Turk J Med Sci
33 (2003) 281-288

PERSPECTIVES IN MEDICAL SCIENCES

The EBMT Activity Survey on Hematopoietic Stem Cell Transplantation: A novel Instrument for Quality Control

Alois GRATWOHL[1], Helen BALDOMERO[1], Alvaro URBANO ISPIZUA[2]
[1]Division of Hematology, Department of Internal Medicine, Kantonsspital Basel, Switzerland
[2]EBMT Secretariat, Hospital Clinic, Barcelona, Spain

Received: June 16, 2003

Abstract: The hematopoietic stem cell transplant activity survey of the European Group for Blood and Marrow Transplantation (EBMT) represents a novel modern tool in health care management. Introduced in 1990, it captures annual numbers of hematopoietic stem cell transplantation (HSCT) by indication, donor type and stem cell source from each individual European transplant team. Supplemented by demographical data and economic factors, team density and transplant rates can be calculated and the impact of economics on HSCT rates can be assessed. As documented in the present analysis, a total of 19,668 HSCT were performed in Europe in 2001 by 599 teams in 31 countries, 6426 (30%) allogeneic and 13,242 autologous (70%) HSCT. The main indications for allogeneic HSCT were leukemias, lymphoproliferative disorders and non-malignant diseases; the main indications for autologous HSCT were lymphoproliferative disorders, solid tumors and leukemias. The main sources of stem cells were peripheral blood (95%) for autologous, peripheral blood (60%) and bone marrow (40%) for allogeneic HSCT. Based on its completeness the EBMT activity survey allows for a rapid description of the status quo that allows us to assess of trends and determine factors influencing transplant rates. As such it provides up-to-date information for patients, treating physicians and health care officials. It can serve as an example for other such surveys to come.

Key Words: Hematopoietic stem cell transplantation, transplant activity, economic factors, public health

Introduction

Hematopoietic stem cell transplantation (HSCT) represents one of the many recent examples of modern high efficiency medical technology under debate in an era of limited resources. It is associated with high costs but is limited to selected groups of patients. HSCT's potential as a therapeutic tool is no longer in question. It has been developed from a last resort in a desperate situation to an accepted therapy for many patients with severe acquired or congenital disorders of the hematopoietic system or with chemo-, radio- or immunosensitive malignancies. Hematopoietic stem cells from different donor types (autologous, syngeneic, allogeneic related and allogeneic unrelated donors) and different stem cell sources (bone marrow, peripheral blood and cord blood) are used depending on the clinical situation and need (1-4). Their use has increased rapidly during the last decade and is today integrated into the therapeutic plan for many diseases. Still, HSCT represents a challenge for treating physicians, patients and health care agencies. Patients are confronted with immediate risks and late benefits, physicians are challenged to give advice to well-informed patients with access to the internet and the most recent publications, and health care officials are obliged to provide the needed infrastructure for this high cost technology. HSCT itself is not linked to one specific device or one specific drug. It is rather the complex network of highly trained physician and nurse specialists and the length of commitment to individual patients that renders the procedure time and cost intensive. As in any evolving field, changes in procedures and technology are rapid. The introduction of new concepts, such as reduced intensity conditioning, might change the short-term outlook for patients or open up the technology to new

patient categories; the advent of new drugs, such as imatinib mesylate, provides alternative approaches to HSCT. In this changing situation, up-to-date information at any level is essential. The activity survey of the European Group for Blood and Marrow Transplantation (EBMT) represents such a tool to provide rapid information on the status quo (5).

Methods

EBMT activity survey

The EBMT activity survey was initiated in 1990 as a part of the EBMT accreditation office and as a rapid tool for quality control and trend assessment (5). It is still closely linked with the EBMT, but includes non-EBMT members as well. Its clear aim is to cover all HSCT activity in Europe, from EBMT members and non-member institutions alike. The activity survey collects annual numbers of HSCTs from each participating institution by indication, donor type and stem stell source on a one-page questionnaire (Fig. 1). For EBMT members it is mandatory to participate under the EBMT constitution and accreditation for unrelated donor transplants depends on participation. Non-members are invited to participate. Lists of transplant teams are compared with national agencies wherever such agencies function to assure completeness.

