Multivariate Cox analysis showed that allo-PBSCT was a significant factor for higher NRM in the standard-risk (aHR = 2.30; 95% CI 1.08–4.88; $P = 0.030$), but not in the high-risk (aHR = 1.29; 95% CI 0.65–2.54; $P = 0.468$).

3.3.5 *Relapse*

The cumulative incidence of relapse at 1 year for the standard-risk group was similar for allo-PBSCT (13.8%; 95% CI 8.9–21.0) and allo-BMT (9.7%; 95% CI 6.1–15.2) ($P = 0.518$ by stratified logrank test). Similarly, in the high-risk group the incidence was 32.4% (95% CI 25.6–40.3) for allo-PBSCT and 31.5% (95% CI 23.7–41.1) for allo-BMT ($P = 0.200$) (Fig. 5).

Multivariate Cox analysis showed no significant difference in the risk of relapse after allo-PBSCT and allo-BMT either in the standard-risk group or in the high-risk group (aHR = 1.17; 95% CI 0.55–2.52; $P = 0.684$ and aHR = 0.81; 95% CI 0.52–1.28; $P = 0.370$, respectively).

4 Discussion

In the present study, we analyzed results for 707 patients who underwent myeloablative HSCT for leukemia from HLA-identical sibling donors between 2000 and 2005. These data were obtained from the JSHCT registry. Health insurance coverage of allo-PBSCT was approved in Japan in 2000, and since then the number of allo-PBSCTs rapidly increased and exceeded the number of allo-BMTs between 2000 and 2003. Subsequently, the number of allo-PBSCTs decreased, and the numbers of allo-PBSCTs and allo-BMTs became equivalent in 2005. Thus, this analysis indicates the rather immature status of allo-PBSCT in Japan.

The Stem Cell Trialists' Collaborative Group [27] reported an individual patient data meta-analysis of nine randomized trials by comparing outcomes of allo-PBSCT versus allo-BMT from HLA-matched related donors for the treatment of hematologic malignancies. Allo-PBSCT was associated with a higher probability of 5-year OS in the subset analysis of patients with late disease due to decreased relapse. International Bone Marrow Transplant registry/European Group for Blood and Marrow Transplantation (IBMTR/EBMT) registry data of 398 adult allo-BMT and 208 allo-PBSCT patients with leukemia were analyzed using information on 6 or more years of follow-up [28]. OS in patients with early and advanced leukemia did not differ significantly between the two groups. The IBMTR report comparing outcomes after allo-PBSCT and allo-BMT for acute leukemia in children and adolescents showed that OS was lower after allo-PBSCT [29]. These controversial data indicate that the difference in stem cell source can affect OS depending on the underlying disease, disease status, and the patients' age.

In our study, OS was lower after allo-PBSCT than after allo-BMT in the standard-risk patients, but not in the high-risk patients. Considering the difference in stem cell source, factors affecting OS include hematopoietic and

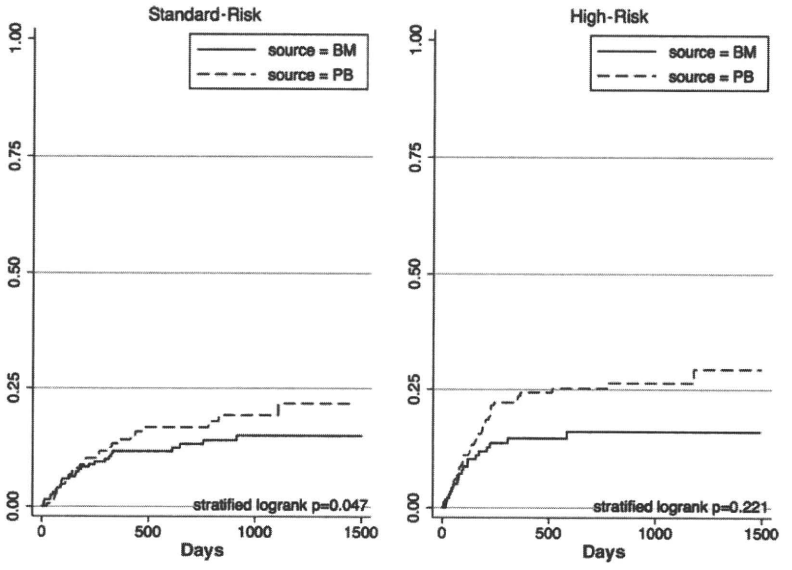

Fig. 4 Cumulative incidences of non-relapse mortality (NRM) after peripheral blood stem cell transplantation compared with bone marrow transplantation. Standard-risk diseases included acute leukemia in first complete remission and chronic myelogenous leukemia in first chronic phase. Other diseases were categorized as high-risk diseases

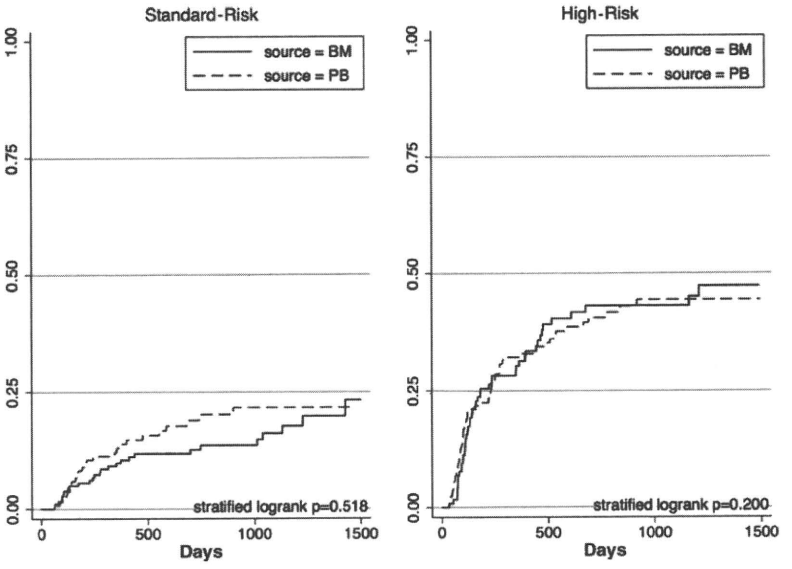

Fig. 5 Cumulative incidences of relapse after peripheral blood stem cell transplantation compared with bone marrow transplantation. Standard-risk diseases included acute leukemia in first complete remission and chronic myelogenous leukemia in first chronic phase. Other diseases were categorized as high-risk diseases

immune recovery, acute and chronic GVHD, and graft-versus-leukemia (GVL) effect or relapse [30].

In our analysis, allo-PBSCT was associated with more rapid hematopoietic recovery than allo-BMT as has been shown in most previous studies [4, 5, 11, 31]. Most randomized trials demonstrated that neutrophil recovery generally occurs 5–7 days earlier after allo-PBSCT compared with allo-BMT without G-CSF post-transplant [27, 32]. The EBMT study reported by Schmitz et al. [5] showed that neutrophil recovery was achieved 3 days earlier after allo-PBSCT than after allo-BMT with G-CSF post-transplant, and transplantation-related mortality did not differ between allo-PBSCT and allo-BMT groups. In Japan, most allo-HSCT patients receive G-CSF post-transplant, and in our study neutrophil recovery was observed 2 days earlier after allo-PBSCT than after allo-BMT. Accordingly, infectious complications may not decrease after allo-PBSCT compared to allo-BMT.

With regard to acute GVHD, the meta-analysis showed that allo-PBSCT was associated with a significant increase in the development of grade III–IV acute GVHD, but not grade II–IV acute GVHD [27]. In the present analysis, allo-PBSCT was also a significant factor in the incidence of grade III–IV acute GVHD. The increased incidence of grade III–IV acute GVHD in allo-PBSCT would have a negative effect on OS [33].

Extensive chronic GVHD was more frequent after allo-PBSCT than after allo-BMT in our study. This finding is in line with those of previous reports [5, 9, 11, 19, 31, 34].

In our analysis, NRM was higher after allo-PBSCT in the standard-risk patients, but not in the high-risk patients. The higher NRM after allo-PBSCT in the standard-risk group was likely due to increased grade III–IV acute GVHD and extensive chronic GVHD. Increased NRM after allo-PBSCT has been reported from children and adolescents suffering with acute leukemia [29]. A higher risk of mortality due to acute and chronic GVHD may counteract any benefit of more rapid hematopoietic recovery in the early transplant period.

