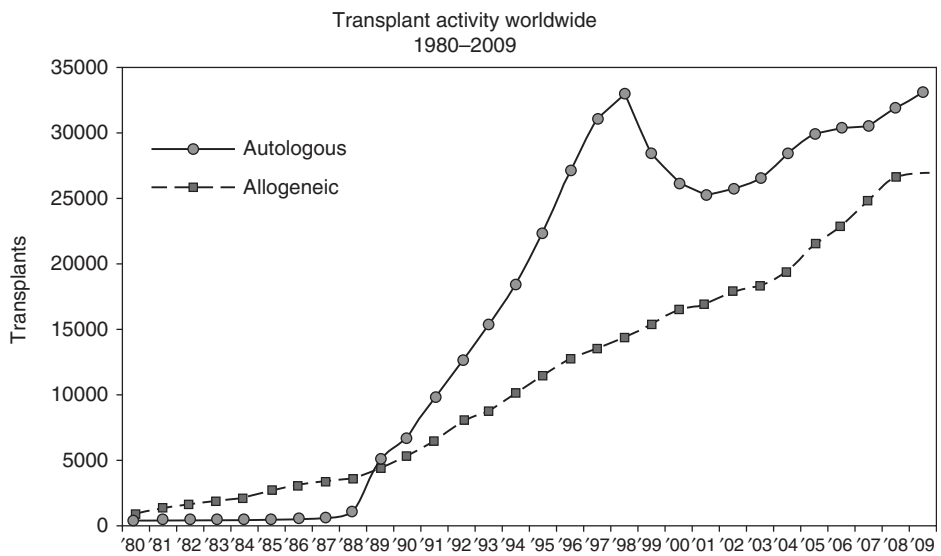
Section 1 **Basic science**

Chapter 1

Hematopoietic cell transplantation: past, present, and future

Reinhold Munker

The transplantation of hematopoietic stem cells (derived from the bone marrow of healthy donors) in the 1970s was considered a highly experimental procedure and was offered only to patients with late-stage leukemia. Later, it was recognized that only a small fraction of the transplanted cells were true stem cells and that the cure effected by allogeneic transplant was mediated by an immune reaction (graft-versus-leukemia reaction). In the last 20 or 30 years, hematopoietic cell transplantation (HCT) became a routine procedure both in the United States and worldwide. It is estimated that currently 60 000 or more patients globally undergo HCT every year. Overall, both allogeneic and autologous transplants have found their indications in the everyday practice of hematology/oncology. As can been seen in the following figures, allogeneic and autologous transplants have enjoyed a huge increase both in the United States and worldwide. In this book, the terms HCT, HSCT (hematopoietic stem cell transplantation), and HPCT (hematopoietic progenitor cell transplantation) will be used interchangeably.



