 30 European countries, between 2001 and 2005, were included. Association of HDI with the outcome was analyzed for 2015 patients with acute myeloid leukemia treated with myeloablative allotransplantation. Countries were classified according to HDI quintiles. Highly significant correlation was found for HDI and the total number of HSCT per population (R = 0.78; *P* < .001), as well as separately for sibling HSCT (R = 0.84; *P* < .001), unrelated HSCT (R = 0.66; *P* < .001), and autologous HSCT (R = 0.43; *P* = .02). The probabilities of leukemia-free survival for 5 consecutive groups of countries with increasing HDI were: 56%, 59%, 63%, 58%, and 68% (*P* = .01). In a multivariate analysis, transplantations performed in countries belonging to the upper HDI category were associated with higher leukemia-free survival compared with the remaining ones (HR = 1.36, *P* = .008), which resulted mainly from reduced risk of relapse (HR = 0.72, *P* = .04). We conclude that, in Europe, the HDI is associated with both rates and results of HSCT for acute leukemia. (*Blood*. 2010; 116(1):122-128)

Introduction

Hematopoietic stem cell transplantation (HSCT) is a well-recognized method with documented curative potential for the treatment of patients with both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).[1,2] Therapeutic options include allogeneic (allo-) and autologous (auto-) HSCT. Allo-HSCT may be performed from either human leukocyte antigen (HLA)-matched or mismatched, related or unrelated donors. HSCT is an expensive procedure, requiring well-organized and equipped transplantation units, advanced supportive care, and highly qualified medical and nursing staff. As life-threatening complications may appear late, adequate monitoring and treatment are necessary for many months to years after transplantation.[3] Therefore, it may be expected that the access to HSCT as well as outcome of the procedure may depend on socioeconomic factors varying among and within countries. Identification of these factors may be essential to rationalize national therapeutic strategies for patients with acute leukemia.

Several studies performed in either developing countries, such as Brazil, or those with high ethnic and demographic diversities, such as the United States or the United Kingdom, demonstrated the association of the socioeconomic status (SES) with the access to HSCT and mortality after transplantation.[4-9] In Europe, as demonstrated by Gratwohl et al, the distribution of transplantations varies strongly among countries, which, in major part, depends on economic conditions defined by the Gross National Income per capita.[10,11] On the other hand, it may be speculated that the background determining availability of HSCT may be more complex and may include socioeconomic factors other than Gross National Income. Furthermore, the impact of the SES on the results of transplantation has not been studied so far in Europe.

The Human Development Index (HDI) is commissioned by the United Nations Organization to evaluate a country's socioeconomic achievements in 3 basic aspects: longevity, knowledge, and standard of living.[12] Longevity is measured by life expectancy at birth and expressed as Life Expectancy Index (LEI). Knowledge is evaluated by a combination of adult literacy rate and the rate of enrollment to primary, secondary, and tertiary schools (Education Index [EI]). Standard of living is measured by the Gross Domestic Product per capita, purchasing power parity US dollars (Gross Domestic Product Index [GDPI]). According to the HDI, the

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countries may have a low (HDI < 0.500), intermediate (HDI $= 0.500$-0.799), or high (HDI ≥ 0.800) development status. Most of the European states belong to the latter category, but even then, there are variations. In this study, we hypothesized that all components used to calculate the HDI may contribute to the availability of HSCT and the treatment results. Hence, our goal was to evaluate the association between the HDI, LEI, EI, and GDPI, and the number of transplantations performed per population as well as early and long-term outcome of adult patients with acute de novo leukemia referred for HSCT.

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 printout of the entered data, cross-checking with the national registries, and on-site visits of selected teams.

Criteria of selection, patients, donors, and HSCT procedure

For the analysis of transplantation rates, inclusion criteria were as follows: (1) diagnosis of AML or ALL, (2) age more than or equal to 18 years, and (3) HSCT performed between 2001 and 2005 in one of 30 European countries (including Israel), reporting to the EBMT. Altogether, 16 403 patients treated with autologous (n = 4641), syngeneic (n = 69), or allogeneic (n = 11 693) HSCT were included.