In the allo-BMT setting, the development of both acute and chronic GVHD is associated with decreased relapse of leukemia, whereas the effect of GVHD on OS appears to be different depending on the study population [33, 35, 36]. The meta-analysis showed that allo-PBSCT was associated with a significant decrease in relapse in both early and late-stage disease patients [27]. On the contrary, increased extensive chronic GVHD in the allo-PBSCT group did not lead to a decrease in relapse in our analysis. We do not have a good explanation for this, but a similar observation was reported from the IBMTR/EBMT [28] registry data of adult patients with leukemia and the IBMTR [29] study in children and adolescents with acute leukemia. The advantage in term of the GVL effect with the cost of increased GVHD after allo-PBSCT relative to after allo-BMT remains controversial [27–29]. The allogeneic GVL effect varies from one disease to another, with the stage of the disease, and with donor histocompatibility. The GVL effect is believed to act while the leukemic burden is relatively

low [37]. Thus, to investigate the relationship between GVHD and relapse, subgroups differing in underlying disease and disease status would be needed.

We used the propensity score method to minimize selection bias. However, retrospective analysis has limitations. We could not exclude the possibility of unidentified confounding variables affecting the transplant outcomes and the inability to adjust the data for unknown or unmeasured factors. For example, we did not have data regarding pre-transplant infectious complications. Since allo-PBSCT is associated with more rapid hematopoietic recovery than allo-BMT, patients with serious infectious problems may have a tendency to undergo allo-PBSCT rather than allo-BMT. In this analysis, standard-risk diseases included acute leukemia in first CR and CML in first CP, while high-risk diseases included other diseases [11]. However, even in first CR acute leukemia patients, cytogenetic and molecular markers affect the prognosis with respect to survival in the allo-HSCT setting [38, 39]. We cannot deny the possibility that higher-risk patients in first CR tended to undergo allo-PBSCT. Thus, the results presented here should be interpreted with caution. It is also important to realize that our analysis was based on matched sibling myeloablative HSCT not on non-myeloablative HSCT. However, contrary to the result of the meta-analysis [27], multivariate Cox analysis showed that the allo-PBSCT group was associated with a lower OS in the populations with standard-risk. Prospective randomized trials are necessary to elucidate the advantages and disadvantages of allo-PBSCT in comparison with allo-BMT from HLA-identical sibling donors for the treatment of adult Japanese patients with leukemia.

Conflict of interest statement The authors declare no financial conflict of interest.

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ORIGINAL ARTICLE

Rituximab in combination with CHOP chemotherapy for the treatment of diffuse large B cell lymphoma in Japan: a retrospective analysis of 1,057 cases from Kyushu Lymphoma Study Group

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Abstract We performed a retrospective analysis of patients with diffuse large B cell lymphoma treated with rituximab plus CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) as a first-line therapy at 22 hospitals of the Kyushu Lymphoma Study Group. During the period 1996–2005, 1,057 patients (aged 22–90 years) were analyzed. Of these, 678 were treated with CHOP, and 379 were treated with rituximab plus CHOP (R-CHOP). The complete response rate was 59.9% in the CHOP group and 67.0% in the R-CHOP group ($P < 0.001$). Three-year

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progression-free survival (PFS) and overall survival (OS) rates were significantly higher in the R-CHOP group than in the CHOP group (61.3 vs. 45.6% for PFS, $P < 0.001$; 68.3 vs. 54.5% for OS, $P < 0.001$). The International Prognostic Index was a good prognostic marker for both groups; a survival benefit of rituximab addition was found for each risk subgroup and also for both age groups ($\leq$60 and >60 years). Among 345 patients who received localized radiation therapy, the adding rituximab to CHOP attenuated the survival difference between CHOP and R-CHOP groups ($P = 0.104$), compared with no radiation group ($P < 0.001$). Results of this large-scale, multicenter study confirm that rituximab plus CHOP provided a greater survival benefit than CHOP alone.

Keywords DLBCL · Rituximab · CHOP · Radiation · Prognosis

1 Introduction

The incidence of non-Hodgkin lymphoma (NHL) has increased recently in Western countries [1] as well as in Japan [2]. According to a recent clinicopathologic investigation of malignant lymphoma in Japan, B cell NHL accounts for 74% of NHL cases, the major subtype being diffuse large B cell lymphoma (DLBCL) [3]. Aggressive NHL, represented by DLBCL, is considered a curable disease. However, the cure rate with standard chemotherapy alone is as low as 30–40% [4, 5]. Rituximab, a chimeric anti-CD20 monoclonal antibody, was originally studied in patients with relapsed and refractory follicular or low-grade NHL and has been clearly shown to prolong progression-free survival (PFS) and overall survival (OS) [6, 7]. Because CD20 is a pan-B cell antigen, rituximab exerts a cytotoxic effect on B cells via mechanisms such as antibody-dependent cytotoxicity, complement-dependent cytotoxicity [8], and downregulation of the anti-apoptotic protein Bcl-2 [9–11]. Therefore, rituximab has a potential application in various types of B cell NHL and continues to be assessed, alone and in combination with chemotherapy, in the management of patients with indolent and aggressive NHL [12, 13]. In particular, results of the European Groupe d'Etude des Lymphomes de l'Adulte LNH-98-5 study and the MabThera International Trial (MInT) (conducted in Europe, Australia, North America and Latin America) have confirmed that rituximab combined with the standard CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) therapy is associated with a significant improvement in OS compared with CHOP alone in previously untreated elderly patients (aged >60 years) and younger patients (aged $\leq$60 years) with DLBCL [12–14]. An intergroup study under the lead of the Eastern Cooperative Oncology Group (study E4494) confirmed these results [15]. The addition of rituximab to CHOP chemotherapy has been reported to have dramatically improved

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outcome compared with that of historical control DLBCL patients of all ages in British Columbia [16]. By several randomized studies, rituximab in combination with CHOP (R-CHOP) has become a new standard therapy for patients with DLBCL in exchange of CHOP. However, these encouraging reports have been limited to Western countries. The aim of the present study was to conduct a retrospective analysis of the effect of rituximab plus CHOP therapy in patients with DLBCL in Japan.

2 Materials and methods

2.1 Patient characteristics

A total of 1,057 patients with newly diagnosed DLBCL were treated at 22 hospitals during the period 1996–2005 and were evaluated by the Kyushu Lymphoma Study Group. The DLBCL patients (1,057 cases) were divided into 707 (66.9%) nodal lymphoma and 350 (33.1%) extranodal lymphoma. The original sites of extranodal lymphoma were stomach (30.9%), intestine (12.0%), bone marrow (10.6%), testis (6.9%), skin (5.4%), nasal cavity (4.3%), thyroid gland (4.0%), breast (3.4%), eyelid (2.3%), parotid gland (2.0%), uterus (1.4%), kidney (1.4%), pancreas (1.4%), adrenal gland (1.4%), urinary bladder (0.9%), lung (0.6%), and other sites (11.1%). Patients with primary mediastinal DLBCL or primary central nervous system lymphomas were excluded from this study. Institutional review board approval was obtained from all of the participating institutions. Clinical staging of DLBCL according to the Ann Arbor classification [17] was performed by physical examination, evaluation of bone marrow specimens, computed tomography of the neck, chest, abdomen, pelvis, and nuclear imaging with gallium scans. The following clinical and laboratory data were available at the time of diagnosis: age, sex, performance status, stage, number of extranodal sites involved, serum lactate dehydrogenase level, and the presence or absence of systemic "B" symptoms. On the basis of this information, International Prognostic Index (IPI) scores were determined for all subjects. Patients were categorized into a low-, low intermediate-, high intermediate-, or high-risk group. None of the patients had a known history of human immunodeficiency virus infection or other forms of immunodeficiency (Table 1) ("Appendix").

2.2 Diagnosis

Histologic sections were reviewed, and the diagnosis of DLBCL was confirmed according to the World Health Organization classification of hematopoietic tumors [19] by pathologists at each institute. To confirm the diagnosis, the sections were reviewed at the Department of Pathology, Kurume University School of Medicine.

2.3 Treatment

All patients received anthracyclin-based regimens. The majority of patients (91.7%) were treated with CHOP or THP-COP, and few patients (8.3%) treated CHOEP and MACOP-B with or without rituximab. All patients were treated with a CHOP-like regimen ± rituximab (CHOP group; $n = 678$, R-CHOP group; $n = 379$) as a first-line therapy during the period 1996–2005. The median follow-up period was 31.2 months in CHOP group. Starting in 2003, most patients were treated with rituximab combined with a CHOP-like regimen. These patients comprised the R-CHOP group. The median follow-up period for the R-CHOP group was 24 months. Patients received a median 6 cycles (range 3–9) of CHOP-like regimen. Rituximab was added at least 3 times. The dosage and schedule of rituximab in this study were 375 mg/m^2 every 3 weeks with standard CHOP. Patients who could not tolerate this standard dose of rituximab were excluded from the analysis.