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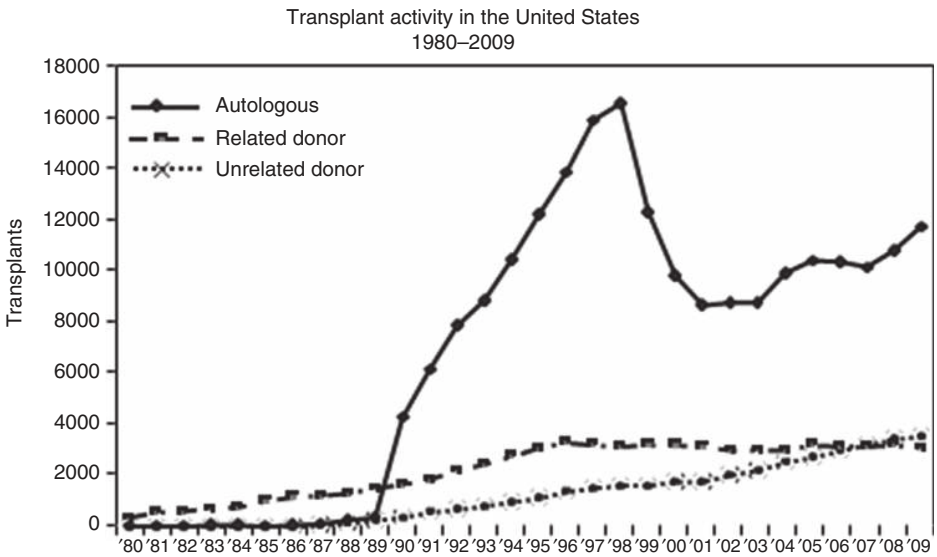
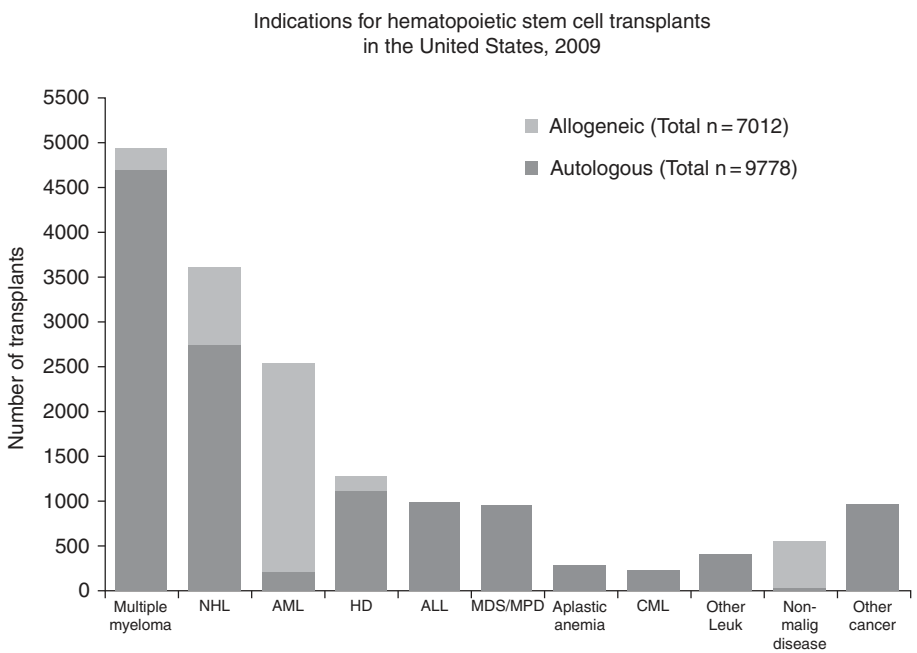


CIBMTR



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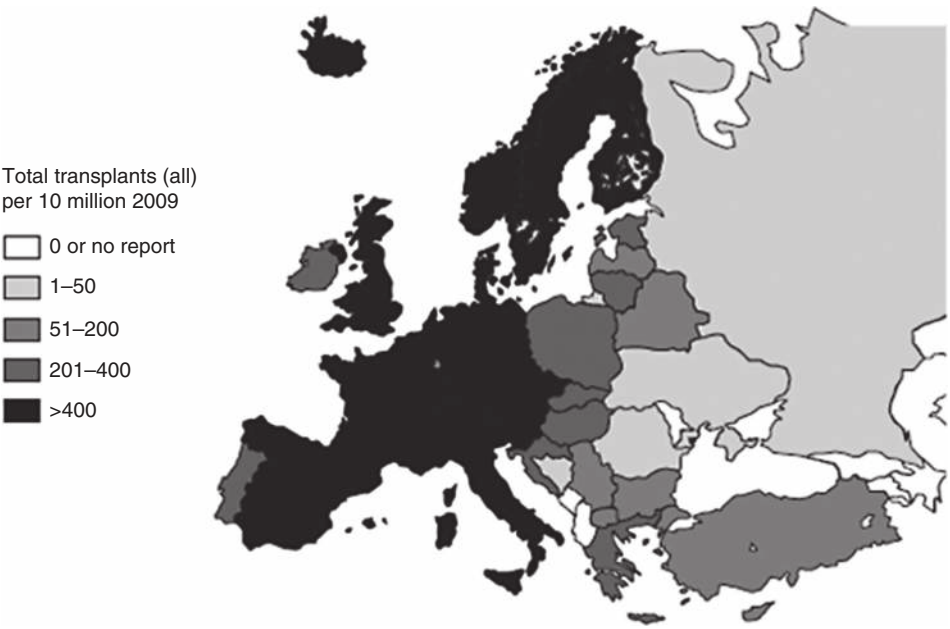
Although the reporting of autologous transplants is voluntary, all accredited transplant centers in the United States submit data to the CIBMTR. Since 2007, when a Stem Cell Transplant Outcomes Database was created, the reporting of allogeneic transplants is mandatory in the United States. In previous years, unrelated transplants facilitated by the National Marrow Donor Program (NMDP) were reported through the NMDP. It was estimated by the CIBMTR that currently more than half of autologous transplants in the United States are reported to a registry.