The impact of socioeconomic factors on outcome, besides fulfilling the aforementioned criteria, was restricted to: (1) patients with de novo AML in first complete remission, (2) HSCT from HLA-identical sibling or from HLA-matched unrelated donor (the minimum donor-recipient compatibility criterion was based on HLA-A, -B, and –DR matching using serologic or low resolution molecular typing), (3) HSCT using bone marrow or peripheral blood as a source of stem cells (cord blood transplantations were excluded), (4) HSCTs with myeloablative conditioning (definition of myeloablative regimen was considered if busulfan was administered at the total dose of ≥ 8 mg/kg or total body irradiation was applied at ≥ 6 Gy), and (5) HSCT without ex vivo T-depletion. For this part of the study, data on 2015 patients were analyzed.

Detailed characteristics of patients, donors, and HSCT procedure are listed in Table 1.

Evaluation of the HDI

Data on the HDI, LEI, EI, and GDPI for European countries in 2001, 2002, 2003, 2004, and 2005 were collected from the Web site of the United Nations Organization.[13-17] For particular indices, mean values in the 5-year period were calculated. For the analysis of outcome, countries were ranked and categorized by quintiles to divide the whole group in cohorts with equivalent number of HSCT procedures. Mean values and results of categorization are presented in Table 2.

Statistical analysis

Correlations between LEI, EI, and GDPI and transplantation rates calculated per 1 million inhabitants were studied using the Pearson correlation coefficient. In the analysis of outcome, 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, with death in remission being treated as a competing event to relapse.[18,19] Univariate analyses were done with the use of log-rank test for LFS, whereas Gray test was applied for RI and NRM.

For the analysis of outcome, all countries were first categorized using the quintiles with increasing values of the SES indices. If the relative event rates (ratio of the observed number of events to the expected number of events in a category with the assumption of no variation across categories) in 2 or more adjacent categories were not substantially different, the categories were merged. If a linear trend was observed in the relative event rates, the variable was used as a continuous factor. Regarding HDI, only the fifth group (the highest HDI) differed from the other 4 categories, which therefore were merged. Multivariate analysis was performed with use of the Cox proportional hazard model, adjusted for the donor type (sibing vs

Table 1. Patients and donors: transplantation procedure

Characteristic	Value
Patients included in the analysis of transplantation rates	
N	16 403
Median patient age, y (range)	41.6 (18-78)
Median year of transplantation (range)	2003 (2001-2005)
Diagnosis	
AML	11 504 (70%)
ALL	4496 (27%)
Acute undifferentiated leukemia	84 (1%)
Acute biphenotypic leukemia	178 (1%)
Other/unknown	141 (1%)
Disease status at HSCT	
CR1	9216 (56%)
CR2	2611 (16%)
CR3 or more advanced	3379 (21%)
Unknown	1197 (7%)
Type of HSCT	
Autologous	4641 (28%)
Syngeneic	69 (0.4%)
Allogeneic	11 693 (71%)
HLA-identical sibling	6279
Matched other related	219
Matched unrelated	3366
Mismatched relative	578
Mismatched unrelated	1154
Other/unknown	97
Chronologic number of HSCT for these patients	
First	9216 (56%)
Second or subsequent	7187 (44%)
Patients included in the analysis of transplantation outcome	
N	2015
Median patient age, y (range)	40.1 (18-70)
Median year of transplantation (range)	2003 (2001-2005)
Donor/recipient sex	
Female/male	379 (19%)
Other combinations	1607 (80%)
Unknown	29 (1%)
Median interval from diagnosis to transplantation, d (range)	149 (40-673)
Donor type	
HLA-identical sibling	1583 (79%)
HLA-matched unrelated	432 (21%)
Type of conditioning	
Chemotherapy-based	972 (48%)
Total body irradiation-based	1040 (52%)
Unknown	3
Source of stem cells	
Bone marrow	696 (35%)
Peripheral blood	1310 (65%)
Bone marrow and peripheral blood	9

CR indicates complete remission.