Table 1 Patient and disease characteristics

Characteristic	Study population		
	Without rituximab ($n = 678$)	With rituximab ($n = 379$)	P value
Male (%)	53.20%	53.00%	n.s
Age (mean)	65.30	64.99	n.s
>60 year (%)	68.40%	67.80%	n.s
ECOG PS II–IV (%)	26.80%	24.80%	n.s
LDH > normal (%)	39.80%	41.40%	n.s
Clinicalstage III·IV (%)	54.40%	51.20%	n.s
No.extranodalsite > 1 (%)	21.70%	22.70%	n.s
HI·High IPI (%)	45.60%	41.20%	n.s
Radiotherapy (%)	37.00%	24.80%	$P < 0.001$
Auto transplantation (%)	7.20%	10.00%	n.s

Radiation therapy was applied in patients with localized stage at the site of the original tumor and the region of residual mass after chemotherapy (345 patients). Most of the patients received doses in the range of 30–40 Gy. High-dose chemotherapy with autologous peripheral stem-cell support was performed as a front-line therapy in 87 patients at some hospitals. All patients were treated with curative intent. Patients who experienced DLBCL recurrence or progression after first-line therapy were treated with a variety of salvage regimens. Response to the therapy was evaluated by the criteria of Cheson et al. [17].

2.4 Statistical analysis

Patient characteristics and therapeutic outcomes were compared between the CHOP and R-CHOP groups. Clinical prognostic factors, including the conventional IPI score, were also compared between the 2 groups by an independent samples t test for continuous variables and χ^2 test for categorical variables. OS was calculated as the time from the date of diagnosis to the date of death. PFS was calculated as the time from the date of therapy until the disease progression or death from lymphoma. PFS and OS were assessed by the Kaplan–Meier method and compared between groups by the log-rank test. A multivariate analysis was performed with the Cox proportional hazards model to assess the independent effect of the addition of rituximab on PFS and OS after controlling for relevant clinical prognostic factors. We also conducted analyses of each group according to IPI subgroup and other clinical prognostic factors. Data were analyzed using the Statistical Software Package for the Social Sciences (SPSS version 11.0 for Windows; SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Patient characteristics

Characteristics of the patients in the CHOP and R-CHOP groups are summarized in Table 1. The median age of all 1,057 patients was 67.0 years (range 22–90 years). There were no statistically significant differences between the 2 groups with respect to sex, age, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, clinical stage, number of extranodal sites, IPI, or number of patients treated with high-dose chemotherapy with autologous stem-cell support. However, larger numbers of patients in the CHOP group were treated with radiation therapy compared with those in the R-CHOP group ($P < 0.001$).

3.2 Outcome

The CR rate was higher in the R-CHOP group than in the CHOP group (67.0 vs. 55.9%, $P < 0.001$). The overall response [CR + partial response (PR)] rate was also higher in the R-CHOP group (93.1 vs. 81.7%, $P < 0.001$). Three-year PFS was significantly higher in the R-CHOP group than in the CHOP group (61.3 vs. 45.6%, $P < 0.001$) (Fig. 1a). Similarly, the OS rate was higher in the R-CHOP group (68.3 vs. 54.5%, $P < 0.001$) (Fig. 1b). When analyzed separately according to age (≤60 and >60 years), the R-CHOP group showed significantly higher OS and PFS rates in both age groups (Fig. 2). OS and PFS clearly correlated with each IPI risk group in the both CHOP and R-CHOP group (Fig. 3a–d). The superiority for OS of adding rituximab to CHOP was noted in both risk groups with IPI (L/LI) and IPI (HI/H) (Fig. 4a, b).

The addition of rituximab attenuated the survival difference between CHOP and R-CHOP groups ($P = 0.104$) in patients who received radiation therapy (Fig. 5b), although the rituximab addition demonstrated the greater survival effect in the patients without radiation ($P < 0.001$) (Fig. 5a). As shown in Table 2, there was no significant difference of clinical background in both treatment groups with radiotherapy.

A multivariate analysis was performed to assess the effect of treatment regimen on survival. The addition of rituximab remained a strong independent prognostic factor for PFS and OS (hazard ratio = 1.584 and 1.626, respectively; $P < 0.001$) (Table 3).

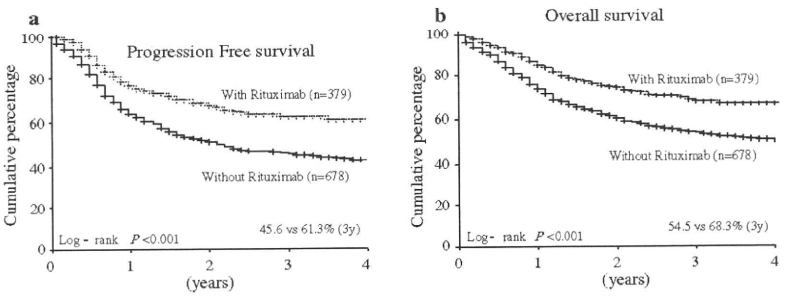

Fig. 1 Overall outcome. **a** Progression-free survival at 36 months was 45.6% in the CHOP group (cyclophosphamide, adriamycin, vincristine and prednisone) and 61.3% in the R-CHOP group (rituximab plus CHOP) ($P < 0.001$). **b** Similarly, overall survival at 36 months was 54.5% in the CHOP group and 68.3% in the R-CHOP group ($P < 0.001$)

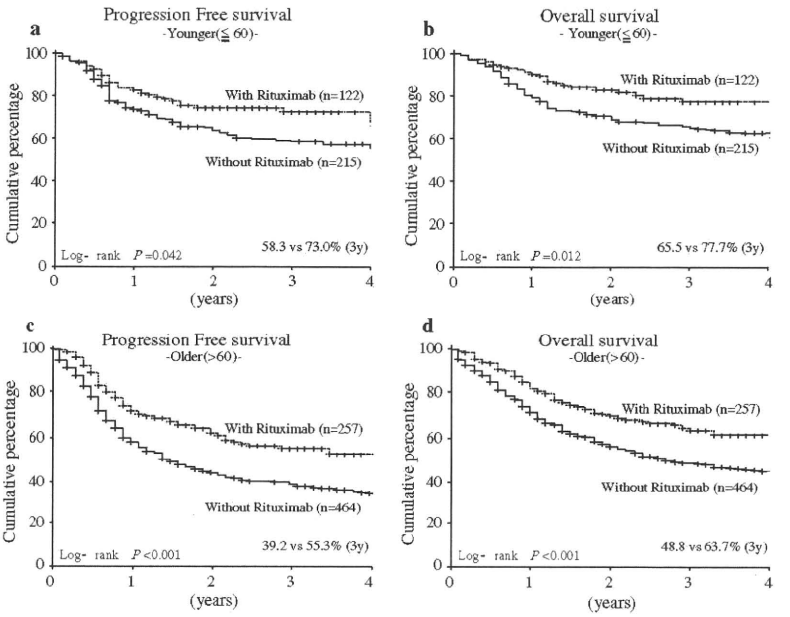

Fig. 2 Overall outcome. Progression-free survival (**a**) and overall survival (**b**) in younger patients (≤60 years). Progression-free survival (**c**) and overall survival (**d**) in older patients (>60 years)

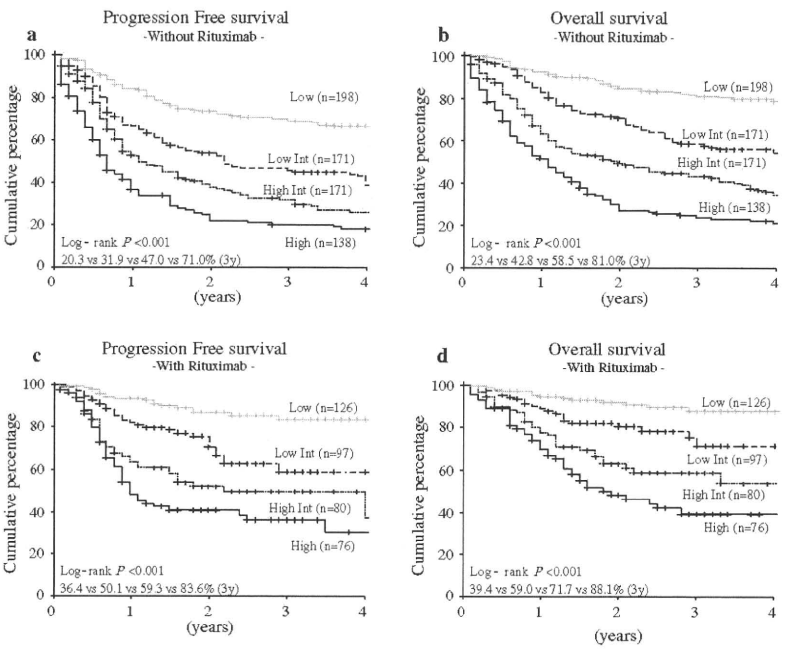

Fig. 3 Outcome according to the standard International Prognostic Index. Progression-free survival (**a**) and overall survival (**b**) in the CHOP group (cyclophosphamide, adriamycin, vincristine and prednisone). Outcome according to the standard International Prognostic Index. Progression-free survival (**c**) and overall survival (**d**) in the R-CHOP group (rituximab plus CHOP)