Participating teams:

Six hundred tewnty-four stem cell transplant teams were contacted in 2001 in 35 European countries. Of these, 599 teams (Table 1) returned the survey sheet, and this corresponds to a 96% return rate and includes 460 of 466 EBMT member teams (6). No major transplant team in Europe is missing from this list. According to informal information no blood and marrow transplants were performed in the following European countries: Albania, Andorra, Armenia, Aserbaijan, Bosnia-Herzegovina, Cyprus, Georgia, Iceland, Liechtenstein, Malta, Moldova, Monaco, San Marino and the Vatican.

Definitions:

Transplants are defined as an infusion of hematopoietic stem cells following a conditioning regimen with the intention of replacing the existing hematopoiesis by the injected stem cells. First transplants refer to the first transplantation of hematopoietic cells and full information is collected only for first transplants. Therefore, each patient is counted only once independent of the number of transplant procedures, and this prevents multiple reporting. Additional procedures such as re- or multiple transplants (Table 2) were collected in total and were not specified by disease to receive an estimate of the absolute number of HSCT procedures. Re-transplants refer to a situation where recipients receive a second HSCT following relapse or rejection. Multiple transplants refer to a planned program of sequential HSCT. Donor lymphocyte infusions were not considered transplants, but general information on new patients treated with DLI was collected.

Transplant rates were defined as the number of HSCTs per 10 million inhabitants (7). They were computed for each year, disease indication, donor type and country. Team density was defined as number of HSCT teams per 10 millions inhabitants. The population data were obtained each year from the U.S census office (http://www.census.gov). Population data were used to determine transplant rates in total for each donor type and each indication. Comparing transplant rates in different countries allows the calculation of a coefficient of variation (CV) for transplant rates (8). A high CV corresponds to a high variation of transplant rates, hence disagreement amongst transplant physicians; a low CV corresponds to a low variation of transplant rates for the given indication (Table 3), hence agreement for specific indication.

Results

Reporting of status quo. HSCT numbers by indication, donor type and stem cell source are collected annually and published rapidly each year in major hematology journals. The results of annual surveys are supplied to participating members including corporate pharmaceutical EBMT members prior to publication. All efforts are undertaken to have the data published not more than one and-a-half years after the survey. These data, which cover more than 90% of autologous and more than 95% of allogeneic HSCTs in Europe are an invaluable tool for transplant teams for self-positioning and patient counseling (9-18). The representative example of the annual survey in the year 2001 is presented in Tables 1 and 2.

The comparison between participating European countries allows for the quantitative assessment of differences between these countries. The EBMT activity

SURVEY ON TRANSPLANT ACTIVITY 2001

Table 1: Report the total number of patients receiving their 1st transplant in 2001 only for each category. List all patients with allogeneic and autologous transplants according to indication and source. BM=bone marrow; PBSC=peripheral blood stem cells or cord blood.
NB: Table 1: 1 patient = 1 transplant only (first). See guidelines.
- non-id* = any family member(matched or mismatched) other than HLA - id sibling or twin
- for allogeneic transplants, please enter combined BM+PBSC under "PBSC"

Table 1	NUMBER OF PATIENTS WITH FIRST TRANSPLANT ONLY IN 2001													
	allogeneic								autologous					
	family						unrelated					Total		
	HLA - id sibling		non - id*		twin				BM	PBSC	BM+	Allo	auto	Total
Indication	BM	PBSC	BM	PBSC	BM	PBSC	BM	PBSC	only	only	PBSC			
AML 1st CR														
non 1st CR														
ALL 1st CR														
non 1st CR														
CML cP														
not 1st cP														
MDS/MPS														
CLL														
Myeloma (incl. Amyloidosis)														
HD														
NHL														
Neuroblastoma														
Glioma														
Soft tissue														
Germinal Ca.														
Breast Ca: stage 2														
stage 3														
inflammatory														
metastatic														
Ewing														
Lung Ca.														
Ovarian Ca.														
Other solid tumors														
SAA+Fanconi														
Thalassaemia														
SCID														
Inborn errors														
Auto immune disease														
Others														
TOTAL (patients)														