Table 2. Classification of European countries according to the HDI, LEI, EI, and GDPI

Country	HDI	Country	LEI	Country	EI	Country	GDPI
Turkey	0.7534	Russia	0.6774	Turkey	0.8124	Turkey	0.6920
Romania	0.7922	Belarus	0.7316	Croatia	0.8658	Belarus	0.7020
Russia	0.7936	Turkey	0.7566	Romania	0.8910	Romania	0.7184
Belarus	0.7956	Romania	0.7704	Slovakia	0.9122	Bulgaria	0.7264
Bulgaria	0.8078	Estonia	0.7740	Bulgaria	0.9152	Russia	0.7524
Croatia	0.8370	Bulgaria	0.7810	Czech Republic	0.9252	Lithuania	0.7882
Lithuania	0.8474	Hungary	0.7898	Israel	0.9432	Poland	0.7926
Slovakia	0.8492	Lithuania	0.7904	Italy	0.9456	Estonia	0.8124
Estonia	0.8514	Slovakia	0.8142	Russia	0.9492	Croatia	0.8126
Poland	0.8562	Poland	0.8212	Hungary	0.9496	Slovakia	0.8212
Hungary	0.8580	Croatia	0.8298	Belarus	0.9512	Hungary	0.8352
Czech Republic	0.8758	Czech Republic	0.8418	Switzerland	0.9512	Czech Republic	0.8578
Portugal	0.8996	Slovenia	0.8588	Poland	0.9542	Portugal	0.8756
Slovenia	0.9014	Portugal	0.8638	Germany	0.9566	Slovenia	0.8804
Greece	0.9106	Denmark	0.8682	Greece	0.9580	Greece	0.8840
Israel	0.9174	Ireland	0.8740	Portugal	0.9590	Israel	0.8974
Germany	0.9286	Finland	0.8876	Lithuania	0.9610	Spain	0.9090
Italy	0.9302	United Kingdom	0.8880	Austria	0.9632	Germany	0.9238
Spain	0.9310	Greece	0.8916	Slovenia	0.9668	Italy	0.9348
France	0.9378	The Netherlands	0.8928	France	0.9684	France	0.9368
Austria	0.9382	Germany	0.8944	Estonia	0.9696	Sweden	0.9390
United Kingdom	0.9382	Austria	0.8974	Ireland	0.9746	Finland	0.9408
Denmark	0.9390	Belgium	0.8974	Spain	0.9754	United Kingdom	0.9438
Sweden	0.9404	Norway	0.9066	United Kingdom	0.9820	Belgium	0.9446
Finland	0.9410	France	0.9078	Belgium	0.9854	Austria	0.9522
Belgium	0.9430	Italy	0.9084	Sweden	0.9856	The Netherlands	0.9532
Switzerland	0.9434	Spain	0.9090	Denmark	0.9886	Switzerland	0.9602
Ireland	0.9454	Israel	0.9102	The Netherlands	0.9896	Denmark	0.9606
The Netherlands	0.9476	Sweden	0.9190	Norway	0.9902	Norway	0.9840
Norway	0.9592	Switzerland	0.9196	Finland	0.9906	Ireland	0.9848

Values for particular indices are calculated as means for the period 2001 to 2005.[13-17]

unrelated), recipient age (less than vs more than or equal to median), year of transplantation (before 2003 vs 2003 or later), type of conditioning (total body irradiation-based vs chemotherapy-based), the interval from diagnosis to HSCT (less than vs more than or equal to median), and the source of stem cells (peripheral blood vs bone marrow). The median follow-up for survivors was 36 months (range, 0.1-91 months).

All *P* values are 2-sided with type 1 error rate fixed at .05. Statistical analyses were performed with SPSS Version 15.0 and S-Plus Version 6.1 (MathSoft Inc) software packages.

