Evolution of Hematopoietic Stem Cell Transplantation in Eastern and Western Europe from 1990 to 2003. A Report from the EBMT Activity Survey

Alois Gratwohl, Helen Baldomero, Boris Labar1, Jane Apperley2, Alvaro Urbano-Ispizua3 for the Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT)

Division of Hematology, Department of Internal Medicine, University Hospital Basel, Basel, Switzerland; 1Zagreb University Hospital Center, Zagreb, Croatia; 2Department of Hematology, Imperial College School of Medicine, Hammersmith Hospital, London, UK; and 3JACIE Office, Hematology Department, Hospital Clinic, Barcelona, Spain

Transplantation of hematopoietic stem cells (HSCT) has seen rapid expansion during the last decade. It is evident that there are differences between eastern and western European countries when this high cost procedure is concerned. In order to obtain more insight into the mechanisms associated with these differences, we compared the transplant rates (number of transplants per 10 million population) for allogeneic and autologous HSCT between selected eastern and western European countries and looked for factors associated with their differences. Data were obtained by the annual European Group for Blood and Marrow Transplantation (EBMT) activity survey for the period from 1990 to 2003. Transplant rates were substantially lower in eastern European countries for autologous, allogeneic, and unrelated HSCT throughout the observation period. The rapid increase in transplant rates during the 1990s occurred later in eastern European countries. Transplant rates continued to rise during the last three years in eastern European countries in contrast to a plateau in transplant rates in western European countries. There was a clear correlation between economic factors, measured as gross national income per capita, and transplant rates for low-income countries. There was also a clear correlation between team density (number of teams per 10 million population) and transplant rates. These data document that economic factors explain the differences in transplant rates between eastern and western European countries only in part. Another important factor seems to be the access to the therapeutic procedure. These data provide a basis for health care planning.

Key words: Europe; hematopoietic stem cells; transplantation

For many patients with severe acquired or congenital disorders of the hematopoietic system or with chemosensitive, radiosensitive, and immunosensitive malignancies, hematopoietic stem cell transplantation (HSCT) offers a unique opportunity for long-term disease control (1-4). HSCT has seen rapid expansion and substantial changes during the last decade (5-6). Today, stem cells from bone marrow, peripheral blood, or cord blood are used as the stem cell source. Donors include the patients themselves for autologous use, HLA-identical siblings, other family members, or unrelated volunteers from one of the increasing worldwide donor pools or cord blood banks. As a result of prospective, randomized control studies, or retrospective analyses, HSCT is now integrated in the therapeutic plan for many hematological malignancies (7-10). The introduction of reduced intensity conditioning transplants has further expanded HSCT to patients of older age and with co-morbidities (11-13).

The increasing demand for this high cost procedure presents a challenge for health care providers. While patients seek access to an optimal therapy, institutions are confronted with limited resources. Information on changes in HSCT technology and on factors associated with its utilization is essential. Also, insights into mechanisms of HSCT use are essential for rational decision making, to avoid the errors of the past, and to be able to react to sudden changes. The transient use of autologous HSCT for breast cancer (5), recent decline of allogeneic HSCT for chronic myeloid leukemia, (6) and increasing demand for HSCT for lymphoid malignancies and multiple myeloma, both based on prospective randomized controlled studies which showed a benefit for autologous HSCT (7-9).

At the same time, transplant number and transplant rates differ among European countries. It is essential to get information on the reasons behind these differences. Associations with economics, e.g. gross national income per capita or health care expenditure

Web-extra: The list of the transplantation teams of the European Group for Blood and Marrow Transplantation.
per capita, have been published earlier (14). However, they explain only part of the differences. In view of the political changes over the last decade and in our search for tools to improve the situation, we were specifically interested in a comparison of the transplant activity between eastern and western European countries. For this purpose we used the European Group for Blood and Marrow Transplantation (EBMT) activity survey (15) and looked at HSCT evolution in selected countries during the last decade.