Overall, allogeneic and autologous transplants in a global perspective have a comparable frequency. The huge increase of autologous transplants in the early and mid-1990s was a result of transplants for breast cancer and multiple myeloma (in the World Health Organization [WHO] classification designated as plasma cell myeloma). The later decrease was caused by the reduced frequency of transplants for breast cancer. More recently, the autologous transplants increased again due to increased salvage transplants for lymphoma (including transplants for older patients). For multiple myeloma, autologous transplant is still the standard of care for most patients, although in older patients its role is challenged now by the introduction of new drugs. Another issue in multiple myeloma is timing of autologous transplantation.

HCT in its autologous form is performed in virtually all cases as a transplantation of mobilized peripheral stem cells. The majority of allogeneic transplantation procedures are performed with peripherally harvested cells, although some indications (severe aplastic anemia, possibly chronic myelogenous leukemia [CML]) still rely upon bone marrow as the graft source.

As seen in the previous figures, allogeneic transplantation has enjoyed a steady growth over the last two decades. During this time, the transplants for CML have decreased significantly due to the introduction of tyrosine kinase inhibitor (TKIs). Other indications like acute leukemias have increased. This correlates with the introduction of reduced-intensity conditioning (RIC) transplants for older patients or patients with comorbidities. At least in the United States, matched-unrelated transplants are about equal with matched-related transplants (or slightly more). This correlates with better outcomes for both types of transplants due to improved typing techniques resulting in better matches and better supportive treatment. In children who need a transplant, a significant number receive stem or progenitor cells from a matched or partially matched cord blood unit.

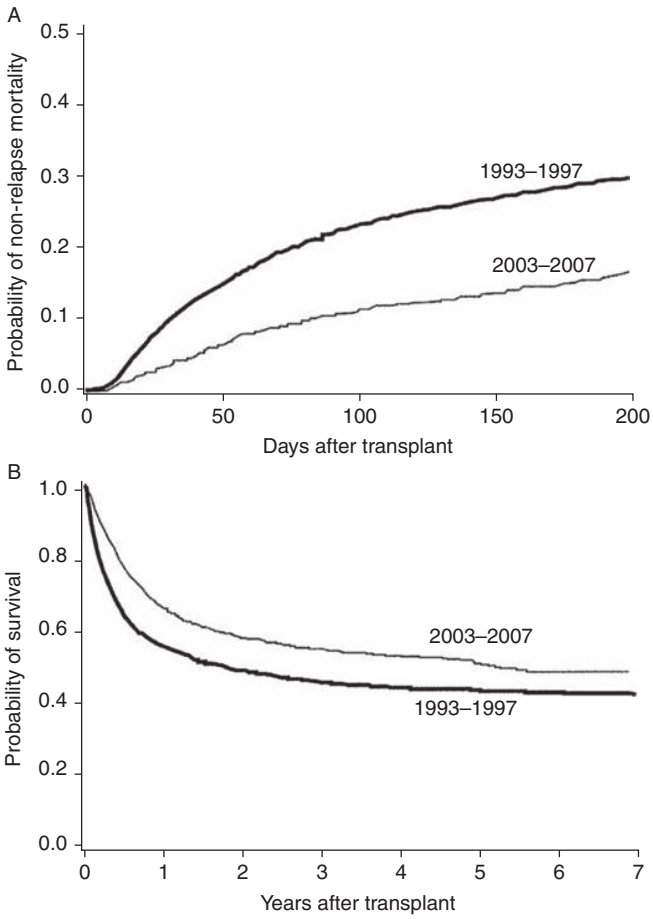
The European Group for Blood and Marrow Transplantation (EBMT) database reported more than 31 000 HCTs for 2009. Among the 28 000 first transplants, 41% were allogeneic and 51% were autologous. As in the North American database, matched unrelated transplants are now more frequent than matched sibling transplants (51% versus 43%). Large differences still exist between the high- and middle-income countries as far as the transplant frequency is concerned. As can be seen in the following figure, the transplant frequency in Western and Middle Europe varies between 50 and more than 400 cases per year among 10 million inhabitants.



Relative transplant frequency in Europe in 2009 (combining autologous and allogeneic transplantation). (Reproduced with permission from Baldomero et al., 2011.)

Autologous transplants following high-dose chemotherapy are generally considered safe. In most centers and for most indications, the transplant-related mortality (TRM) in 2012 is between 1% and 5% at day 100.

As far as complications of allogeneic transplants are concerned, a clear improvement occurred over the last 10–15 years. When a large transplant center in the United States compared the mortality at day 200 (excluding relapses) between the time periods 1993–1997 and 2003–2007, the mortality decreased by 60%. The overall mortality at seven years also decreased by 41%–52%. Generally, allogeneic transplant is now safer despite older and more high-risk patients being treated. The improvement is due to a lower risk of hyperacute acute graft-versus-host disease, fewer severe infections, and fewer liver, kidney, and pulmonary complications.