Tables 2 and 3: Other transplants (excluding the first) in 2001, see guidelines:

Table 2: Allogeneic transplants

No. allogeneic retransplants in 2001	
No. of additional allogeneic transplants in 2001	

Table 3: Autologous transplants

No. autologous retransplants in 2001	
No. of additional autologous transplants in 2001	

Table 4: Other information

Total cord blood transplants in 2001	
Total non myeloablative / reduced intensity (mini allo - RIC) in 2001	

Non transplant procedures

Total No. patients receiving donor lymphocyte infusions (DLI) in 2001	

Table 5: Totals

	ALLO	AUTO	TOTAL
Total No. of TRANSPLANTS in 2001			

Please return by Fax +41 61 265 44 50 to A. Gratwohl, Div. Hematology, Kantonsspital Basel, CH-4031 Basel, or in the self-addressed envelope.

E-mail:baldomeroh@uhbs.ch

Form sent in by:.....

Figure 1. Activity survey sheet as distributed to European HSCT teams.

Table 1. Number of patients treated in Europe in the year 2001 by HSCT according to indication, donor type and stem cell source.

Year = 2001 TEAMS = 599	DONOR SOURCE													
	No. of patients													
	Allogeneic								Autologous			Total		
	Family						Unrelated							
	HLA-id		non-id		twin				BM	PBPC	BM +	Allo	Auto	Total
	BM	PBPC	BM	PBPC	BM	PBPC	BM	PBPC	only	only	PBPC			
Leukemias	**1007**	**1581**	**58**	**214**	**6**	**19**	**843**	**801**	**214**	**1386**	**49**	**4529**	**1649**	**6178**
Acute myeloid leukemia	**347**	**684**	**18**	**101**	**1**	**7**	**256**	**299**	**157**	**838**	**40**	**1713**	**1035**	**2748**
1st complete remission	258	407	7	22	1	6	103	88	116	695	36	**892**	**847**	**1739**
not 1st complete remission	89	277	11	79		1	153	211	41	143	4	**821**	**188**	**1009**
Acute lymphatic leukemia	**300**	**277**	**20**	**57**	**1**	**3**	**283**	**220**	**39**	**269**	**8**	**1161**	**316**	**1477**
1st complete remission	161	147	10	14	1	2	93	75	24	175	4	**503**	**203**	**706**
not 1st complete remission	139	130	10	43		1	190	145	15	94	4	**658**	**113**	**771**
Chronic myeloid leukemia	**263**	**335**	**9**	**38**	**3**	**4**	**187**	**155**	**6**	**46**	**0**	**994**	**52**	**1046**
chronic phase	223	269	6	21	2	3	135	93	1	27		**752**	**28**	**780**
not 1st chronic phase	40	66	3	17	1	1	52	62	5	19		**242**	**24**	**266**
Myelodysplastic syndrome	78	196	11	16	1	4	103	105	4	34		**514**	**38**	**552**
Chronic lymphatic leukemia	19	89		2		1	14	22	8	199	1	**147**	**208**	**355**
Lymphoproliferative disorders	**127**	**514**	**2**	**32**	**1**	**17**	**69**	**100**	**148**	**9268**	**99**	**862**	**9515**	**10377**
Myeloma	43	157	1	10		6	22	34	12	4065	17	**273**	**4094**	**4367**
Hodgkin's lymphoma	7	52		6		3	8	11	58	1220	32	**87**	**1310**	**1397**
Non Hodgkin lymphoma	77	305	1	16	1	8	39	55	78	3983	50	**502**	**4111**	**4613**
Solid tumors	**4**	**140**	**0**	**4**	**0**	**0**	**0**	**1**	**61**	**1842**	**14**	**149**	**1917**	**2066**
Neuroblastoma	1			1					25	247	5	**2**	**277**	**279**
Glioma									2	60		**0**	**62**	**62**
Soft tissue sarcoma		5							5	97	2	**5**	**104**	**109**
Germinal tumors		2							2	290		**2**	**292**	**294**
Breast cancer. stage 2										153		**0**	**153**	**153**
Breast cancer: stage 3										134		**0**	**134**	**134**
Breast cancer: inflammatory										58		**0**	**58**	**58**
Breast cancer: metastatic		21								146		**21**	**146**	**167**
Ewing	1	2							8	213	3	**3**	**224**	**227**
Lung cancer										42		**0**	**42**	**42**
Ovarian cancer		8							1	91		**8**	**92**	**100**
Other solid tumors	2	102		3				1	18	311	4	**108**	**333**	**441**
Non malignant disorders	**294**	**134**	**41**	**61**	**4**	**1**	**138**	**67**	**9**	**74**	**2**	**740**	**85**	**825**
Severe aplastic anemia + Fanconi	129	70	3	13	3	1	55	28				**302**	**0**	**302**
Thalassemia	101	46	6	8			16	1		1		**178**	**1**	**179**
SCID	17	8	24	21			13	9	6	2		**92**	**8**	**100**
Inborn errors	47	9	8	18	1		54	28		3		**165**	**3**	**168**
Auto immune disease		1		1				1	3	68	2	**3**	**73**	**76**
Others	48	39	3	10	1		27	18	4	71	1	**146**	**76**	**222**
TOTAL	**1480**	**2408**	**104**	**321**	**12**	**37**	**1077**	**987**	**436**	**12641**	**165**	**6426**	**13242**	**19668**