Results

Association of HDI, LEI, EI, and GDPI with HSCT rates

The total number of transplantations calculated per 1 million inhabitants correlated with the HDI (correlation coefficient, R = 0.78; $P < .001$). When subindices were analyzed separately, the strongest associations were found for HSCT rates with LEI (R = 0.84, $P < .001$) and GDPI (0.77, $P < .001$), and only marginal significance was observed in case of EI (R = 0.39, $P = .03$; Table 3). Similar patterns of correlations were observed in an analysis restricted to sibling HSCT and unrelated HSCT. For the rates of auto-HSCT, the correlation coefficients with the HDI, LEI, and GDPI were lower, but statistically significant, whereas no correlation was found with the EI (Table 3).

Association of HDI, LEI, EI, and GDPI with leukemia-free survival

The association of the SES with outcome was analyzed for patients with AML treated with HLA-matched related or unrelated HSCT in first complete remission. The probabilities of LFS at 3 years for the 5 consecutive groups of countries with increasing HDI were as follows: 56% plus or minus 3%, 59% plus or minus 2%, 63% plus or minus 3%, 58% plus or minus 4%, and 68% plus or minus 3% ($P = .01$; Table 4; Figure 1). In a multivariate analysis, transplantations performed in countries belonging to the upper HDI category were associated with significantly higher LFS compared with the remaining ones (HR = 1.36, $P = .008$; Table 5). In a univariate analysis, significant differences were also found for the

Table 3. Correlations of transplantation rates with the HDI, LEI, EI, and GDPI

	HDI		LEI		EI		GDPI	
	R	*P*	R	*P*	R	*P*	R	*P*
All transplantations	0.78	< .001	0.84	< .001	0.39	.03	0.77	< .001
Allogeneic sibling	0.84	< .001	0.85	< .001	0.47	.01	0.83	< .001
Allogeneic unrelated	0.66	< .001	0.63	< .001	0.43	.02	0.66	< .001
Autologous	0.43	.02	.55	.001	.09	.62	.41	.02

R indicates Pearson correlation coefficient.

Table 4. Univariate effects of the HDI, LEI, EI, and GDPI on results of HLA-matched allo-HSCT for adults with AML in first complete remission

	LFS		RI		NRM		NRM	
	3-year KM	*P*	3-year CI	*P*	3-year CI	*P*	100-day CI	*P*
HDI		.01		.03		.2		.74
First quintile	56 ± 3		28 ± 3		22 ± 3		7 ± 1	
Second quintile	59 ± 2		27 ± 2		19 ± 2		6 ± 1	
Third quintile	63 ± 3		23 ± 3		18 ± 2		9 ± 1	
Fourth quintile	58 ± 4		27 ± 4		20 ± 3		8 ± 2	
Fifth quintile	68 ± 3		19 ± 3		16 ± 2		5 ± 1	
LEI		.89		.64		.5		.64
First quintile	63 ± 3		24 ± 3		19 ± 2		5 ± 1	
Second quintile	58 ± 4		26 ± 4		21 ± 3		8 ± 2	
Third quintile	59 ± 2		24 ± 2		21 ± 2		8 ± 1	
Fourth quintile	65 ± 3		22 ± 3		16 ± 2		5 ± 1	
Fifth quintile	59 ± 4		29 ± 4		16 ± 3		7 ± 2	
EI		.24		.26		.61		.92
First quintile	61 ± 2		24 ± 2		19 ± 2		6 ± 1	
Second quintile	55 ± 2		30 ± 2		21 ± 2		7 ± 1	
Third quintile	63 ± 3		22 ± 2		18 ± 2		8 ± 1	
Fourth quintile	55 ± 5		33 ± 5		18 ± 4		6 ± 2	
Fifth quintile	64 ± 3		20 ± 2		19 ± 2		6 ± 1	
GDPI		.001		.005		.09		.63
First quintile	57 ± 3		29 ± 3		20 ± 3		7 ± 1	
Second quintile	54 ± 3		32 ± 3		22 ± 2		7 ± 1	
Third quintile	65 ± 3		22 ± 3		16 ± 2		5 ± 1	
Fourth quintile	65 ± 2		21 ± 2		17 ± 2		7 ± 1	
Fifth quintile	63 ± 3		21 ± 2		20 ± 2		7 ± 1	

