

REVIEW

Why are there regional differences in stem cell transplantation activity? An EBMT analysis

A Gratwohl¹, H Baldomero², K Frauendorfer³ and D Niederwieser⁴, for the Joint Accreditation Committee of the International Society for Cellular Therapy ISCT and the European Group for Blood and Marrow Transplantation EBMT (JACIE)

¹Department of Hematology, University Hospital Basel, Basel, Switzerland; ²EBMT Activity Survey Office, Department of Hematology, University Hospital Basel, Basel, Switzerland; ³Institute for Operations Research and Computational Finances, University of St Gallen, St Gallen, Switzerland and ⁴Department of Hematology, University Hospital, Leipzig, Germany

Differences in the number of hematopoietic SCTs (HSCT), in transplant rates, in indications and in techniques between countries have been reported. They were attributed mainly to differences in the economic situation of the countries or to differences in prevalences of the disease. On the basis of the results of the annual activity survey on HSCT of the European Blood and Marrow Transplantation (EBMT), we have analyzed the factors associated with differences between more than 600 teams participating from more than 40 countries over a time span of 15 years. The results show a more complex situation. The gross national income per capita, number of transplant teams per 10 million inhabitants or per 10 000 km², team size and team experience all impact on transplant activity. Furthermore, hitherto unknown factors must add to the decisions to perform or not to perform HSCT. These data illustrate that more research is needed to understand the mechanism of HSCT activity and to enable health-care agencies to provide the necessary infrastructure.

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Introduction

HSCT has seen rapid expansion over the past two decades. It is considered the treatment of choice for many patients with severe malignant or non-malignant, acquired or congenital disorders of the hematopoietic system or for patients with chemosensitive, radiosensitive or immunosensitive tumors. HSCT has evolved from an experimental procedure to the standard of care and is integrated into the treatment algorithm for many disease categories. Better management of the patients, improved supportive care, increased donor pools and novel conditioning regimens have extended its use to new patient categories and new disease indications. On the basis of current data, more

than 25 000 patients are now treated annually in Europe with HSCT and an estimated near 100 000 patients worldwide.^{1,2}

Reports from the European Blood and Marrow Transplantation (EBMT) and the Centre for International Blood and Marrow Transplant Registry (CIBMTR) have illustrated earlier that the number of transplants differ significantly between different countries.³ This is true for all regions, but little detailed information is available. There are now instruments to better analyze the situation. In 1990, the EBMT introduced the activity survey as a novel instrument to capture comprehensive information on transplant numbers and to distribute this information rapidly. All EBMT members and affiliated teams report since then, on an annual basis, their number of HSCT by indication, stem cell source and donor type.⁴ By now, the survey has evolved to a mandatory self-reporting system and forms an integral part of the comprehensive quality assurance program JACIE (<http://www.jacie.org>). These EBMT reports have previously shown that part of the differences in transplant activity among European countries is based on the different economic strengths of the participating individual countries. They explained some of the differences between Eastern and Western European countries. Transplant rates were higher in countries with higher gross national income (GNI) or health-care expenditures (HCE) per capita.⁵ Still, these basic economic differences were not sufficient. This report, based on the activity survey of 2006 and on previous analyses, tries to capture some additional factors.

Patients and methods

Data collection and validation

Participating teams reported their data by indication, stem cell source and donor type as listed in Table 1 for the year 2006. Data were validated by three independent systems: through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with MED-A data sets in the ProMISE data capture system of the EBMT (www.msbi.nl/Promise) and by cross-checking with national registries where they exist.