Table 2. Total number of additional HSCTs or retransplants in Europe in 2001.

Indication	Allogeneic HSCT	Autologous HSCT	Total
1st transplants = patients	6426	13,242	19,668
Retransplants	673	542	1215
Additional transplants	173	2098	2271
TOTAL	7272	15,882	23,154

Table 3. Coefficients of variations (CV)in transplant rates for individual disease indications. Low CV's correspond to agreement, high CVs to disagreement among transplant physicians in Europe on the given indication.

CV	Allogeneic HSCT	Autologous HSCT
< 50	AML 1st CR	MM
	AML not 1st CR	HD
	ALL 1st CR	NHL
	ALL not 1st CR	ES
	CML 1st cP	NB
	CML not 1st cP	
	MDS	
	NHL	
50 - 80	MM	AML 1st CR
	CLL	AML not 1st CR
>80	HD	ALL 1st CR
		ALL not 1st CR
		CML 1st cP
		CML not 1st cP
		MDS
		CLL
		ST

AML: Acute myeloid leukemia
ALL: Acute lymphoid leukemia
CML: Chronic myeloid leukemia
CLL: Chronic lymphocytic leukemia
MM: Multiple myeloma
MDS: Myelodysplastic syndrome
HD: Hodgkin's lymphoma
NHL: Non-Hodgkin's lymphoma
ES: Ewing's sarcoma
NB: Neuroblastoma
ST: all other solid tumors

survey early on revealed such differences in HSCT activity, as illustrated in Figure 2, for the year 2001. These differences relate to all aspects analyzed, e.g., indication, donor type, stem cell source, transplant rates and team density.

Repeat examinations of the annual survey reveal insights into several mechanisms. Not surprisingly, transplant rates clearly correlate with national economics such as gross national product (GNP), health care expenditures (HCE) or purchasing power-parity (PPP), but only to a certain extent (Fig. 3). For those with a higher economic status, there is no longer a correlation. This correlation from the health care structure is illustrated in the figure. There are basically three different economic health care systems in Europe: the decentralized type as in Eastern European countries, a tax funded system and a social security based system (7).

Transplant rates correlate with team density, but again only to a certain extent. Low team density correlates with low transplant rates. This means that there is the need for several transplant teams to be present in a given country in order to disseminate the technology.

There is also a saturation point at about 10 teams per 10 million inhabitants. With more teams, there is no related increase in transplant rates.

The comparison of transplant rates for individual indications provides an instrument to assess with quantitative methods consensus or disagreement among European specialists and transplant indications. A CV in transplant rates allows for numerical description; a CV of

Figure 2. Map of European HSCT transplant rates for 2001.