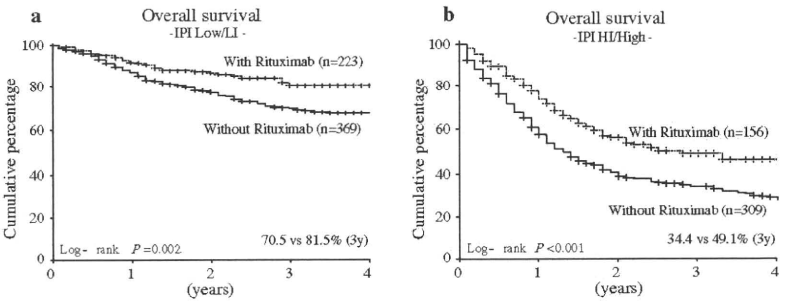

Fig. 4 Overall survival (OS) in CHOP and R-CHOP groups according to IPI (L/LI) (**a**) and IPI (HI/H) (**b**)

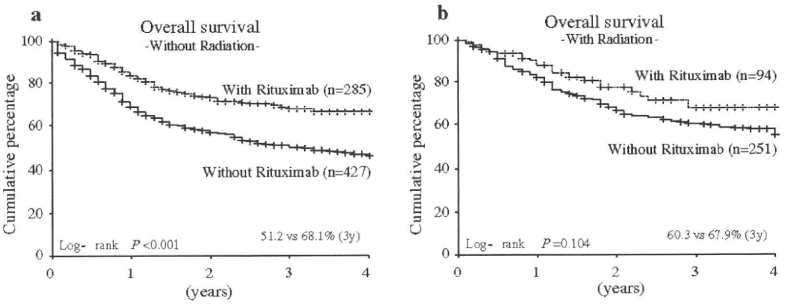

Fig. 5 Kaplan–Meier survival curves for the CHOP and R-CHOP groups treated with or without radiation (**a** radiation−, **b** radiation+)

Table 2 Clinical characteristics in diffuse large B cell lymphoma (DLBCL) patients treated with or without radiation

Characteristic	Study population								
	Without radiation (n = 712)	With radiation (n = 345)	P value	Without radiation			With radiation		
				Without rituximab (n = 427)	With rituximab (n = 285)	P value	Without rituximab (n = 251)	With rituximab (n = 94)	P value
Male (%)	52.90%	53.60%	n.s	52.90%	53.00%	n.s	53.80%	53.20%	n.s
Age (Mean)	65.70	64.10	<0.05	65.84	65.52	n.s	64.37	63.42	n.s
>60 year (%)	70.20%	64.10%	<0.05	70.30%	70.20%	n.s	65.30%	60.60%	n.s
ECOG PS II–IV (%)	28.40%	21.40%	<0.05	29.50%	26.70%	n.s	22.30%	19.10%	n.s
LDH > normal (%)	34.40%	52.80%	<0.001	32.30%	37.50%	n.s	52.60%	53.20%	n.s
Clinical stage III·IV (%)	62.20%	34.80%	<0.001	64.40%	58.90%	n.s	37.50%	27.70%	n.s
No. of extranodalsite > 1 (%)	24.30%	17.40%	<0.05	24.10%	24.60%	n.s	17.50%	17.00%	n.s
HI·High IPI (%)	50.00%	31.60%	<0.001	52.20%	46.70%	n.s	34.30%	24.50%	n.s
Auto transplantation (%)	8.40%	7.80%	n.s	7.50%	9.80%	n.s	6.80%	10.60%	n.s

High-dose chemotherapy combined with autologous stem-cell support showed its superiority for PFS, but less advantage for OS (Table 3).

4 Discussion

According to the results of large-scale clinical studies in Europe and the US, addition of rituximab to CHOP therapy resulted in a significant advantage with respect to outcome in patients with DLBCL. The R-CHOP regimen has thus become the gold standard for the treatment of DLBCL. However, only a few small-scale studies have been performed in Japan [19, 20]. Therefore, we conducted a retrospective outcome analysis of a large number of patients with DLBCL. Results of the present study showed that rituximab provided a significant survival advantage in all IPI risk groups and all age groups. This

Table 3 Cox proportional hazard regression analysis for PFS and OS

Clinical outcome	Progression-free survival		Overall survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Rituximab (without vs. with)*	1.584 (1.280–1.959)	<0.001	1.626 (1.283–2.060)	<0.001
Radiation therapy (without vs. with)*	0.913 (0.786–1.107)	n.s	0.842 (0.683–1.038)	n.s
Transplantation (without vs. with)*	1.589 (1.116–2.262)	<0.010	1.345 (0.920–1.965)	n.s

* Adjusted for age, PS, clinical stage, LDH, extranodal, center effect

was consistent with results of previous clinical studies in other countries.

Among various biologic prognostic markers, including cell origin (germinal center B cell and activated B cell type) and expression patterns of Bcl-2 [21], p53 [22], CD5 [23], and Skp2 [24, 25], the IPI is a well-known, convenient, and useful prognostic marker for DLBCL patients [26]. Sehn et al. [27] advocated the use of the revised IPI in evaluations of rituximab. The addition of rituximab to CHOP therapy attenuated survival differences with respect to prognostic factors such as Bcl-2 expression [28] and cell origin [29, 30]. In the present study, the IPI as well as the revised IPI showed significant survival effects of rituximab in patients with DLBCL.

Involved field radiation therapy (IFRT) is a conventional therapy for patients with lymphoma with a localized stage and/or bulky mass [31]. However, the survival benefit of addition of IFRT to chemotherapy remains controversial. Reyes et al. investigated the survival of patients younger than 61 years of age with previously untreated aggressive lymphoma, randomly assigned to chemotherapy followed by IFRT or ACBVP chemotherapy alone. The chemotherapy plus IFRT group showed no survival advantage compared with the chemotherapy group [32]. S0014 trial was the first study to demonstrate a benefit of combining IFRT and R-CHOP for patients with limited stage aggressive B cell lymphoma [33]. In contrast, MInT trial demonstrated that 6 cycles of R-CHOP resulted in a comparable outcome in patient with IFRT [13]. On the basis of these encouraging results, in limited DLBCL, it is a new policy recommending either the 3 cycles R-CHOP followed by IFRT or 6 cycles R-CHOP. In the present study, patients who underwent radiotherapy showed less benefit of rituximab addition to chemotherapy than patients who did not undergo radiation therapy with respect to OS. This may result from a greater survival effect of rituximab addition. The effect of IFRT should be clarified in further prospective clinical trials in R-CHOP era.

Survival benefit of the upfront high-dose chemotherapy with autologous stem-cell support was reported in disseminated aggressive lymphoma [34]. Currently, the S9704 study (US Intergroup) has been finished to establish the usefulness of high-dose chemotherapy followed by auto-PBSCT in up-front setting in aggressive DLBCL (NCT00004031). This clinical trial will bring a final conclusion about the usefulness of auto-PBSCT.

In summary, this study demonstrated the addition of rituximab to chemotherapy provided a benefit with respect to outcome at any IPI status and any age and in Japanese patients with DLBCL.

Finally, this study was retrospective analysis with some limitations. To obtain definitive results, the well-controlled prospective study should be necessary.

Acknowledgments This study was performed in collaboration with the many hematologists and pathologists associated with the Kyushu Lymphoma Study Group. We express our appreciation to all of them.