Correspondence: Professor Dr A Gratwohl, Department of Hematology, University Hospital Basel, Basel CH-4031, Switzerland.
E-mail: hematology@uhbs.ch

Table 1 Number of patients treated in Europe during the year 2006 with a first hematopoietic stem cell transplant listed by indication, donor type and stem cell source

| Year = 2006 Teams = 605 | Allogeneic | | | | | Autologous | Total |
|--------------------------------------|------------------------|--------|-------|-----------|-------|------------|-------|
| | HLA identical siblings | Family | Twins | Unrelated | Total | | |
| <i>Leukemias</i> | 3256 | 348 | 28 | 3152 | 6784 | 1179 | 7963 |
| AML | 1527 | 186 | 15 | 1292 | 3020 | 811 | 3831 |
| Acute lymphatic leukemia | 749 | 86 | 7 | 848 | 1690 | 151 | 1841 |
| Chronic myeloid leukemia | 336 | 19 | 2 | 263 | 620 | 13 | 633 |
| MDS/MPS | 487 | 51 | 4 | 618 | 1160 | 47 | 1207 |
| Chronic lymphatic leukemia | 157 | 6 | 0 | 131 | 294 | 157 | 451 |
| <i>Lymphoproliferative disorders</i> | 878 | 52 | 10 | 657 | 1597 | 12572 | 14169 |
| Plasma cell disorders | 285 | 10 | 5 | 204 | 504 | 6190 | 6694 |
| Hodgkin's lymphoma | 134 | 16 | 0 | 110 | 260 | 1770 | 2030 |
| Non-Hodgkin's lymphoma | 459 | 26 | 5 | 343 | 833 | 4612 | 5445 |
| <i>Solid tumors</i> | 44 | 23 | 3 | 15 | 85 | 1479 | 1564 |
| Neuroblastoma | 10 | 10 | 2 | 3 | 25 | 332 | 357 |
| Soft tissue sarcoma | 2 | 7 | 1 | 0 | 10 | 72 | 82 |
| Germinal tumors | 1 | 1 | 0 | 2 | 4 | 306 | 310 |
| Breast cancer | 8 | 4 | 0 | 3 | 15 | 134 | 149 |
| Ewing | 4 | 0 | 0 | 3 | 7 | 246 | 253 |
| Renal cancer | 6 | 0 | 0 | 2 | 8 | 8 | 16 |
| Melanoma | 2 | 0 | 0 | 0 | 2 | 0 | 2 |
| Colon cancer | 0 | 0 | 0 | 0 | 0 | 5 | 5 |
| Other solid tumors | 11 | 1 | 0 | 2 | 14 | 376 | 390 |
| <i>Non-malignant disorders</i> | 623 | 113 | 2 | 377 | 1115 | 127 | 1242 |
| BM failures | 323 | 20 | 2 | 161 | 506 | 0 | 506 |
| Hemoglobinopathies | 197 | 20 | 0 | 30 | 247 | 3 | 250 |
| Immune deficiencies | 75 | 56 | 0 | 127 | 258 | 3 | 261 |
| Inherited disorders of metabolism | 23 | 17 | 0 | 50 | 90 | 2 | 92 |
| Autoimmune disease | 5 | 0 | 0 | 9 | 14 | 119 | 133 |
| Others | 37 | 3 | 0 | 40 | 80 | 32 | 112 |
| Total | 4838 | 539 | 43 | 4241 | 9661 | 15389 | 25050 |

Abbreviations: MDS = myelodysplastic disorder; MPS = myeloproliferative disorder.

On-site visits of selected teams were part of the quality control program (www.jacie.org).

Teams

The 2006 survey data are based on 605 teams in 43 countries (38 European and 5 affiliated countries). This corresponds to a 97% return rate of active teams and includes 498 active EBMT member teams. No major transplant team in Europe is missing from this survey. We received information that in 2006 no blood or BM transplants were performed in the following European countries: Albania, Andorra, Armenia, Georgia, Liechtenstein, Malta, Moldavia, Monaco, San Marino and the Vatican. Non-European countries include, by EBMT tradition, Algeria, Iran, Israel, Saudi Arabia, South Africa and Tunisia. Their data are included in the analyses.

Definitions

Transplant numbers. The EBMT survey focuses on the number of patients treated for the first time with HSCT. Information on additional transplants was collected only generically. The following definitions were used:²

Re-transplants (autologous or allogeneic) were defined as an unplanned HSCT for rejection or relapse after a first HSCT. **Multiple transplants** were defined as being part of a planned double or triple autologous or allogeneic transplant protocol. Information on stem cell source was collected as BM, peripheral blood or cord blood. Combined BM, peripheral blood or cord blood transplants were reported as peripheral blood HSCT.