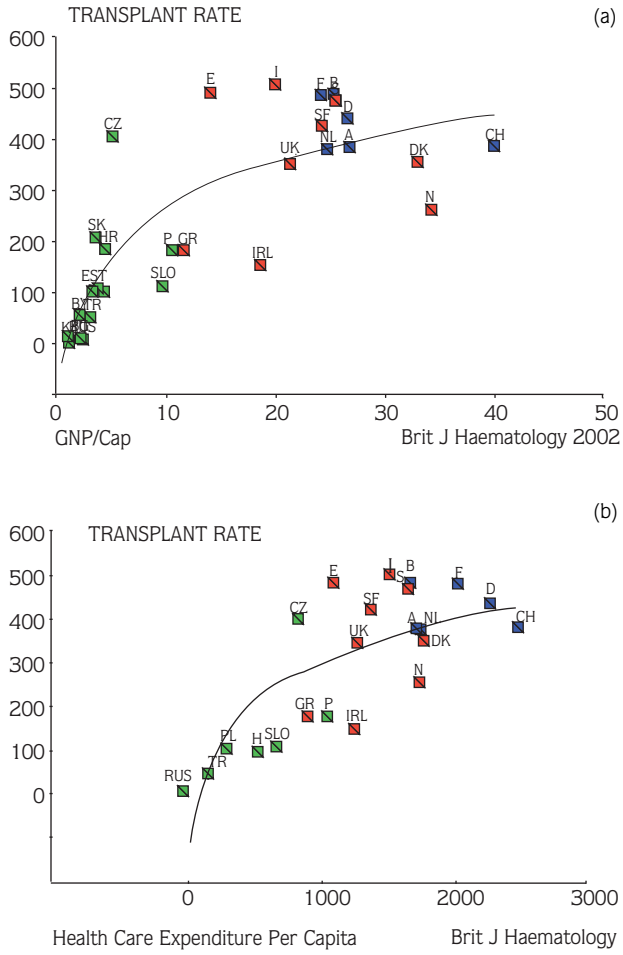

Figure 3. Transplant rates and economic factors in Europe.
HCE = health care expenditures per capita in US$
GNP = gross national product per capita in US$
(reprinted with permission, British Journal of Hematology)

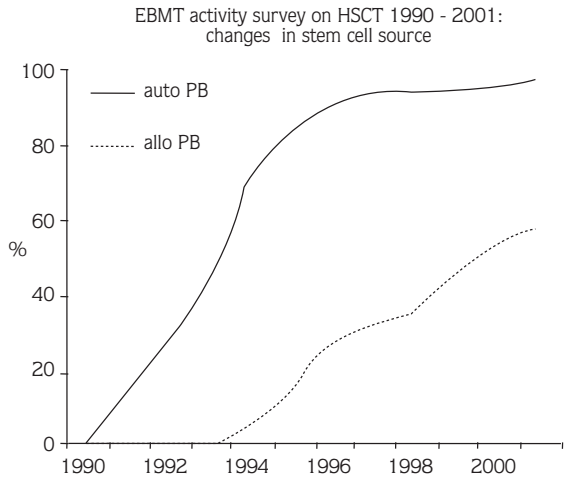

Figure 4. Change in stem cell source.

≤ 50 strongly suggests consensus, while a CV > 100 strongly suggests disagreement (Table 3) (8).

Changes over time and midterm projections

HSCT is a highly complex, cost intensive but powerful therapeutic strategy. It is also an expanding field with additional rapid changes in technology as illustrated in Figure 4. In 1990 all HSCTs were still bone marrow derived. Within a decade the picture had changed completely with peripheral blood being used as a stem cell source in the autologous setting and about 50% of the time in the allogeneic setting (18).