Appendix: Kyushu Lymphoma Study Group

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Acute Lymphoblastic Leukemia of Male-Recipient Origin Demonstrating Female Karyotype After Cord Blood Transplantation

A 12-year-old boy was diagnosed with French-American-British classification L2 acute lymphoblastic leukemia (ALL). He was treated according to the pediatric ALL protocol and achieved a complete remission (CR). When the patient was 22 years old, he presented with dyspnea. A CBC revealed a WBC of 1.2×10^9/L (blasts, 2%), a hemoglobin level of 5.8 g/dL, and a platelet count of 160×10^9/L. Bone marrow aspiration showed 88% blasts that were cytochemically negative to myeloperoxidase staining (Fig 1A). Flow cytometric immunophenotyping showed that the blasts were CD10−, CD19+, CD13−, CD33+, CD34+, and HLA-DR+. Cytogenetic analysis showed a normal male karyotype, 46,XY, in each of the 20 metaphase cells analyzed (Fig 2A).

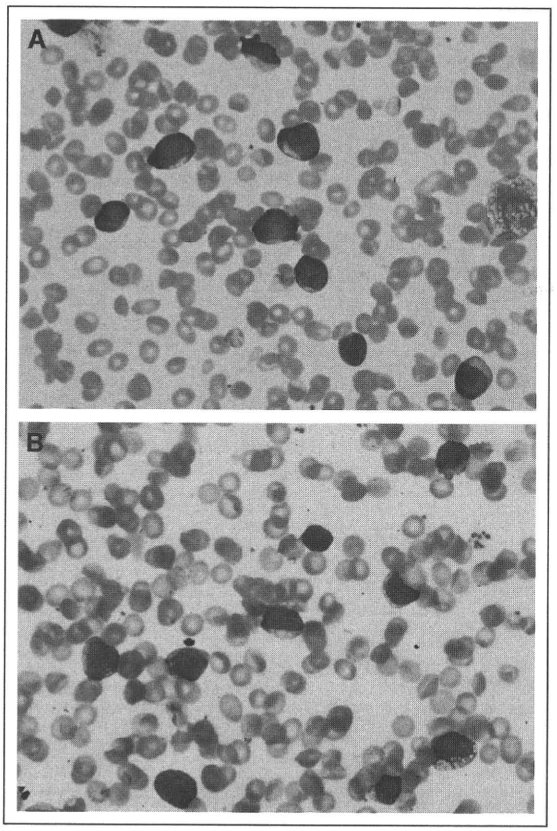

Fig 1.

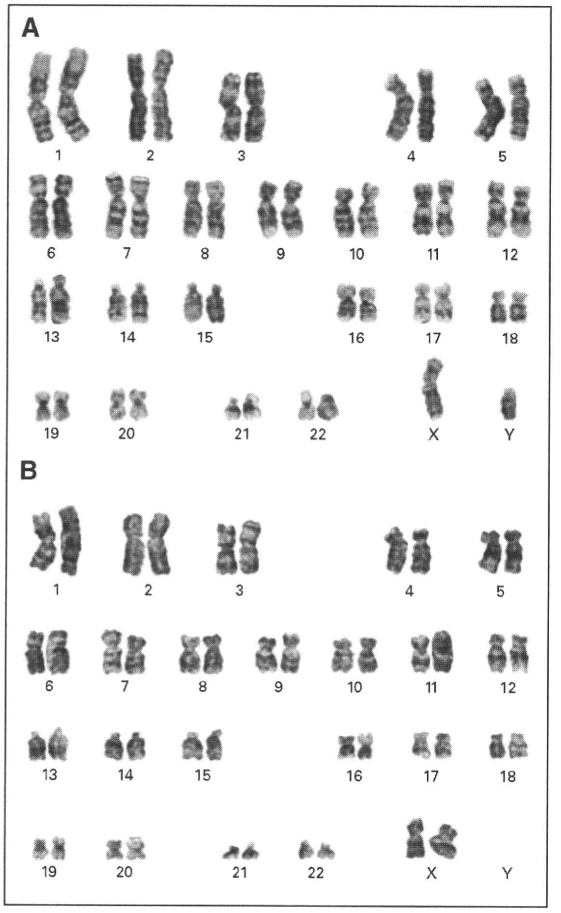

Fig 2.

On the basis of these results, the patient was diagnosed with a relapse of ALL (first relapse). After the patient achieved CR with intensive chemotherapy, three courses of consolidation therapy were administered. Seven months after diagnosis of the first relapse, an unrelated cord blood transplantation (CBT) from a human leukocyte antigen (HLA)–mismatched female donor was performed with a preparative regimen of cytarabine, cyclophosphamide, and total-body irradiation. Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and short-term methotrexate. Neutrophil engraftment occurred on day 25. The patient developed skin-only, grade II acute GVHD, which resolved with topical corticosteroids. Tacrolimus was discontinued 6 months after the transplantation with no evidence of chronic

ORIGINAL CONTRIBUTION

Hematopoietic Stem Cell Transplantation
A Global Perspective

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Context Hematopoietic stem cell transplantation (HSCT) requires significant infrastructure. Little is known about HSCT use and the factors associated with it on a global level.

Objectives To determine current use of HSCT to assess differences in its application and to explore associations of macroeconomic factors with transplant rates on a global level.

Design, Setting, and Patients Retrospective survey study of patients receiving allogeneic and autologous HSCTs for 2006 collected by 1327 centers in 71 participating countries of the Worldwide Network for Blood and Marrow Transplantation. The regional areas used herein are (1) the Americas (the corresponding World Health Organization regions are North and South America); (2) Asia (Southeast Asia and the Western Pacific Region, which includes Australia and New Zealand); (3) Europe (includes Turkey and Israel); and (4) the Eastern Mediterranean and Africa.

Main Outcome Measures Transplant rates (number of HSCTs per 10 million inhabitants) by indication, donor type, and country; description of main differences in HSCT use; and macroeconomic factors of reporting countries associated with HSCT rates.

Results There were 50 417 first HSCTs; 21 516 allogeneic (43%) and 28 901 autologous (57%). The median HSCT rates varied between regions and countries from 48.5 (range, 2.5-505.4) in the Americas, 184 (range, 0.6-488.5) in Asia, 268.9 (range, 5.7-792.1) in Europe, and 47.7 (range, 2.8-95.3) in the Eastern Mediterranean and Africa. No HSCTs were performed in countries with less than 300 000 inhabitants, smaller than 960 km^2, or having less than US $680 gross national income per capita. Use of allogeneic or autologous HSCT, unrelated or family donors for allogeneic HSCT, and proportions of disease indications varied significantly between countries and regions. In linear regression analyses, government health care expenditures (r^2=77.33), HSCT team density (indicates the number of transplant teams per 1 million inhabitants; r^2=76.28), human development index (r^2=74.36), and gross national income per capita (r^2=74.04) showed the highest associations with HSCT rates.

Conclusion Hematopoietic stem cell transplantation is used for a broad spectrum of indications worldwide, but most frequently in countries with higher gross national incomes, higher governmental health care expenditures, and higher team densities.

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HEMATOPOIETIC STEM CELL transplantation (HSCT) has become the standard of care for many patients with defined congenital or acquired disorders of the hematopoietic system or with chemosensitive, radiosensitive, or immunosensitive malignancies.[1-3] Over the last 2 decades, HSCT has seen rapid expansion in use and a constant evolution in its technology. Novel indications are currently under evaluation.[4,5] Bone marrow is supplemented as a stem cell source by peripheral blood or cord blood. More than 14 million typed volunteer donors or cord blood units from the many registries worldwide provide stem cells for patients without family donors. Novel conditioning regimens with lower intensity have expanded the use of HSCT to older patients and to those with comorbidities.[6-9]

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Still, HSCT remains associated with significant morbidity and mortality and represents one example of high-cost, highly specialized medicine. It requires significant infrastructure and a network of specialists from all fields of medicine. Hence, information on indications, use of specific technologies, and trends in the application of HSCT is essential for correct patient counseling and for health care agencies to prepare the necessary infrastructure and to avoid planning errors.[10-13] In addition, HSCT is no longer limited to countries with abundant resources. For selected indications, HSCT might represent the most cost-effective therapy in some countries.[14] An assessment of global HSCT activity is warranted.

In view of the increasing numbers of transplant teams and HSCTs worldwide and the increasing awareness of the need for a global perspective for all cell, tissue, and organ transplants by the World Health Organization,[15] the recently founded Worldwide Network for Blood and Marrow Transplantation decided to collect standardized HSCT activity data on a global level. Results of the first worldwide HSCT survey are presented herein.

METHODS

Study Design

This is a retrospective survey among all HSCT teams known to the investigators, which was organized by the Worldwide Network for Blood and Marrow Transplantation through established international and regional organizations. The study was approved by the ethics committee of the University of Basel; and the need for informed consent of patients was waved because no individualized data was transferred to the investigators.