The probability of death not preceded by relapse at day 200 (A) and the probability of overall survival (OS) at seven years (B) in the two time periods are shown. (Reproduced with permission from Gooley et al., 2011.)

Allogeneic transplantation also has become an option for patients older than 60 years. In a multicenter study using conditioning with low-dose total body irradiation (TBI) ± fludarabine, a five-year risk of non-relapse mortality (NRM) of 27% (95% CI, 22%–32%), of relapse of 41% (95% CI, 36%–46%) and an OS of 35% (95% CI, 30%–40%) were reported (Sorror et al., 2011).

What is next? A survey initiated by the American Society of Blood and Marrow Transplantation shows that a growth in transplant activities of 5%–10% per year can be expected over the next decade (Schriber et al., 2010). This growth will result in a need for training of specialists and new facilities, especially in the developing world. It can be expected that more specific cellular therapies will be developed, and ultimately, the promises of gene therapy will be realized.

Details on the indications in 2012, complications and methods of stem cell and bone marrow transplantation, as well as new cellular therapies will be given in the subsequent chapters in this book.

References and further reading

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Section 1 Basic science

Chapter 2

Basic science

Reinhold Munker and Kerry Atkinson

The human hemopoietic system

Understanding of the human hemopoietic and immune systems has advanced markedly during the past 30 years. The key components of the human hemopoietic system are the hemopoietic growth factors, the hemopoietic stem cell, and the marrow microenvironment. Transcription factors direct hematopoietic differentiation. Each of these components is detailed further in the following sections.

Hemopoietic growth factors

- Colony-stimulating factors (CSFs)
  Granulocyte colony-stimulating factor (G-CSF)
  Granulocyte–macrophage colony-stimulating factor (GM-CSF)
  Macrophage colony-stimulating factor (M-CSF)
  Interleukin (IL)-3
  Erythropoietin
  Thrombopoietin
  IL-5

The BMT Data Book, Third Edition, ed. Reinhold Munker et al. Published by Cambridge University Press.

- Stem cell factors
  Kit ligand (stem cell factor)
  Flt ligand
- Synergistic factors
  IL-1
  IL-6
  IL-7
  IL-9
  IL-10
  IL-11
  IL-12
  Leukemia inhibitory factor (LIF)
- Inhibitors/bidirectional regulators
  Tumor necrosis factor-alpha (TNF-α)
  Transforming growth factor-beta (TGF-β)
  Macrophage inflammatory protein-1β (MIP-1β)
  Interferon gamma (IFN-γ)

Registered hematopoietic growth factors

Native molecule	Form	Generic name	Brand name	Dosage	Manufacturer
G-CSF	Non-glycosylated	Filgrastim	Neupogen®	5 μg/kg/d	Amgen
Peg-G-CSF	Non-glycosylated	Pegfilgrastim	Neulasta®	6 mg/14 d	Amgen
G-CSF	Glycosylated	Lenograstim	Granocyte®	5 μg/kg/d	Chugai/ Sanofi-Aventis, and others
GM-CSF	Non-glycosylated	Molgramostim	Leukomax®	250 μg/m^2/d	Novartis, Schering-Plough, and others
GM-CSF	Glycosylated	Sargramostim	Leukine®	250 μg/m^2/d	Genzyme
EPO		Epoetin α	Procrit®	50–150 U/kg 3 times weekly	Amgen/Ortho
EPO		Epoetin β	NeoRecormon®	60–150 U/kg (1–3 times weekly)	Roche
Darbepoietin-α		Darbepoietin	Aranesp®	25–500 μg/kg/ week or 50 μg/kg/d	Amgen
IL-11		Oprelvekin	Neumega®	5–30 μg/kg/d	Pfizer
Stem cell factor Romiplostim (thrombomimetic) Eltrombopag (thrombomimetic)		Ancestim	Stemgen® Nplate® Promacta®	20 μg/kg/d* 1–5 μg/kg/wk sq 50–75 mg po/d	Amgen Glaxo-Smith-Kline

* Dosage for stem cell mobilization; not licensed in the United States.