There have been massive changes in the absolute numbers of HSCTs between 1990 and 2001, though not to the same extent for all indications (Fig. 5 (a,b). Allogeneic HSCT has increased more than five fold for

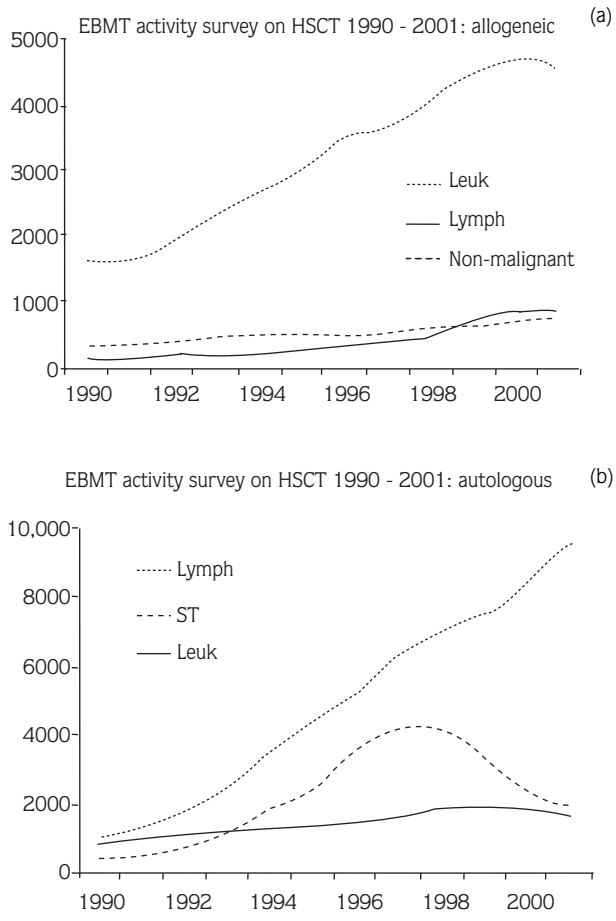

Figure 5. Development of main indications for HSCT in Europe from 1990 to 2001
Figure 5a: Changes in allogeneic HSCT
Figure 5b: Changes in autologous HSCT

patients with leukemia. There is a clear increase for lymphoproliferative disorders over the last 3 years and non-malignant indications show a steady low increase. For autologous HSCT, there was a massive increase in HSCT for lymphoproliferative disorders, though this was less so in hematological malignancies. In contrast, there has been a massive expansion in autologous HSCT for solid tumors in the early 1990s with a peak in 1997 and a rapid decline thereafter. This was mainly due to the expectations in breast cancer and the misinformation based on negative prospective randomized studies (19-21).

The EBMT activity survey has now been developed with the help of health care management specialists as a tool for midterm projections (22). Preliminary data so far give a clear answer: HSCT rates for individual indications follow clear mathematical models and the trends are highly predictable over the short term. However, changes can occur. If they occur they are rapid, unpredictable and substantial (20,22). They tend to occur 2-4 years before major publications related to these events. Changes in technology e.g., the shift from bone marrow to peripheral blood in autologous HSCT, were completed at the time of publication of the leading article. The expectations of physicians and patients are currently discussed as main factors influencing such decisions.

Discussion

As it stands, the EBMT activity survey provides a unique tool. It covers a whole continent and captures almost all procedures for a given speciality field. Because it concentrates on rapid data capture it reflects the status quo as it stands. It provides the most up-to-date basis for decision making for physicians, patients and health care administrators alike. It serves as a quality control instrument for individual teams, national societies and global structures as well.

In addition, it opens the field to new aspects. Risk assessment for individual patients is well established and decision making at the individual patient level follows accepted rules (23). Little is known in contrast, of factors influencing team decisions. Clearly, more information and better understanding is warranted. Instruments such as the EBMT activity survey might provide us with such answers.

Acknowledgments

The cooperation of all participating teams and the staff of the EBMT secretariat (A. Urbano-Ispizua, F. McDonald), the European EBMT Data Office in Paris (V. Chesnel, N.C. Gorin), the EBMT Registry Subcommittee (P. Ljungman, 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. Gritsch), the Italian Registry (M. Vignetti, W. Arcese, R. Oneto), the German Registry (H. Ottinger, C. Müller, B. Kubanek, N. Schmitz, U.W. Schaefer), the Swiss Registry (J. Passweg, H. Baldomero), the British Registry (K. Towlson, N. Russell), the Turkish Registry (M. Arat, G. Gurman), and the Spanish Transplantation Office (ONT) (M. Naya) is greatly appreciated. The authors also thank A. Weber for excellent secretarial assistance, as well as L. John for technical assistance associated with data management.