The main outcome measures were the determination of transplant rates (number of HSCTs per 10 million inhabitants) by indication, donor type, and country on a global level. Secondary outcomes were the description of the main differences in HSCT use and the key macroeconomic factors of the reporting countries and regions associated with their transplant rates.

Participating Groups, Continents, Countries, and Teams

There were 1327 teams in 71 reporting countries over 5 continents (see eTable at http://www.jama.com) that provided information on numbers of HSCT for 2006 by indication and donor type (TABLE 1).[16] They were subdivided into 4 regions: (1) the Americas (the corresponding World Health Organization regions are North and South America), (2) Asia (Southeast Asia and the Western Pacific Region, which includes Australia and New Zealand), (3) Europe (which includes Tur-

Table 1. Hematopoietic Stem Cell Transplants Worldwide in 2006[a]

	Allogeneic Donor				
	Family (n = 11 928)	Unrelated (n = 9588)	Total (n = 21 516)	Autologous Donor (n = 28 901)	Total (N = 50 417)
Leukemia	8122 (68.1)	7088 (73.9)	15 210 (70.7)	1839 (6.4)	17 049 (33.8)
Acute myeloid leukemia	3907 (48.1)	3119 (44.0)	7026 (46.2)	1372 (74.6)	8398 (49.3)
Acute lymphoblastic leukemia	1799 (22.1)	1850 (26.1)	3649 (24.0)	216 (11.7)	3865 (22.7)
Myelodysplastic, myeloproliferative syndromes	1151 (14.2)	1248 (17.6)	2399 (15.8)	60 (3.3)	2459 (14.4)
Chronic myeloid leukemia	877 (10.8)	519 (7.3)	1396 (9.2)	14 (1.0)	1410 (8.3)
Chronic lymphocytic leukemia	336 (4.1)	269 (3.8)	605 (4.0)	175 (9.5)	780 (4.6)
Other leukemia	52 (1.0)	83 (1.2)	135 (1.0)	2 (<1.0)	137 (1.0)
Lymphoproliferative disorders	2088 (17.5)	1414 (14.7)	3502 (16.3)	23 990 (83.0)	27 492 (54.5)
Plasma cell disorders	546 (26.1)	287 (20.3)	833 (23.8)	11 877 (49.5)	12 710 (46.2)
Hodgkin disease	270 (12.9)	235 (16.6)	505 (14.4)	3275 (13.7)	3780 (13.7)
Non–Hodgkin lymphoma	1109 (53.1)	708 (50.1)	1817 (51.9)	7943 (33.1)	9760 (35.5)
Other lymphoma (type unknown)	163 (8.0)	184 (13.0)	347 (10.0)	895 (4.0)	1242 (5.0)
Solid tumors	113 (1.0)	40 (<1.0)	153 (<1.0)	2772 (9.6)	2925 (5.8)
Neuroblastoma	22 (19.5)	8 (20.0)	30 (19.6)	615 (22.2)	645 (22.1)
Germinal cancer	3 (3.0)	2 (5.0)	5 (3.3)	518 (18.7)	523 (17.9)
Breast cancer	13 (11.5)	4 (5.0)	17 (11.1)	273 (9.8)	290 (10.0)
Ewing sarcoma	17 (15.0)	6 (20.0)	23 (15.0)	176 (6.3)	199 (6.8)
Other	58 (51.3)	20 (50.0)	78 (51.0)	1190 (42.9)	1268 (43.4)
Nonmalignant disorders	1512 (12.7)	884 (9.0)	2396 (11.1)	197 (1.0)	2593 (5.1)
Bone marrow failures	879 (58.1)	457 (52.0)	1336 (55.8)	0	1336 (51.5)
Hemoglobinopathies	348 (23.0)	54 (6.1)	402 (16.8)	3 (1.5)	405 (15.6)
Immune deficiencies	216 (14.3)	241 (27.3)	457 (19.1)	3 (1.5)	460 (17.7)
Inherited diseases of metabolism	63 (4.0)	122 (13.8)	185 (7.7)	2 (1.0)	187 (7.2)
Autoimmune disorders	6 (<1.0)	10 (1.1)	16 (1.0)	189 (96.0)	205 (8.0)
Other	93 (1.0)	162 (2.0)	255 (1.2)	103 (<1.0)	358 (1.0)

[a] Values are expressed as number (column percentage of total and within subgroup). Percentages may not equal 100% due to rounding.

key and Israel), and (4) the Eastern Mediterranean and Africa.

Data were provided by the Asian Pacific Blood and Marrow Transplant Group, the Australian Bone Marrow Transplant Recipient Registry, the Canadian Blood and Marrow Transplant Group, the Center for International Blood and Marrow Transplantation, the Sociedade Brasileira de Transplante de Medula Ossea, the Eastern Mediterranean Blood and Marrow Transplant Group, and the European Group for Blood and Marrow Transplantation (see eTable at http://www.jama.com).[17-20]

Collection System and Data Validation

Data were obtained from mandatory reporting systems of initial transplant data (Australian Bone Marrow Transplant Recipient Registry, Canadian Blood and Marrow Transplant Group, and Center for International Blood and Marrow Transplantation) or collected on separate survey data forms from individual centers or national registries (Asian Pacific Blood and Marrow Transplant Group, European Group for Blood and Marrow Transplantation, Eastern Mediterranean Blood and Marrow Transplant Group, and Sociedade Brasileira de Transplante de Medula Ossea).

Data were validated by several independent methods. The data were first confirmed by the reporting team, which received a computer printout of the entered data. Selective comparison also was used with Med-A data sets in the European Group for Blood and Marrow Transplantation Promise data system or by cross-checking with national registries. Onsite visits of selected teams were part of the quality-control program within the Center for International Blood and Marrow Transplantation and the European Group for Blood and Marrow Transplantation.

Based on quality controls and contacts with regulatory agencies or national offices, response rates of allogeneic HSCT was greater than 95% in Australia, Brazil, Canada, Europe, Japan, Korea, Malaysia, New Zealand, Taiwan, and the United States. No formal response rate can be evaluated for the other participating countries; there is no formal regulatory framework for cross-confirmation. Concerning autologous HSCT, the response rate in Europe was greater than 90% and it can be estimated to be between 80% and 90% for Australia, Brazil, Canada, Europe, Japan, Korea, Malaysia, New Zealand, Taiwan, and the United States. For autologous HSCT, no formal framework exists to capture nonreporting teams and to validate response rates with accuracy.

Definitions

This Worldwide Network for Blood and Marrow Transplantation survey focused on the numbers of patients treated for the first time with HSCT in 2006. Information on additional transplants (eg, retransplants or multiple HSCTs[21]) was not included.

Transplant rates were computed as the number of HSCTs per 10 million inhabitants.[21] Transplant rates refer to the number of transplants in a given country compared with its own population, without adjustments for patients who cross borders and receive a HSCT in a foreign country. Population data were obtained from the US census office.

Team density refers to the number of transplant teams per 1 million inhabitants.[22] The definition of a team followed the principles of the Foundation for the Accreditation of Cellular Therapy and the Joint Accreditation Committee of the International Society for Cellular Therapy and the European Group for Blood and Marrow Transplantation.

Transplant rates within the reporting participating countries were compared with a range of macroeconomic health care indicators: gross national income per capita; total health care expenditures; governmental health care expenditures; adult, infant and maternal mortality rate; number of hospital beds per capita; cesarean delivery rates; human developmental index, which is a composite index reflecting the developmental status of all countries in the world in a scale from 0 to 1.0; and team density, which indicates the number of transplant teams per 1 million inhabitants. Data were obtained from the World Bank, the World Health Organization, and the United Nations. Data from 2006 were used for all comparisons whenever possible.

Statistical Analysis

The association of the macroeconomic factors with HSCT rates was estimated by single linear and multiple linear regression analysis, using the least squares method. The linear relationship, positive or negative, between the macroeconomic factors and HSCT rates after transformation was measured using the t statistic; a level of 5% was considered significant. The goodness of fit was measured using the coefficient of determination (r^2). For the single and multiple linear regression analyses, the dependent variables were transformed to point out the linear associations. In the multiple regression analyses, all factors were assessed for their multicollinearity. Taiwan and Hong Kong were excluded from the multiple economic comparisons because of missing information on governmental health care expenditures. Cesarean delivery rates were included in the single linear analyses but not the multiple regression analyses, because data from too many countries were missing.

The t test was used to evaluate if the 4 world regions had a significant difference in the relative proportion of main indications and donor type (allogeneic vs autologous, unrelated vs family donors); $P = .05$ was considered significant. All statistical analyses were performed with EViews version 5.1 (Quantitative Micro Software, Irvine, California).