Patients and Methods

Data Collection and Validation

Data collection was based on the EBMT activity surveys introduced in 1990 (15). All EBMT members and affiliated non-members are requested annually to report on a survey sheet the number of new patients transplanted during the preceding year by indication, stem cell source, and type. In addition, the form collects generic information on the number of re- or multiple transplants, on the percentage of cord blood HSCT and, since 1999, on the percentage of transplants with reduced intensity conditioning.

The EBMT survey, which was adopted by the General Assembly as a mandatory self-reporting system, forms an integral part of a prospective quality assurance program (http://www.EBMT.org). The latter includes revalidation of a computer print-out of entered data by reporting teams, cross-checking with national transplant registries, and onsite visits.

Teams

For the 2003 report, 652 teams in 40 European countries were contacted (web extra). Of them, 578 reported their data (preliminary data; end September 2004), and 39 reported being inactive. This corresponds to a 94% return rate for all participating teams and includes 98% of the 461 transplanting EBMT team members reporting to the survey. Thirty five teams known by the investigators to have been performing HSCT in 2003 were also contacted, but chose not to reply or for unknown reasons failed to do so, despite several efforts to reach them. No major transplant team in Europe is missing from this list.

Table 1. Population, gross national income per capita, transplant rates and team density in selected eastern and western European countries in 2003*

<table>
<thead>
<tr>
<th>Country</th>
<th>Population in mil.</th>
<th>GNI/cap</th>
<th>No. of teams</th>
<th>No. of transplant per 10 million</th>
<th>HSCT per 10 million</th>
<th>No. of allogeneic HSCT</th>
<th>No. of autologous HSCT</th>
<th>No. of unrelated HSCT per 10 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Europe:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>8.2</td>
<td>26.7</td>
<td>15</td>
<td>18.3</td>
<td>319</td>
<td>390</td>
<td>134</td>
<td>164</td>
</tr>
<tr>
<td>Belgium</td>
<td>10.3</td>
<td>25.8</td>
<td>20</td>
<td>19.4</td>
<td>544</td>
<td>529</td>
<td>184</td>
<td>179</td>
</tr>
<tr>
<td>Switzerland</td>
<td>7.4</td>
<td>39.9</td>
<td>10</td>
<td>13.5</td>
<td>354</td>
<td>478</td>
<td>114</td>
<td>154</td>
</tr>
<tr>
<td>Germany</td>
<td>82.4</td>
<td>25.3</td>
<td>107</td>
<td>13.0</td>
<td>3,750</td>
<td>455</td>
<td>1,406</td>
<td>171</td>
</tr>
<tr>
<td>Denmark</td>
<td>5.4</td>
<td>13.8</td>
<td>3</td>
<td>5.6</td>
<td>209</td>
<td>388</td>
<td>98</td>
<td>108</td>
</tr>
<tr>
<td>Spain</td>
<td>40.2</td>
<td>17</td>
<td>67</td>
<td>16.7</td>
<td>1,673</td>
<td>416</td>
<td>455</td>
<td>113</td>
</tr>
<tr>
<td>Finland</td>
<td>5.2</td>
<td>27</td>
<td>7</td>
<td>13.5</td>
<td>274</td>
<td>528</td>
<td>116</td>
<td>224</td>
</tr>
<tr>
<td>Italy</td>
<td>58.0</td>
<td>21.6</td>
<td>91</td>
<td>15.3</td>
<td>127</td>
<td>324</td>
<td>46</td>
<td>117</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16.2</td>
<td>26.3</td>
<td>13</td>
<td>8.0</td>
<td>676</td>
<td>419</td>
<td>269</td>
<td>167</td>
</tr>
<tr>
<td>Norway</td>
<td>4.6</td>
<td>43.4</td>
<td>5</td>
<td>10.9</td>
<td>126</td>
<td>274</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>Portugal</td>
<td>10.5</td>
<td>12.1</td>
<td>6</td>
<td>5.7</td>
<td>243</td>
<td>231</td>
<td>87</td>
<td>83</td>
</tr>
<tr>
<td>Sweden</td>
<td>9.0</td>
<td>28.8</td>
<td>8</td>
<td>8.9</td>
<td>478</td>
<td>531</td>
<td>149</td>
<td>166</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>60.1</td>
<td>28.4</td>
<td>53</td>
<td>8.8</td>
<td>2,210</td>
<td>368</td>
<td>785</td>
<td>131</td>
</tr>
<tr>
<td>Eastern Europe:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Croatia</td>
<td>4.5</td>
<td>5.4</td>
<td>2</td>
<td>4.4</td>
<td>110</td>
<td>244</td>
<td>25</td>
<td>56</td>
</tr>
<tr>
<td>Czech</td>
<td>10.3</td>
<td>6.7</td>
<td>10</td>
<td>9.7</td>
<td>508</td>
<td>493</td>
<td>143</td>
<td>139</td>
</tr>
<tr>
<td>Estonia</td>
<td>1.4</td>
<td>5</td>
<td>1</td>
<td>7.1</td>
<td>12</td>
<td>85</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>Hungary</td>
<td>10.0</td>
<td>6.3</td>
<td>4</td>
<td>4.0</td>
<td>174</td>
<td>173</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>Lithuania</td>
<td>3.6</td>
<td>4.5</td>
<td>2</td>
<td>5.6</td>
<td>49</td>
<td>136</td>
<td>20</td>
<td>56</td>
</tr>
<tr>
<td>Poland</td>
<td>38.6</td>
<td>5.3</td>
<td>17</td>
<td>4.4</td>
<td>706</td>
<td>183</td>
<td>268</td>
<td>69</td>
</tr>
<tr>
<td>Slovakia</td>
<td>5.4</td>
<td>4.9</td>
<td>4</td>
<td>7.4</td>
<td>118</td>
<td>217</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td>Slovenia</td>
<td>2.0</td>
<td>11.8</td>
<td>1</td>
<td>5.0</td>
<td>35</td>
<td>175</td>
<td>9</td>
<td>45</td>
</tr>
</tbody>
</table>