Data are probability ± SE (percentage).
KM indicates Kaplan-Meier estimate; and CI, cumulative incidence.

categories of countries classified according to the GDPI (Table 4). The LFS rates with increasing GDPI were 57% plus or minus 3%, 54% plus or minus 3%, 66% plus or minus 3%, 65% plus or minus 2%, and 63% plus or minus 3% ($P = .001$). However, the independent impact of the GDPI status on the probability of LFS has not been confirmed in a multivariate model ($P = .09$; Table 5). Similarly, no significant associations were found for LFS in relation to LEI and EI.

Association of HDI, LEI, EI, and GDPI with NRM

The cumulative incidence of early transplantation-related mortality (up to day 100) for the 5 consecutive groups of countries with increasing HDI were as follows: 7% plus or minus 1%, 6% plus or minus 1%, 9% plus or minus 1%, 8% plus or minus 2%, and 5% plus or minus 1% ($P = .74$; Table 4). Accordingly, the overall NRM at 3 years equaled 22% plus or minus 3%, 19% plus or minus 2%, 18% plus or minus 2%, 20% plus or minus 3%, and 16% plus or minus 2% ($P = .2$; Table 4; Figure 1). In a multivariate model adjusted to other potential risk factors, there was a tendency for decreased risk of NRM in countries with the highest HDI; however, the effect did not reach statistical significance ($P = .1$; Table 5). As well, the impact on NRM could not be demonstrated for any of the analyzed subindices (Table 5).

Association of HDI, LEI, EI, and GDPI with relapse incidence

The cumulative incidence of relapse with significant difference for the upper HDI category compared with the remaining ones ($P = .03$; Table 4; Figure 1). In the Cox model, the mean HDI more than 0.9238 independently reduced the risk of relapse (hazard ratio, HR = 0.72; $P = .04$; Table 5). With regard to subindices contributing to the HDI, the univariate analysis revealed a lower incidence of relapse for the 3 upper classes as defined by the GDPI (a range of 21% ± 2% to 22% ± 3%) compared with the 2 lower GDPI categories (29% ± 3% and 32% ± 3%; Table 4). However, after adjustment to other prognostic factors, the effect of the GDPI more than 0.9238 lost its significance ($P = .16$; Table 5). The LEI and EI did not appear to be associated with the incidence of relapse.

Discussion

The impact of socioeconomic factors on the treatment of patents with acute leukemia was studied by several investigators. Factors, such as the parental educational level, father's occupation, ethnicity, and SES-related malnutrition, were found to be associated with survival of pediatric ALL patients in the Brazilian, North American, Australian, and Dutch populations.[20-27] With regard to adults with acute leukemia, the impact of the SES on survival was indirectly demonstrated by studies comparing patients treated between 1982 and 1996 in Estonia and Western Sweden, the 2 regions characterized by different political and economic systems, with similar ethnic and geographic background.[28,29] Swedish patients had a significantly higher chance of cure compared with their Estonian counterparts.[28,29] Fagundes et al, using the HDI to evaluate the SES of adults with AML in Brazil, showed the differences of outcome, which were in major part dependent on the compliance to chemotherapy protocol.[30]

Until now, few studies focused on the association of socioeconomic factors with HSCT. The analysis by Mitchell et al revealed that, in the United States, between 1988 and 1991, the access to HSCT was restricted for black compared with white patients, which resulted mainly from the differences in the insurance coverage.[9] In 2 subsequent studies, it was demonstrated that the American Hispanic patients with either acute or chronic leukemias