RESULTS

A total 50 417 first HSCTs were reported for 2006; 21 516 allogeneic (43%) and 28 901 autologous (57%) (Table 1). The main indications were lymphoproliferative disorders (27 492

patients [54.5%]; 3502 allogeneic [13%] and 23 990 autologous [87%]); leukemias (17 049 patients [33.8%]; 15 210 allogeneic [89%] and 1839 autologous [11%]); solid tumors (2925 patients [5.8%]; 153 allogeneic [5%] and 2772 autologous [95%]); nonmalignant disorders (2593 patients [5.1%]; 2396 allogeneic [92%] and 197 autologous [8%]), and other nonspecified disorders (358 patients; 1%).

The most frequent malignant disease for an allogeneic HSCT was acute myeloid leukemia (n = 7026; 33%), the most frequent nonmalignant disease was bone marrow failure syndrome (n = 1336; 6%), and the most frequent indication for an autologous HSCT was a plasma cell disorder (n = 11 877; 41%).

Most of the 50 417 HSCTs were performed in Europe with 24 216 (48%) (median [range], 255 [6-4619] per country) followed by the Americas with 17 875 (36%) (median [range], 61 [8-15 082] per country), Asia with 7096 (14%) (median [range], 139 [5-3823] per country), and the Eastern Mediterranean and Africa with 1230 (2%) (median [range], 63 [10-360] per country). The absolute numbers of HSCTs in the participating countries ranged from 15 082 in the United States to 5 in Vietnam.

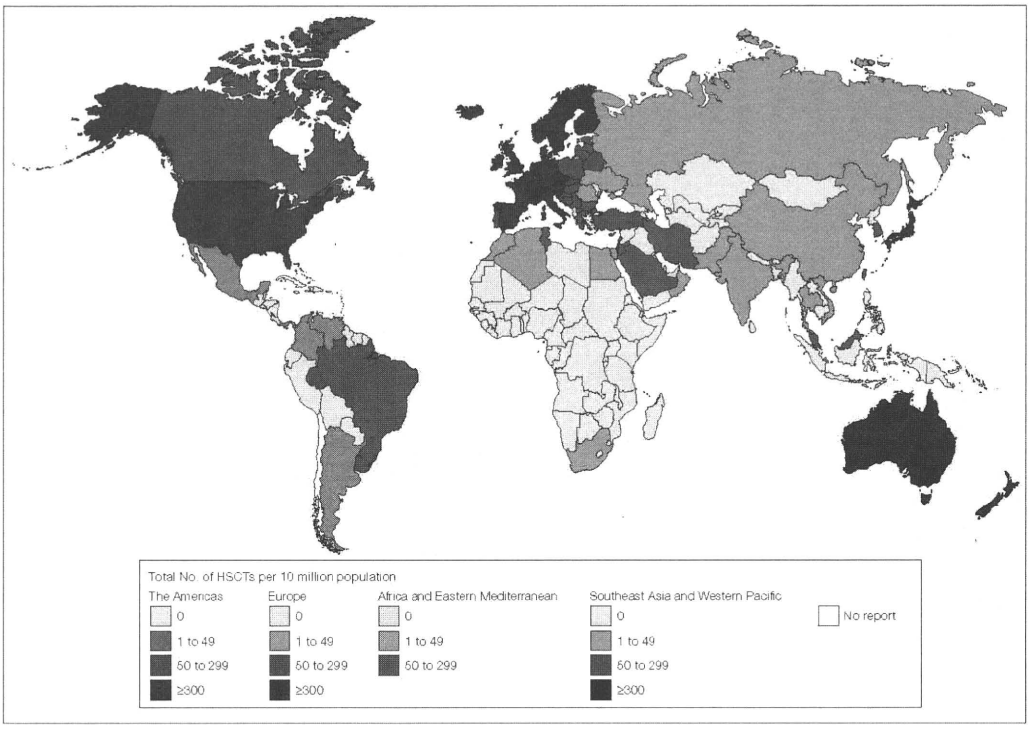
Transplant Rates in 2006

The median HSCT rates varied between the continental regions and between participating countries from 48.5 (range, 2.5-505.4) in the Americas, 184 (range, 0.6-488.5) in Asia, 268.9 (range, 5.7-792.1) in Europe, and 47.7 (range, 2.8-95.3) in the Eastern Mediterranean and Africa (FIGURE 1). Transplant rates for allogeneic HSCT ranged from 434.9 in Israel to 0.2 in Vietnam. Transplant rates for autologous HSCT ranged from 500 in Iceland to 0.3 in Mexico.

Regional Differences in Donor Type and Main Indications

Overall, there were more autologous HSCTs (n = 28 901; 57%) than allogeneic HSCTs (n = 21 516; 43%) (TABLE 2). Most of the autologous HSCTs occurred in the Americas and Europe. In other regions, allogeneic HSCTs were more common (Asia:

Figure 1. Global Distribution of Hematopoietic Stem Cell Transplantations (HSCTs) in 2006



Regions are colored by World Health Organization regional office code (see text) (http://www.who.int/about/regions/en/). Transplant rates indicate the number of first HSCTs per 10 million inhabitants in 2006 and are allogeneic and autologous by continental region.

Table 2. Allogeneic and Autologous Hematopoietic Stem Cell Transplants by Region[a]

	Americas (n = 17 875)	Asia (n = 7096)	Europe (n = 24 216)	Eastern Mediterranean and Africa (n = 1230)	Total (N = 50 417)
Allogeneic donor	7527 (42.1)	4058 (57.2)	9128 (37.7)	803 (65.3)	21 516 (42.7)
Relationship					
Family	4277 (57.0)	1948 (48.0)	4906 (53.7)	797 (99.3)	11 928 (55.4)
Unrelated	3250 (43.2)	2110 (52.0)	4222 (46.3)	6 (<1.0)	9588 (44.6)
Leukemia	5156 (68.5)	3119 (76.9)	6443 (70.6)	492 (61.3)	15 210 (70.7)
Lymphoproliferative disorders	1466 (19.5)	429 (10.6)	1579 (17.3)	28 (3.5)	3502 (16.3)
Solid tumors	32 (<1.0)	37 (1.0)	83 (1.0)	1 (<1.0)	153 (<1.0)
Nonmalignant disorders	755 (10.0)	418 (10.3)	946 (10.4)	277 (34.5)	2396 (11.1)
Other	118 (2.0)	55 (1.4)	77 (1.0)	5 (<1.0)	255 (1.2)
Autologous donor	10 348 (57.9)	3038 (42.8)	15 088 (62.3)	427 (34.7)	28 901 (57.3)
Leukemia	443 (4.3)	202 (6.6)	1136 (7.5)	58 (13.6)	1839 (6.4)
Lymphoproliferative disorders	8936 (86.4)	2380 (78.3)	12 336 (81.8)	338 (79.2)	23 990 (83.0)
Solid tumors	895 (8.6)	389 (12.8)	1459 (9.7)	29 (6.8)	2772 (9.6)
Nonmalignant disorders	49 (<1.0)	23 (1.0)	123 (1.0)	2 (<1.0)	197 (1.0)
Other	25 (<1.0)	44 (1.4)	34 (<1.0)	0	103 (<1.0)

[a]Values are expressed as number (column percentage of total and within subgroup). Percentages may not equal 100% due to rounding.

57.2%; the Eastern Mediterranean and Africa: 65.3%). The differences in the prevalences of allogeneic HSCTs and the proportions of unrelated donor HSCTs are presented in TABLE 3. The proportion of unrelated donor HSCT was highest in Asia (52%), but it was negligible in the Eastern Mediterranean and Africa (1%).

Leukemia was the main indication for allogeneic HSCT globally (71% overall; the Americas, 68%; Asia, 77%; Europe, 71%; Eastern Mediterranean and Africa, 61%). Nonmalignant diseases comprised about 11% in the Americas, Asia, and Europe and 34% in the Eastern Mediterranean and Africa (see Table 2). Lymphoma was the most common indication for autologous HSCT (79%) in the Eastern Mediterranean and Africa. Plasma cell disorders were the most common indications for autologous HSCT in the Americas and Europe. Compared with Asia, among individuals in the Eastern Mediterranean and Africa there were more allogeneic HSCTs for chronic myelogenous leukemia (28% vs 7%, respectively) and hemoglobinopathies (26% vs 11%).