The hemopoietic stem cell

- 1 in 2000 bone marrow cells
- 2000-fold increase in ability to confer radioprotection
- The murine phenotype is Sca-1^+ Thy 1^{lo} Lin^-. Sca-1^+ Thy 1^{lo} $LinMac^-$ 1^{-1} $CD4^-$ is the phenotype of stem cells with long-term repopulating ability. These have extensive self-renewal capacity and represent 80% of stem cells. Only 4%, however, are in the $S/G_2/M$ phases of the cell cycle at any one time (0.005% of bone marrow cells)
- Sca 1^+ Thy 1^{lo} Lin-Mac 1^{lo} $CD4^-$ and Sca-1^+ Thy l^{lo} Lin^-Mac 1^{lo} $CD4^+$ are the phenotypes of stem cells with short-term repopulating ability, representing 20% of stem cells in the marrow
- The human phenotype is $CD34^+$ Thy 1^{lo} $Lin^-Rho^{123\ lo}$ (rhodamine^{123} is a mitochondrial dye, the uptake of which correlates with self-renewal capacity)
- Phenotype variations: $CD34^+$, HLA-$DR^{+/-}$, $CD38^{+/-}$, Thy $1^{+/-}$, Lin^-, *c-kit*$^+$, $Rho^{123\ dull}$; $CD34^+$/HLA-DR^+ do not produce long-term culture initiating cells (LTCIC); $CD34^+$/HLA-DR–do produce LTCIC

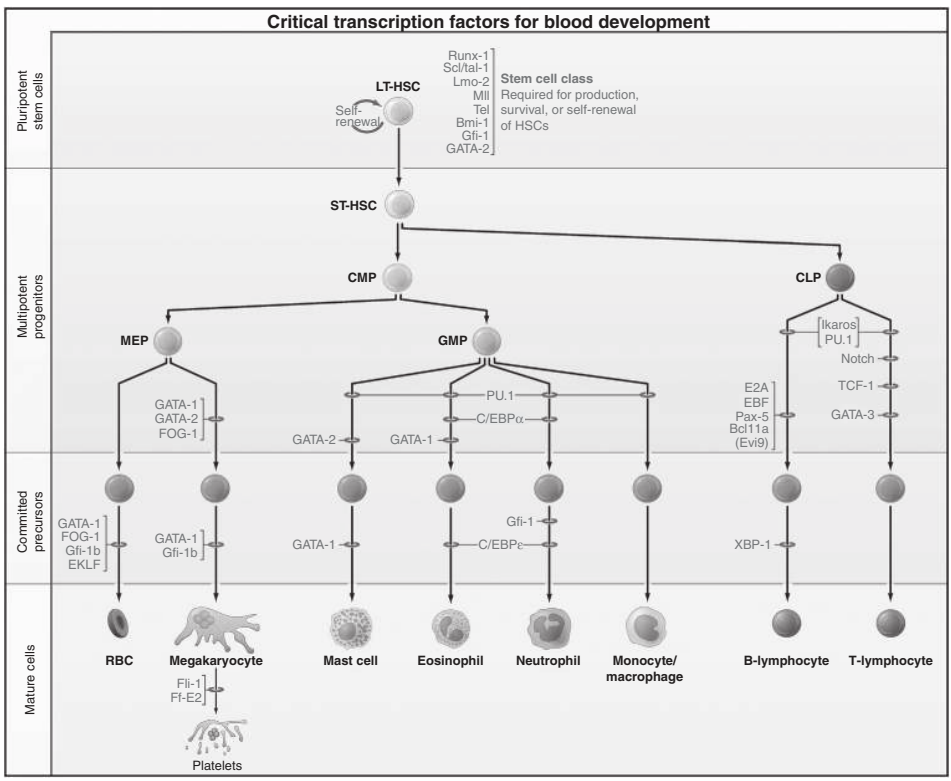
The phenotypic markers of human hematopoietic progenitor and stem cells were recently reviewed by Beksac and Preffer (2012).

- Human multipotential stem cell characteristics:
  Multilineage differentiation
  Self-renewal capacity
  Ability to reconstitute myeloablated patient
- Lineage negativity includes absence of the following:

Lineage	Cell surface antigens
T-cell	CD7, 2, 3, 4, 8
B-cell	CD19, 20
NK cell	CD56, 57
Myeloid	CD33, 15
Erythroid	Glycophorin

Hematopoietic stem cell differentiation is regulated by transcription factors.

Hematopoietic stem cell differentiation



The stages at which hematopoietic development is blocked in the absence of a certain transcription factor (as determined by conventional gene knockouts) are indicated by solid bars. Often these factors have been associated with oncogenesis. Factors depicted in a light font have not yet been found translocated or mutated in human or rodent hematologic malignancies. CLP, common lymphoid progenitor; CMP, common myeloid progenitor; GMP, granulocyte/ macrophage progenitor; LT-HSC, long-term hematopoietic stem cell; MEP, megakaryocyte/ erythroid progenitor; RBC, red blood cell; ST-HSC, short-term hematopoietic stem cell. (Reproduced with permission from Orkin and Zon, 2008.)