*Abbreviations: GNI/cap – gross national income per capita, in US$; HSCT – hematopoietic stem cell transplant.
transplant rates with the economic power of each of selected countries. Economic data, e.g. gross national income (GNI) per capita, were obtained from the World Bank (http://www.worldbank.com). For the purpose of this study we restricted the analysis to the countries presented in Table 1. This selection was made to have a homogeneous comparison and to avoid bias from countries with very low number of HSCT.

**Statistical Analysis**

Different descriptive statistical methods were used to analyze the data. Mean, median, and standard deviations of numerical variables were calculated on an Excel spreadsheet. The relationship between transplant rates and GNI per capita or between transplant rates and team density was estimated with regression analysis using the SPSS program, version 11 (SPSS Inc., Chicago, IL, USA).

**Results**

**Participating Teams**

Of a total of 578 teams reporting HSCT in 2003, 334 (58%) did both allogeneic and autologous transplants; 222 (38%) restricted their activity to autologous, and 8 teams (1%) to allogeneic transplants only. Fourteen teams (3%) reported not to have performed any transplants in 2003. The restriction to the 8 eastern and 15 western European countries includes 41 teams in eastern and 475 teams in Western Europe.

**HSCT in 2003: First Transplants 2003**

A total of 20,598 first transplants, 6,901 (34%) allogeneic and 13,697 (66%) autologous were carried out in Europe in 2003. The selected European countries performed a total of 18,732 first transplants, 6,048 (32%) allogeneic and 12,684 (68%) autologous (Table 1).

**Transplant Rates in 2003**

The transplant rates for all HSCT, autologous, allogeneic, and unrelated transplants, are illustrated in Table 1 and Figure 1. There were differences between and within eastern and western European countries in all aspects analyzed. In western European countries transplant rates were higher with only slight differences compared to the donor type or indication.