Table 3. Allogeneic and Unrelated Donor Hematopoietic Stem Cell Transplantations (HSCTs)

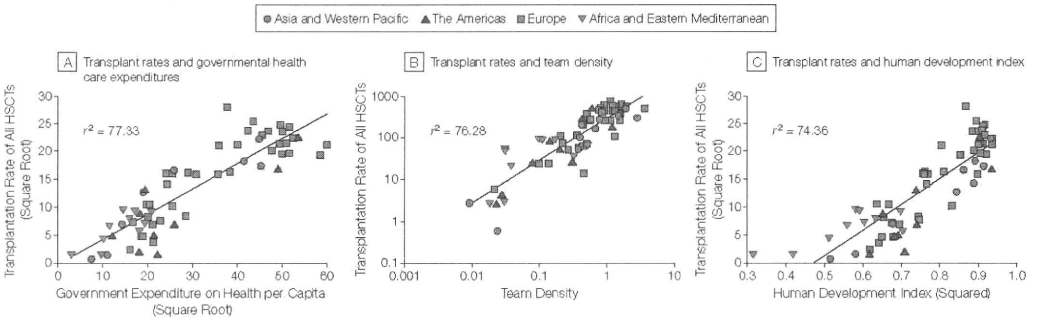
Comparison	Allogeneic HSCT, %	Test Statistic	Critical Value at 5% Level	Degrees of Freedom	*P* Value
Asia	57				
vs Americas	42	3.34	2.16	13	.005
vs Europe	38	4.24	2.20	12	.001
Americas	42				
vs Eastern Mediterranean and Africa	65	−4.21	2.23	11	.002
vs Europe	38	1.66	2.10	18	.11
Europe	38				
vs Eastern Mediterranean and Africa	65	−4.96	2.23	10	.001
	Family vs Unrelated Donor				
Eastern Mediterranean and Africa	99				
vs Americas	57	−10.00	2.23	11	<.001
vs Asia	48	−8.40	2.20	12	<.001
vs Europe	54	−13.31	2.02	17	<.001
Americas	57				
vs Asia	48	−0.92	2.11	17	.37
vs Europe	54	0.15	2.11	17	.88
Asia	48				
vs Europe	54	−0.885	2.13	15	.39

Transplant Rates and Macroeconomic Factors

No HSCTs were performed in countries with less than 300 000 inhabitants, smaller than 960 km^2, or having less than US $680 gross national income per capita. All macroeconomic factors had a significant positive or negative association with transplant rates in single regression analyses with a widely variable explanatory content: gross national income per capita (r^2=74.04); total health care expenditures (r^2=73.41); governmental health care expenditures (r^2=77.33) (FIGURE 2A and interactive graphs at at http://www.jama.com); adult (r^2=49.03), infant (r^2=66.31), and maternal (r^2=63.21) mortality rates; hospital beds (r^2=32.04); cesarean section rates (r^2=30.56); and team density (r^2=76.28) (Figure 2B); and human developmental index (r^2=74.36) (Figure 2C).

The first factor in the multiple linear regression analysis, government health care expenditure (GOV), explained 77.33% of the variance of the

Figure 2. Macroeconomic Factors and Transplant Rates



Transplant rates indicate the number of first hematopoietic stem cell transplantations (HSCTs) per 10 million inhabitants. Team density indicates the number of transplant teams per 1 million inhabitants. See "Methods" section for explanation of the human development index. Interactive graphs are available at http://www.jama.com.

HSCT rates. The second factor, team density (TD), increased R^2 to 79.83%, and the third factor, gross national income (GNI) per capita, added another 4.41% of explanation. All other factors, including the human development index, became insignificant, mainly due to multicollinearity with gross national income per capita, meaning that several factors did correlate highly with each other. Therefore, the equation of the multiple regressions was

$$\sqrt{TR} = c_1\sqrt{GOV} + c_2\ln(TD) + c_3\ln(GNI) + \varepsilon$$

Hence, the combined explanatory content was $R^2 = 84.24$.

COMMENT

This first report by the Worldwide Network for Blood and Marrow Transplantation documents the current state of HSCT on a global level. It describes the achievements, illustrates the major differences, and points to the key needs. Transplant activity is concentrated in countries with higher governmental health care expenditures, higher gross national income per capita, and higher team density. Hence, availability of resources, governmental support, and access to a transplant center are the key factors related to regional HSCT activity. However, disease prevalence can differ between regions and could contribute to differences in HSCT rates; those data were not included in this report.

The close link of HSCT rates with gross national income per capita was recognized many years ago; HSCT is an expensive procedure with a substantial investment for a single patient.[21] No HSCTs were performed in countries with less than US $700 gross national income per capita. However, gross national income per capita explained only parts of the variations. Therefore, we were specifically interested in other macroeconomic factors associated with HSCT rates. These factors were chosen with intention. They were either directly linked to availability of resources (gross national income per capita, health care expenditures), to governmental support (governmental health care expenditures), or to the overall infrastructure in a country (human development index). Others reflect quality measures of the health care system (mortality rates) or indicate potential overuse of the health care system (hospital beds, cesarean delivery). Of all macroeconomic factors, this study identified governmental health care expenditures as the most closely associated factor with HSCT rates.

Our study could not assess the role of the health care system in the participating countries because there is no globally accepted definition available. Definitive explanations cannot be given, but some assumptions can be made. The cost-effectiveness of HSCT compared with conventional treatment has at least recently been discussed for patients with chronic myeloid leukemia in middle-income countries.[14,23] Transplant rates were strongly associated with team density. There was no indication for saturation in this association. Hence, a minimum number of transplant teams per inhabitants must be available so that patients have sufficient access. It does not appear that transplant teams overuse their infrastructure.[22,24] None of the other traditional health care indicators or the composite human development index provided a higher explanatory content or added information in the multiple regression analyses.

There were significant differences between the regions concerning indications and donor type, with fewer autologous HSCTs in Asia and the Eastern Mediterranean and Africa than in the Americas and Europe. There were more unrelated donors for HSCTs in the Americas, Asia, and Europe than in the Eastern Mediterranean and Africa; the highest proportion of unrelated donors for HSCTs was in Japan. There also were more HLA identical sibling donor HSCTs for congenital disorders or

for aplastic anemia in countries with limited resources. A matched sibling donor HSCT might represent the most efficient way of therapy for a patient with aplastic anemia, thalassemia, or severe combined immunodeficiency in a country with some but still limited resources. No induction, consolidation chemotherapy is needed as would be the case for patients with acute leukemia.[15,23]

There are some limitations of this study that warrant caution in interpretation. The organizations collecting the data had neither legal enforcement to obtain nor the possibility to control all data locally for accuracy and completeness. Cross-checks with national organizations indicate that the report covers nearly 100% of all HSCTs within their country. A few countries choose not to report any data. Most missing information relates to numbers of autologous HSCTs because they are performed in some countries outside of the realm of national transplant organizations and in nonuniversity institutions. Despite these limitations, the main observations of this study regarding the main indications, donor type, transplant rates, and associations with macroeconomic factors should remain valid. Finally, we had neither information on outcome of the transplant procedures nor on correctness of the indication; this is beyond the scope of this study and would require a much longer follow-up time.[24]

This study was in part triggered by the increasing awareness by scientific and health care organizations, including the World Health Organization, to address key aspects of cell, tissue, and organ transplantation on a global level. In contrast to solid organ transplantation, HSCT faces limitations other than donor organ shortage.[25] Patients are in need of a closely matched donor, family or unrelated donor, but there are many unrelated donor registries and public cord blood banks throughout the world. In 2008, there were, for the first time, more unrelated donor HSCTs than family donor HSCTs reported to the European survey and more unrelated HSCTs across than within borders. In addition to traditional HSCT, novel treatment forms with hematopoietic stem cells for nonhematopoietic use or transplantation of nonhematopoietic stem cells for organ and tissue repair are under investigation.[26-29] The challenges with these new forms of therapy have recently been addressed; stem cell tourism has become a topic of concern.[30] Information on the current status of HSCT use has become a necessity for correct patient counseling and health care planning.

In conclusion, this global overview on HSCT activity demonstrates that it is an accepted therapy worldwide, with different needs and priorities in different regions. Transplant activity is concentrated in countries with higher health care expenditures, higher gross national income per capita, and higher team density; hence, the availability of resources, governmental support, and access to a transplant center determine regional HSCT activity.

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Acquisition of data: Baldomero, Aljurf, Pasquini, Bouzas, Yoshimi, Lipton, Horowitz, Kodera.
Analysis and interpretation of data: A. Gratwohl, Baldomero, Bouzas, Yoshimi, Szer, Schwendener, M. Gratwohl, Frauendorfer, Niederwieser, Horowitz, Kodera.
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