Developments and Quality Assurance in Stem Cell Transplantation
Data from a German National Registry

Hellmut Ottinger, Carlheinz Müller, Dietrich W. Beelen, Gerhard Ehninger, Norbert Schmitz, Axel Zander, Hubert Schrezenmeier

SUMMARY
Introduction: The Deutsches Register für Stammzelltransplantationen e.V. (DRST) collects unique data on all hematopoietic stem cell transplantations (HSCT) in Germany from 1998 onwards, in close cooperation with all German centers for HSCT. Methods: Analysis of DRST data. Results: Peripheral blood stem cells (PBSCT) are now the preferred stem cell source over bone marrow. Since 1998 the number of allogeneic stemcell transplantations in Germany has increased steadily. In 2001 for the first time the majority of allogeneic HSCT in Germany were sourced from unrelated donors. After a transient decrease, the number of autologous HSCT has been rising again since 2002, reflecting in particular transplants performed for multiple myeloma and Non-Hodgkin's-Lymphoma. The number of autologous SCT for solid tumours, on the other hand, which was transiently one of the main indications for autologous SCT in the 1990s, has now dropped considerably. Discussion: The DRST has successfully established itself as the National Registry for HSCT in Germany. It provides the basis for quality assurance measures and serves as a platform for scientific studies with the aim of further improvement of HSCT.


Key words: hematopoietic stem cell transplantation, hematopoietic stem cells, stem cell donors, national registry, quality assurance

Hematopoietic stem cells (blood stem cells) are the cells of origin of the blood. They give rise to all of the formed elements in the bloodstream: erythrocytes, leukocytes, and platelets. In hematopoietic stem cell transplantation (HSCT), blood stem cells are transferred from a donor to a recipient so that they can assume biological functions in the recipient’s body and then carry out these functions permanently.

In autologous HSCT, the donor and the recipient are the same individual. In allogeneic HSCT, the donor and the recipient are genetically different members of the same species, e.g., two siblings or two unrelated persons.

Blood stem cells can be obtained by bone marrow aspiration after stimulation with the growth factor G-CSF (granulocyte colony stimulating factor), by leukapheresis of peripheral venous blood with a cell separator, or immediately after birth from "cord blood," i.e., venous blood from the umbilical cord. Accordingly, the three possible types of allogeneic HSCT are bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT), and umbilical venous blood transplantation.

The medical and societal importance of hematopoietic stem cell transplantation
Hematopoietic stem cell transplantation is of special importance in clinical medicine and in governmental health policy, because:
It is used exclusively to treat life-threatening illnesses. Among these are malignant disorders of the hematopoietic system, particularly leukemia and lymphoma, including multiple myeloma; impairments of hematopoiesis and congenital disorders of the immune system (aplastic anemia, congenital severe combined immune deficiency); inborn errors of metabolism (enzyme deficiencies); and some solid tumors (germ cell tumors, soft-tissue sarcomas).

It is the only treatment of these diseases that offers the prospect of a cure.

Its cost is high despite the relatively small number of cases: in 2004, 1,513 allogeneic and 2,442 autologous initial transplantations were carried out in Germany, at a cost of approximately 250 million euros (310 million dollars).

**Quality assurance procedures**

Among all medical treatments, HSCT is particularly well suited to quality assurance analysis because of the seriousness of the diseases for which it is used, its high cost, and the relatively small number of patients treated. On 1 June 1997, the Scientific Advisory Committee of the German Medical Association (Bundesärztekammer, BÄK) issued guidelines on the transplantation of stem cells from peripheral blood, with specific requirements for both the "clinical unit" (Chap. 6) and the "preparing unit" (Chap. 7). Furthermore, the chapter on "documentation, registration, and scientific evaluation" (Chap. 8) explicitly requires, among other things, the recording and evaluation of all HSCT procedures and their outcomes in a central registry, as a means of external quality control (1).

**Certification procedure**

In 1998, the responsible committee of scientific experts, i.e., the German Working Group for Bone Marrow and Blood Stem Cell Transplantation (Deutsche Arbeitsgemeinschaft für Knochenmark- und Blutstammzell-Transplantation, DAG-KBT), put these guidelines into practice by initiating a certification procedure for all German clinical units performing HSCT. The DAG-KBT also decided to create a central registry for the recording of the essential clinical data from all transplantations performed in Germany from 1 January 1998 onward.

The certification procedure will be described here only briefly. It is based on an extensive catalogue of quality standards, issued by an expert committee and specifying requirements with regard to the staffing, architectural layout, technical apparatus, expert qualifications, and organization of HSCT units. When an HSCT unit is to be evaluated for certification, the certification office arranges a site visit by an independent commission, which checks whether the quality standards are appropriately met (e-mail contacts: volkmar.boehme@ak-stge-org.lbk.hh.de, norbert.schmitz@ak-stge-org.lbk.hh.de). In the meantime, the German certifying procedure was adapted to conform to the specifications of the European Union’s “Joint Accreditation Committee ISCT-EBMT” (JACIE), which went into effect in 1999 (see www.jacie.org for details). The JACIE-adapted procedure is recognized internationally. A list of the transplantation units certified to date can be found at www.dag-kbt.de under the menu item “Zertifizierung” (certification). In addition to these units, a number of others are now under evaluation.