Transplant rates. Transplant rates were computed as the number of HSCTs per 10 million inhabitants, as previously defined.⁵ Population data were obtained from the US census office (<http://www.census.gov>).

Team density and team distribution. *Team density* refers to the number of transplant teams per 10 million inhabitants, and *team distribution* refers to the number of transplant teams per 10 000 km².

Economic factors. Countries were categorized by their GNI per capita, according to the World Bank definitions, into high-income, intermediate-income and low-income countries (<http://www.worldbank.org>), as previously defined.⁵

Non-European countries were not included in the analysis on economic factors.

Results

Participating teams

Of the 605 teams, 361 (60%) did both allogeneic and autologous transplants; 227 (37%) restricted their activity to autologous transplants and 8 teams (1%) to allogeneic transplants only. Nine teams (2%) reported zero transplants.

Number of HSCTs in 2006

First transplants in 2006. A total of 25 050 first transplants, 9661 (39%) allogeneic and 15 389 (61%) autologous transplants were performed in 2006 (Table 1). Overall, this corresponds to a slight increase in the number of HSCTs compared with 2005, when there were 24 168 first transplants. The number of allogeneic HSCTs increased by 9% from 8890 in 2005 to 9661 in 2006. In contrast, the number of autologous HSCTs declined with the same order of magnitude from 15 278 in 2005 to 15 389 in 2006.

Transplant rates in 2006. There were marked differences in transplant rates between European countries and countries affiliated with EBMT as presented in Figure 1. They ranged from less than 10 to more than 400 per 10 million inhabitants. These differences relate to all transplants (Figure 1a) as well as to donor type, stem cell source or transplant rates for individual disease indications, as exemplified by the use of allogeneic HSCT for acute lymphoblastic leukemia (Figure 1b).

Disease indications

Indications for HSCT in 2006 are listed in detail in Table 1. The main indications were lymphoproliferative disorders with 14 169 patients (56%), 1597 patients with allogeneic HSCT (11%), 12 572 patients with autologous HSCT (89%); leukemias with 7963 patients (32%), 6784 patients with allogeneic HSCT (85%), 1179 with autologous HSCT (15%); solid tumors with 1564 patients (6%), 85 with allogeneic HSCT (5%), 1479 with autologous HSCT (95%) and non-malignant disorders with 1242 patients (5%), 1115 with allogeneic HSCT (90%), 127 with autologous HSCT (10%). The latter, autologous HSCT for non-malignant disorders, predominantly include patients (119) with autoimmune disorders. An additional 112 patients, 80 with allogeneic HSCT and 32 with autologous HSCT, were listed as 'other indications.'

Factors associated with differences

Several factors proved to be associated with transplant rates (Table 2). This includes previously reported, well-known economic factors such as GNI per capita, HCE per capita and team density. Interestingly, team distribution was equally important. There were also clear differences in transplant rates for certain disease indications, which might relate to a different prevalence of the disease, for example,