**Changes in Transplant Activity 1990-2003**

The total number of transplants increased from 4,234 HSCT in 1990 to their current number and this increase was paralleled by an increase in transplant rates (Fig. 2). Transplant rates started at a higher level in western European countries in 1990, increased earlier and to a greater extent at the beginning of the 1990s, and were always about one-third to one-half higher than in eastern European countries. Autologous HSCT reached a plateau in 1997 and allogenic HSCT in 2000 and both remained unchanged until the present time. However, there was no plateau in eastern European countries. The “plateau” in Western Europe reflects the sum of the still decreasing number of HSCT for solid tumors but also the increasing number of HSCT for lymphoid malignancies and multiple myeloma in autologous HSCT, as well as the decreasing number of HSCT for chronic myeloid leukemia and the increasing number of HSCT for acute leukemias in allogeneic HSCT. As evident from Figure 1, transplant rates in a few selected eastern European
countries reached the similar level as in Western Europe by the year 2003.

Correlation between Transplant Rates and Macroeconomic Factors

Macroeconomic factors of the individual countries strongly influenced transplant rates. In general, countries with higher GNI per capita had higher transplant rates than countries with lower GNI per capita (Fig. 3). There were marked differences between and within the eastern and western European countries in GNI per capita and transplant rates. In general, GNI per capita on transplant rates were lower in eastern European countries, with a few exceptions, such as in the Czech Republic where transplant rates paralleled the transplant rates of some western European countries despite a lower GNI per capita (Fig. 3). The regression analysis suggests a saturation effect of GNI per capita on transplant rates at about US$20,000 per capita with no further increase in transplant rates, which could be attributed to higher income of the countries at higher GNI per capita. There was a clear correlation between team density and transplant rates (Fig. 4). Transplant rates were substantially higher in the countries with higher team density, hence in the countries with fewer patients to be served by an individual transplant team. In general, team density was markedly lower in eastern compared to western European countries with some exceptions on both sides. There was a clear but weak correlation between GNI per capita and team density, even though, team density had a higher impact on transplant rates than GNI per capita. Other factors might impact on transplant rates as well, and further studies are required to obtain more insight. For this survey, the analysis was restricted to GNI per capita and team density.

Discussion

The present analysis from the 2003 EBMT activity survey documents similarities and differences between eastern and western European countries and gives insight into the most recent developments. Transplant rates and team densities were in general lower in Eastern Europe. They were lower in Eastern Europe at the beginning of the EBMT activity survey in 1990 (15) and, with a few exceptions, remained lower despite a continuing increase in HSCT in the majority of countries during the observation period (6). Transplant rates were lower in Eastern Europe for autologous, allogeneic, or unrelated HSCT and for all indications alike. Eastern European countries started at a lower level in 1990 and followed the massive increase which was observed in the early 1990s in western European countries with a delay from a few to several years. Specifically, HSCT from unrelated donors has only begun to be an important part of HSCT activity in Eastern Europe in the most recent years (5,15,17-19).

The data also provide some explanations for the differences. The correlation between transplant rates and certain macroeconomic factors, such as GNI per capita in low-income countries and the absence of such correlation in high-income countries, is easily understood. Below a certain level of economic power, no country can afford a substantial number of HSCT (14). Transplants are just too expensive. This has been presented earlier for HSCT and is in general considered to be the case for most of high cost medical procedures (20-23). Vice versa, there is no indication that the number of patients with the diseases which are considered as indications for a HSCT increases with increasing GNI per capita. Hence, there
should be a plateau. A note of caution is necessary. The risk of overuse of resources cannot be neglected in medicine (22). As such, part of the major increase in HSCT in Western Europe during the mid-1990s was due to a rapid increase in autologous HSCT for breast cancer. Despite thousands of HSCT for breast cancer, the final role of HSCT in this disease remains unknown, and many of these HSCT might in retrospect have been of little benefit (24). Eastern European countries at least made more judicious use of their resources during that time.

The data of this analysis point to an additional important macroeconomic factor – team density (15). More transplants were performed in countries with more transplants teams per number of inhabitants. The fewer patients a team has to serve, the higher the likelihood that the individual patient will have access to this procedure. There is a need to disseminate a given technology within a country for its optimal use (22). An access to the procedure is a prerequisite for obtaining a transplant. The question remains, what is the optimal number of transplant teams compared to the number of inhabitants. The present data at least indicate the need for more than one team per country. They also indicate a plateau. A reasonable number seems to be one center per one to two million inhabitants; there is certainly no obvious advantage with a larger number of teams. This statement includes a cautionary remark. EBMIT has no information about the distances patients have to travel and what distances they would be prepared to travel. There are major differences in the distances between the countries, in Eastern and Western Europe alike.