**The central national stem cell transplant registry**

A central national registry of clinical data was called into being by the DAG-KBT in 1998. The German Registry for Stem Cell Transplantation (Deutsches Register für Stammzelltransplantationen, DRST) has its secretariat at the University Clinic in Essen and its database at the Central Bone Marrow Donor Registry (Zentrales Knochenmarkspenderegister, ZKRD) in Ulm. The DRST collaborates closely with the Pediatric Registry for Stem Cell Transplantation (Pädiatrisches Register für Stammzelltransplantationen, PRST) in Frankfurt.

The DRST collaborates closely, too, with the Europe-wide registry of the “European Group of Blood and Marrow Transplantation” (EBMT). The creators of the DRST considered it important to establish detailed regulations on the composition (membership) of the DRST, the rules of procedure for DRST member conferences, and the creation of an independent committee to deal with issues of data access. As a national body, the DRST plays a key role in seeing to it that the data are complete and that quality is optimally assured.
All of the more than 100 active transplantation units in Germany have signed a registry contract in which they commit themselves to cooperating with the DRST. The registry contract not only specifies the form in which data are to be reported, but also requires the centers to obtain informed consent and to safeguard their data appropriately. Furthermore, the DRST, in collaboration with the EBMT, enables all German units to publish their data on the Internet. Figure 1 shows the locations of the German transplantation centers currently contributing to the DRST database.

**FIGURE 1**

Centers for autologous stem cell transplantation (left) and allogeneic stem cell transplantation (right) in Germany, as of October 2006.

**FIGURE 2**

Trend in the number of allogeneic HSCT procedures performed yearly in Germany, 1998-2005 (increased from 1,198 procedures in 1998 to 2,060 in 2005). The number of procedures shown for each year is the sum of all initial transplantations, retransplantations because of recurrent disease or transplant failure, and allogeneic HSCT after previous autologous HSCT.

**FIGURE 3**

Trends in the number of allogeneic initial transplantations performed yearly in Germany, 1998-2005, for each of the four most common indications. AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia; MDS, myelodysplastic syndromes.
Every January, in order to keep abreast of changes in the field in timely fashion, the DRST (in cooperation with the “EBMT Transplant Activity Center” in Basel) tabulates global summary data on allogeneic and autogenous HSCT from all of the transplantation units in Germany. In addition, a detailed set of data on each transplantation procedure must be reported to the DRST. The global data from the annual tabulation enable a check on the completeness of documentation in each individual case.

The rest of this paper provides an overview of allogeneic and autologous transplantation in Germany. This information is based on a review of complete data from all transplantation centers. The trends shown here are thus definitely real and not attributable to sampling error (a so-called “registry effect”).

For further discussion, and for an overview of the scientific studies that have been and are being carried out on the basis of DRST data, see the DRST annual reports (2).

**Allogeneic HSCT: current status and developments**

The data collected from 1998 to 2005 reveal the following developments in allogeneic hematopoietic stem cell transplantation in Germany:

The number of allogeneic transplantations per year rose steadily over the period of study. The annual tally of initial transplantations, retransplantations because of recurrent disease or transplant failure, and cases of allogeneic HSCT after a previous autologous HSCT is shown in Figure 2 as a single, overall figure for each year.

Among all European countries, Germany ranks near the top in the number of allogeneic hematopoietic stem cell transplantation procedures per million inhabitants in 2003 (Table 1).

**TABLE 1**

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>17.6</td>
</tr>
<tr>
<td>Germany</td>
<td>17.1</td>
</tr>
<tr>
<td>Netherlands</td>
<td>16.8</td>
</tr>
<tr>
<td>Switzerland</td>
<td>15.6</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>13.2</td>
</tr>
<tr>
<td>France</td>
<td>12.2</td>
</tr>
<tr>
<td>Spain</td>
<td>11.4</td>
</tr>
</tbody>
</table>

Source: EBMT Transplant Activity Center, Basel

**TABLE 2**

<table>
<thead>
<tr>
<th>Land</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>40.8</td>
</tr>
<tr>
<td>France</td>
<td>37.2</td>
</tr>
<tr>
<td>Switzerland</td>
<td>32.8</td>
</tr>
<tr>
<td>Spain</td>
<td>30.7</td>
</tr>
<tr>
<td>Germany</td>
<td>28.4</td>
</tr>
<tr>
<td>Netherlands</td>
<td>26.2</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>24.1</td>
</tr>
</tbody>
</table>

Source: EBMT Transplant Activity Center, Basel
From 1998 to 2005, there was not only an increase in the overall number of allogeneic transplantations, but also a marked shift in the spectrum of indications, donor types, and stem cell sources.

**Indications**

The individual disease entities contributed variably to the rise in case numbers. Figure 3 shows that the number of transplantations performed annually for chronic myeloid leukemia (CML) has markedly declined. This fact is traceable to the introduction of a new medication, imatinib mesylate, a specific inhibitor of bcr/abl-tyrosine kinase. Nonetheless, the decline of transplantations for CML was more than compensated for by a rise in transplantations for acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndromes (MDS) (Figure 3) (3-6).