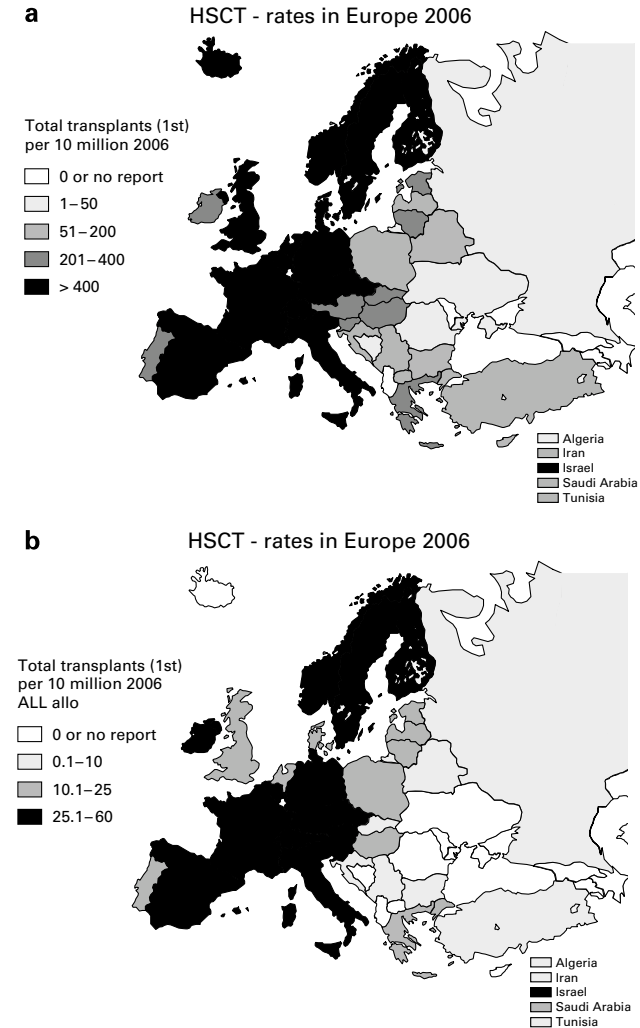


Figure 1 Transplant rates (number of HSCTs per 10 million inhabitants) in European countries in 2006. (a) All HSCTs combined. (b) Acute lymphocytic leukemia, allogeneic transplants only.

Table 2 Factors associated with differences in transplant rates between European countries

| |
|-------------------------|
| <i>Economic factors</i> |
| GNI per capita |
| HCE per capita |
| Health-care system |
| <i>Logistic factors</i> |
| Team density |
| Term distribution |
| <i>Local factors</i> |
| Disease prevalence |
| Infrastructure |
| Ongoing studies |
| Unknowns |

Abbreviations: GNI = gross national income; HCE = health-care expenditure.

hemoglobinopathies. The survey cannot, by its nature, account for the prevalence of non-transplanted patients within a country.

Discussion

The data from this report summarize the current state of HSCT in Europe in 2006. The survey documents the diversity of the procedure, which includes autologous and allogeneic stem cells from the three main sources, BM, peripheral blood and cord blood, for a broad range of malignant and non-malignant disorders.¹ Allogeneic HSCT continued to increase for nearly all indications in all countries compared with the previous reports with high-income and middle income by World Bank categories. This increase is most pronounced for patients with acute leukemias and is observed for related and unrelated HSCT as well.⁶

The survey points as well to the differences in transplant rates. The factors for these differences were shown here and in a previous report.^{5,7} Economic factors of the country, its strength as measured by GNI per capita or HCE per capita and the number of teams compared with its inhabitants and with its size correlate with transplant rates. This correlation is clear but with an s-shaped form and with a broad variation. This leaves wide space for interpretation. HSCT is a cost-intensive therapy; therefore, infrastructure and trained personnel are needed. Hence, transplants in high numbers can only be performed in countries with a stable economic background. Furthermore, patients need to have access to a transplant team. Too few teams per inhabitants or too big a distance to a transplant team prevent significant patient numbers from being transplanted.

Despite these clear associations, many open questions remain. As previously reported, transplant rates were similar for some indications between high-income and middle-income countries, for example, for chronic myeloid leukemia.⁸ Compared with conventional modern drug treatment, which needs to be taken lifelong, HSCT might become more cost-effective as a once-in-a-lifetime procedure. As such, these data illustrate the need for more research into the mechanisms of technology diffusion. If possible, such studies should be performed on a worldwide collaborative basis. This appears essential to provide adequate infrastructure for this high-cost procedure.

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Conflict of interest

Dr Gratwohl has received consulting fees from Novartis, Bristol Myers Squibb and Pfizer and research support from Novartis, Roche, Amgen, Pfizer, BMS, and Osiris. None of the other authors declared any financial interests.

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