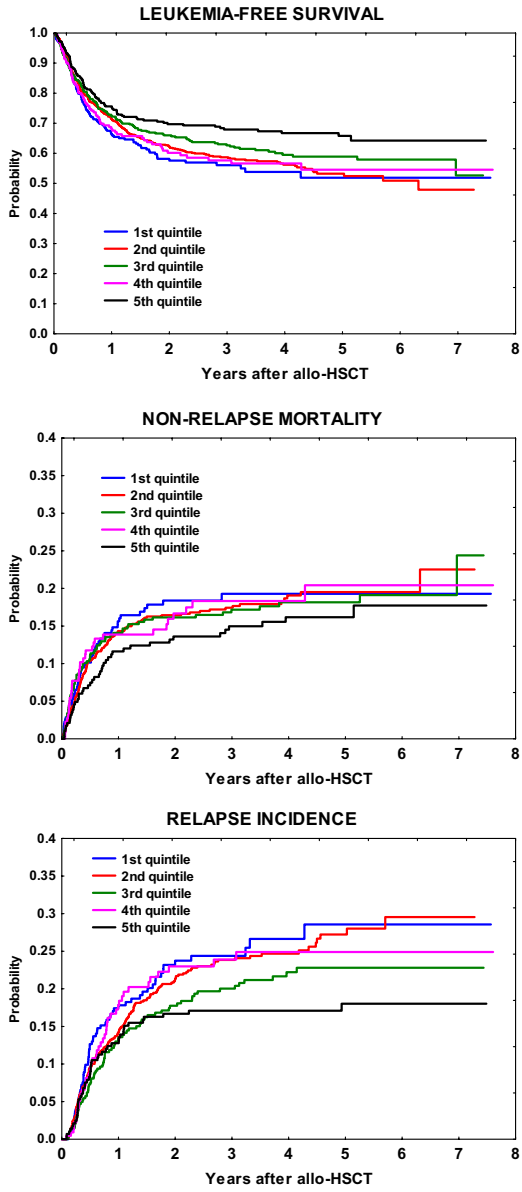

Figure 1. Results of HLA-matched allo-HSCT for adults with AML in first complete remission, according to the HDI. Countries were categorized by quintiles with increasing values of the HDI: first quintile indicates Belarus, Bulgaria, Croatia, Czech Republic, Estonia, Greece, Hungary, Israel, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, and Turkey (n = 349); second quintile, Germany and Italy (n = 748); third quintile, France and Spain (n = 412); fourth quintile, Austria and the United Kingdom (n = 220); and fifth quintile, Belgium, Denmark, Finland, Ireland, Norway, Sweden, Switzerland, and The Netherlands (n = 286).

treated with HSCT had lower survival rates compared with the whites, raising the need to further examine the role of social, economic, and cultural factors.[4,5] Indeed, Armenian et al showed that Hispanic Americans are less likely to self-report the presence of life-threatening chronic post-transplantation complications compared with non-Hispanic Americans, which was explained mainly by the differences in the educational status.[8] Similarly to the American studies, an adverse effect of ethnicity (black vs white patients) with regard to NRM was reported in the United Kingdom.[6] Finally, the negative impact of poor SES on outcome of HSCT has recently been demonstrated for patients treated in Brazil.[7]

In view of the so far published studies, it appears that both the availability and outcome of HSCT may depend on many factors related to the SES of patients with acute leukemia. In Europe, the social, economic, cultural, and ethnic diversity is less pronounced compared with other regions of the world, and the majority of countries are classified as well developed. Even then, however, the differences exist with regard to the standard of living, education, and organization of the healthcare, which may be reflected by variations in the GDPI, EI, LEI, and the composite HDI, all used in our study as surrogates of the SES.

As HSCT, especially allo-HSCT, is an expensive way of treatment, it could be thought that the access to this procedure is restricted mainly by the financial coverage available in particular countries, dependent on the national income. Indeed, in line with the finding of Gratwohl et al,[10,11] we demonstrated a strong correlation of HSCT rates with the GDPI. However, the effect was even stronger with regard to the LEI and could also be demonstrated for the EI. Hence, not only purely economic conditions, but probably also organization of the healthcare and education system, translates into the availability of HSCT. In addition, allo-HSCT is a very complex procedure that involves several professional skills (eg, hematology, internal medicine, radiotherapy, sophisticated laboratories), which probably depend on the HDI. As expected, the correlations of the HDI and subindices with the transplantation rates were more pronounced in the case of allo-HSCT, compared with auto-HSCT, reflecting substantial differences associated with the logistics and costs of the aforementioned procedures. Our analysis was based on the assumption that the incidence of acute leukemia does not vary substantially among countries and does not depend on the HDI. Although exact epidemiologic data from all countries were unavailable, some publications suggest no association of the SES with rates of leukemia in Europe.[31]