This report gives no information on the outcome differences between eastern and western European countries. These differences, if there are any, will be reported elsewhere. This report just illustrates the status quo of HSCT in Europe 2003, showing the similarities and differences between eastern and western European countries. This information should give health care officials a rational basis for their decision making.

Acknowledgements

The cooperation of all participating teams and their staff (listed in the Appendix), the JACIE Accreditation Office (A. Urbano-Ispizua, F. McDonald, E. McGrath), the European EBMT Data Office in Paris (V. Chesnel, N. Corin), the EBMT Registry Subcommittee (C. Ruiz de Elvira), the French Registry SFGM (J.P. Jouet), the Dutch Registry TYPHON (A. Hagenbeek, A. v. Biezen, N. Tazelaar), the Austrian Registry (H. Greinix, B. Lindner), the Italian Registry (M. Vignetti, W. Arrese, R. Oneto), the Czech Registry (M. Trnkova, K. Benešova), the German Registry (H. Ottinger, C. Müller, K. Kubanek, N. Schmitz, U.W. Schaefer), the Swiss Registry (J. Passweg, H. Baldomero), the British Registry (K. Towlson, N. Russell), the Turkish Registry (C. Gurman, M. Arat), and the Spanish Transplantation Office (ONT) (M. Naya) is greatly appreciated. The authors also thank A. Maerki for excellent secretarial assistance, R. Brand (Leiden) for statistical help, as well as L. John for technical assistance with data management.

Figure 3. Correlation between transplant rates and gross national income per capita in selected eastern and western European countries. Individual points reflect participating countries. Regression curve is based on all European countries (data points restricted to selected countries; Table 1). Green – eastern Europe; red – western Europe; GNI/cap – gross national income per capita, in US$; A – Austria; B – Belgium; CH – Switzerland; CR – Croatia; CZ – Czech Republic; D – Germany; DK – Denmark; E – Spain; EE – Estonia; F – France; FIN – Finland; HU – Hungary; I – Italy; IRL – Ireland; Lit – Lithuania; N – Norway; NL – Netherlands; P – Portugal; PL – Poland; S – Sweden; SK – Slovakia; SL – Slovenia; UK – United Kingdom.

Figure 4. Correlation between transplant rates and team density in selected eastern and western European countries. Individual points reflect participating countries. Regression curve is based on all European countries (data points restricted to selected countries; Table 1). Green – eastern Europe; red – western Europe; GNI/cap – gross national income per capita, in US$; A – Austria; B – Belgium; CH – Switzerland; CR – Croatia; CZ – Czech Republic; D – Germany; DK – Denmark; E – Spain; EE – Estonia; F – France; FIN – Finland; HU – Hungary; I – Italy; IRL – Ireland; Lit – Lithuania; N – Norway; NL – Netherlands; P – Portugal; PL – Poland; S – Sweden; SK – Slovakia; SL – Slovenia; UK – United Kingdom.
The work was supported in part by a grant from the European Leukemia Net, the Swiss National Research Foundation No. 3200B0-106105/1, the Swiss Cancer League / Oncosuisse, the Regional Cancer League and the Horton Foundation. EBMT is supported by grants from the corporate members: Amgen Europe, Hoffmann-La Roche Ltd., Gilead Sciences, Baxter Oncology, Pharmacia Corporation, Chugai-Aventis, Fresenius HemoCare, SangStat, Schering AG, Gambro BCT, Elan Pharmaceuticals, Miltenyl Biotec GmbH, Therakos, Wyeth-Lederlé, Astra, Cobe International, Nextar, Liposome Co, Imtix, Octapharma, Stem Cell Technologies, ICN Pharmaceuticals, and Bristol-Meyers Squibb.

References

Correspondence to:
Alois Gratwohl
Division of Hematology
Department of Internal Medicine
University Hospital Basel
CH-4031 Basel, Switzerland
hematology@uhbs.ch

Received: September 29, 2004
Accepted: November 6, 2004