**Donor types**

The number of transplantations from unrelated donors has risen each year and has outstripped the number of SCTs from related donors every year since 2001. In 2005, for example, 62% of allogeneic first transplantations involved stem cells from unrelated donors (Figure 4). This is a result of the increased chance of finding a compatible unrelated donor in the ever-expanding international donor registries. Furthermore, the outcomes of transplantation from related and unrelated donors are now nearly identical.

**Stem cell sources**

At the outset of DRST documentation, peripheral blood stem cells were used for allogeneic transplantation almost as often as bone marrow stem cells. Since then, the fraction of allogeneic transplantations performed with peripheral blood stem cells in Germany has markedly increased. In 2005, only 15% of all allogeneic first transplantations involved bone marrow stem cells (Figure 5). Over the years 1998-2005, peripheral blood stem cells were increasingly preferred, regardless of whether the donor was related or unrelated. The fraction of transplantations performed with peripheral blood cells was especially high – over 90% – in patients with advanced leukemia and lymphoma. Yet, for non-malignant diseases such as aplastic anemia, thalassemia, and immune system defects, more than 50% of all transplantations were still being performed with bone marrow stem cells, even in 2005.

In contrast, umbilical cord venous blood is used very rarely in Germany as a source of stem cells, with only 14 cases in 2004 and 10 in 2005.
Current extent of data in the DRST

Beyond the initial data entered for every patient in the EBMT/DRST Survey, the DRST also contains a large amount of follow-up data in the EBMT’s MED-A format. 10,575 cases of allogeneic HSCT have been documented to date, among them 3,120 transplantations in patients with acute myeloid leukemia (AML), 1,766 in patients with chronic myeloid leukemia (CML), and 1,658 in patients with acute lymphocytic leukemia (ALL). The DRST has also collected extensive data on allogeneic transplantation for rarer diseases such as aplastic anemia and immune system defects (247 and 104 cases, respectively, as of April 2006).

For the major disease entities, the DRST yields statistics on important clinical endpoints, such as survival, treatment-associated mortality, and disease recurrence. Figure 6, for example, shows survival curves after transplantation for AML, depending on the stage of disease. The individual transplantation units can compare their own data with the nationwide data to detect any potential deficiencies in treatment outcome.

Developments in autologous HSCT

Trends are seen in autologous HSCT as well. The number of patients receiving autologous transplants declined markedly from 1998 to 2001 (Figure 7), as a consequence of the mostly negative results of comparative studies of autologous HSCT in breast cancer (Figure 8). The number of autologous transplantations began to rise again in 2002 and has since outstripped the original 1998 level. This is mainly due to the increased number of patients with multiple myeloma (plasmacytoma) undergoing the procedure, while the case numbers for other types of non-Hodgkin’s lymphoma (NHL) have risen relatively little (Figure 8) (5-7).

Germany occupies a middle position among European countries in the number of autologous first transplantations performed per million inhabitants in 2003 (Table 2) (8, 9).

Peripheral blood stem cells were preferred for nearly all autologous transplantation procedures for all indications. The fraction of autologous transplantations involving bone marrow stem cells was only 1% for patients with lymphoma, myeloma, or solid tumors. As of April 2006, the DRST database contains follow-up data on 19,973 cases of autologous HSCT, from 1998 to the present. 6,796 of these procedures were carried out for plasmacytoma and 5,634 were carried out for other types of non-Hodgkin’s lymphoma (NHL).

Acknowledgment

This information on the development of stem cell transplantation in Germany could not have been obtained without the collaboration of the German transplantation centers with the German Registry for Stem Cell Transplantation (DRST). The authors thank these centers, as well as the European Group for Blood and Marrow Transplantation (EBMT), for their cooperation; the German Cancer Aid group (Deutsche Krebshilfe) for its support in the initial phase, up to 2003; and the German José Carreras Leukemia Foundation for its support for DRST projects from 2004 onward. Special thanks are due to the parent institutions in Essen and Ulm for their support over the past 9 years and into the present, as well as to the German Bone Marrow Donor File (Deutsche Knochenmarkspenderdatei, DKMS) for its subsidy to the pediatric subregistry.
Contacts for further information
DRST Secretariat, Institute for Immunology, University Clinic Essen, Virchowstr. 171, 45147 Essen, Germany; DRST Data Center, c/o ZKRD (Central Bone Marrow Donor Registry for the Federal Republic of Germany), Helmholtzstr. 10, 89032 Ulm, Germany.

Conflict of Interest Statement
The authors declare that no conflict of interest exists according to the Guidelines of the International Committee of Medical Journal Editors.


Translated from the original German by Ethan Taub, M.D.

REFERENCES
2. DRST-Jahresberichte; www.drst.de

Corresponding author
Prof. Dr. med. Hubert Schrezenmeier
Institut für Transfusionsmedizin des Universitätsklinikums Ulm
und Institut für Klinische Transfusionsmedizin
und Immunogenetik Ulm gGmbH
Helmholtzstr. 10, 89081 Ulm, Germany