Results of our study indicate that in Europe the HDI is associated not only with the availability but also with results of transplantation. Studying HLA-matched, T-replete, myeloablative allo-HSCT for AML patients in first complete remission as a representative model with well-established indications and a quite homogeneous population, we showed that the probability of LFS was significantly increased for patients treated in 8 countries with the highest HDI, compared with the remaining 22 states where the results were super-imposable. Hence, our findings indicate that, apart from the transplantation rates, European countries with lower HDI (first quintile) may achieve comparable quality of treatment to those better-developed (second to fourth HDI quintile). On the other hand, it appears that, for the majority of European states, there is still room for improvement to reach the outcomes achieved by the highest-HDI states. Identification of specific factors contributing to these differences seems essential.

Allo-HSCT raises a lot of requirements related to the adequate donor selection, standard of hospitalization, intensive and expensive supportive therapy, and highly specialized medical monitoring for a long period after transplantation. The reasons of failure are leukemia relapse as well as early and late complications, including graft-versus-host disease and infections. Whereas early mortality may vary according to the standard of hospital care, late events depend in major part on the patients' behavior during their stay at home. Hence, exposure to infectious agents, awareness of possible complications, and easy access to specialized medical staff are all of importance. Our analysis showed only a tendency for the association of the HDI with the overall NRM. No difference could be demonstrated at day 100. Based on these findings, we can speculate that the quality of medical care during the hospital stay is equivalent across Europe.

In contrast to the NRM, the effect of HDI on the risk of relapse could be demonstrated in both univariate and multivariate analyses,

Table 5. Results of the multivariate analysis of factors affecting outcome of HLA-matched allo-HSCT for adults with AML in first complete remission

	LFS		RI		NRM	
Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Donor type (URD vs sibling)	0.62 (0.53-0.74)	< .001	1.61 (1.28-2.04)	< .001	1.59 (1.23-2.04)	< .001
Conditioning (TBI vs Cht)	1.2 (1.03-1.4)	.02	0.74 (0.6-0.9)	.003	0.96 (0.77-1.2)	.76
Year of HSCT (2003 or earlier vs later than 2003)	1.13 (0.96-1.33)	.14	0.98 (0.78-1.22)	.87	0.79 (0.62-1)	.05
Patient age (≥ 40 vs < 40 y)	0.75 (0.64-0.87)	< .001	1.1 (0.89-1.33)	.38	1.72 (1.37-2.17)	< .001
Interval of diagnosis HSCT (≥ 5 vs < 5 mo)	1.04 (0.89-1.21)	.66	0.8 (0.65-0.98)	.035	1.2 (0.96-1.52)	.11
Source of stem cells (PB vs BM)	0.83 (0.7-0.97)	.02	1.3 (1.04-1.64)	.02	1.1 (0.86-1.39)	.44
HDI (> 0.9382 vs ≤ 0.9382)	1.36 (1.08-1.71)	.008	0.72 (0.53-0.99)	.04	0.76 (0.54-1.05)	.1
GDPI (> 0.9382 vs ≤ 0.9382)	1.15 (0.98-1.35)	.09	0.85 (0.69-1.06)	.16	0.88 (0.7-1.14)	.34

HDI and GDPI were analyzed separately because of internal correlation. Values for other prognostic factors are presented for the models, including HDI. The entire models, including GDPI, have not been shown.

HR indicates hazard ratio; CI, confidence interval; URD, unrelated donor; TBI, total body irradiation; Cht, chemotherapy-based conditioning; HSCT, hematopoietic stem cell transplantation; PB, peripheral blood; and BM, bone marrow.

with decreased RI in countries with the highest HDI. The risk of relapse may depend on the disease biologic features, quality of preceding induction-consolidation chemotherapy, and the transplantation procedure itself. To explore the possible reasons of our findings, we compared the patient and HSCT characteristics for countries belonging to the upper HDI category with the remaining ones (Table 6). We found that better results in countries with the highest HDI were achieved despite increased recipient age. Similarly, the interval from diagnosis to HSCT was decreased in these countries, whereas in the Cox model prolonged interval diagnosis HSCT was associated with reduced risk of relapse. The fact that results in countries with the highest HDI are improved across this factor may indicate higher efficacy of the induction-consolidation regimens or better compliance to chemotherapy protocol, in particular higher density of chemotherapy courses. The intensity of initial chemotherapy and the duration of the total induction and consolidation program may influence the quality of remission at the time of allo-HSCT and translate into improved long-term outcome. Finally, total body irradiation-based conditioning was more frequently used in countries with the highest HDI compared with the remaining ones. However, because the advantageous effect of total body irradiation has been independently confirmed in a multivariate model, it cannot explain the impact of HDI on RI.

Trying to identify specific aspects of the SES that contribute to the effect of HDI on results of allo-HSCT, we analyzed separately the potential influence of the LEI, EI, and GDPI. Although results of a univariate analysis suggested the association of GDPI with all LFS, RI, and NRM, results of the multivariate analysis did not confirm it. As well, no significant effect could be demonstrated for the LEI and EI. Therefore, it appears that the impact of SES on results of allo-HSCT is multifactorial and that the HDI as a composite index may be representative.

Altogether, results of our study indicate that the HDI, being a surrogate of the SES, is associated with the rates of all types of HSCT in Europe, as well as the outcome of patients with AML treated with allo-HSCT. However, the positive effect on results is observed only with regard to few countries with particularly high HDI, whereas the outcome in the remaining ones is comparable. Some limitations of our study should, however, be emphasized. Because of its retrospective nature, some important information was lacking, including data on cytogenetic and molecular risk factors, details on induction, and consolidation protocols, reasons of NRM. Therefore, there is need for further prospective studies with detailed patient and procedure characteristics. In addition, future investigation should take into account particular aspects of the SES, including organization of the health system, allocation of transplantation centers, as well as environmental factors, which differ among countries and regions. Identification of detailed relationships between socioeconomic factors and results of allo-HSCT may indicate areas for future improvement.

Authorship

Contribution: S.G. designed and performed research, interpreted data, and prepared the manuscript; M.L. analyzed data and interpreted results; G.E., D. Beelen, D. Blaise, A.G., A.B., T.C., and

Table 6. Comparison of patient and transplantation characteristics in countries with the highest values of the HDI and the remaining countries

Characteristic	**HDI ≤ 0.9382**	**HDI > 0.9382**	***P***
N	1729	286	
Median patient age, y (range)	39.6 (18-70)	42.6 (18-60)	< .001
Recipient sex, male/female	50.3%/49.7%	50.7%/49.3%	.62
Donor sex, male/female	57.6%/42.4%	56%/44%	.62
Median WBC at diagnosis, $\times 10^9$/L (range)	15 (0.5-676)	12.5 (0.5-304)	.14
Median interval from diagnosis to CR1, d (range)	46 (10-287)	40 (19-153	.03
Median interval from CR1 to transplantation, d (range)	88 (20-658)	82 (20-239)	.12
Median interval from diagnosis to transplantation, d (range)	151 (40-699)	140 (71-673)	.008
Donor type, sibling/unrelated	78.5%/21.5%	78.7%/21.3%	.96
TBI-based conditioning	50.1%	61.5%	< .001
Peripheral blood as a source of stem cells	65.2%	67.1%	.52

WBC indicates white blood cell; CR1, first complete remission; and TBI, total body irradiation.

J.H. collected and provided data; E.M.F., E.N., and F.F. interpreted data and reviewed manuscript; and V.R. designed research, interpreted data, and reviewed manuscript.

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