The work was supported in part by a grant from the Swiss National Research Foundation, 32-52756.97, the Swiss Cancer League, Oncosuisse and the Horten Foundation. EBMT is supported by grants from the following 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.

Corresponding author:
A. GRATWOHL
Div. Hematology, Dept. Internal Medicine
Kantonsspital Basel
CH-4031 Basel, Switzerland
E-Mail: hematology@uhbs.ch

References

1. Thomas DD. Bone marrow transplantation: a review. Semin Hematol 36 (Suppl. 7): 95-103, 1999.
2. Forman SJ, Blume KG, Thomas ED (eds.). Hematopoietic Cell Transplantation, 2nd ed. Blackwell Scientific Publishers: London, New York, 1998.
3. Lennard AL, Jackson GH. Stem cell transplantation. Br Med J; 321: 433-437, 2000.
4. Urbano-Ispizua A, Schmitz N, de Witte T., et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. Bone Marrow Transplant 29: 639-646, 2002
5. Gratwohl A. Bone marrow transplantation activity in Europe 1990. Report from the European Group for Bone Marrow Transplantation (EBMT). Bone Marrow Transplant 8: 197-201, 1991
6. Gratwohl A, Baldomero H, Passweg J. et al. Increasing use of reduced intensity conditioning transplants: report of the 2001 EBMT activity survey. Bone Marrow Transplant 30: 813-831, 2002
7. Gratwohl A, Passweg J, Baldomero H, et al. Economics, health care systems and utilization of haemopoietic stem cell transplants in Europe. Br J Haematol 117: 451-468, 2002.
8. Gratwohl A, Baldomero H, Hermans J. Quantitative Assessment of Consensus on Indications for Blood or Marrow Transplantation in Europe 1995. Cancer Research Therapy and Control, 10: 123-144, 1999.
9. Gratwohl A, Hermans J, Goldman JM, et al. Bone marrow transplantation in Europe: major geographical differences. J Int Med 233: 333-341, 1993.
10. Gratwohl A, Hermans J. Bone marrow transplantation activity in Europe 1992: Report from the European Group for Bone Marrow Transplantation (EBMT). Bone Marrow Transplant 13: 5-10, 1994.
11. Gratwohl A, Hermans J. Special report Part 1. Bone marrow transplantation worldwide. EBMT survey on bone marrow transplant activity in Europe: regional differences. Bone Marrow Transplant 13: 683-688, 1994.
12. Gratwohl A, Hermans J. Indications and donor source of hematopoietic stem cell transplants in Europe 1993: Report from the European Group for Blood and Marrow Transplantation (EBMT). Clin Transplantation 9: 355-363, 1995.
13. Gratwohl A, Hermans J, Baldomero H, et al. Indications for haemopoietic precursor cell transplants in Europe. Br J Haematol 92: 35-43, 1996.
14. Gratwohl A, Hermans J, Baldomero H. Hematopoietic precursor cell transplants in Europe: Activity in 1994. Report from the European Group for Blood and Marrow Transplantation (EBMT). Bone Marrow Transplant 17: 137-148, 1996.
15. Gratwohl A, Hermans J, Baldomero H. Blood and marrow transplantation activity in Europe 1995. Bone Marrow Transplant 19: 407-419, 1997.
16. Gratwohl A, Passweg J, Baldomero H, et al. Special report: Blood and marrow transplantation activity in Europe 1996. Bone Marrow Transplant 22: 227-240, 1998.
17. Gratwohl A, Passweg J, Baldomero H, et al. Hematopoietic stem cell transplantation in Europe 1998. The Hematology Journal 1: 333-350, 2000.
18. Gratwohl A, Passweg J, Baldomero H, et al. Hematopoietic stem cell transplantation activity in Europe 1999. Bone Marrow Transplant 27: 899-916, 2001.
19. Gratwohl A, Baldomero H. Stem cell transplant numbers decline; research continues J Natl Cancer Inst. 93: 949, 2001.
20. Gratwohl A, Baldomero H, Urbano-Ispizua A. Transplantation in chronic myeloid leukaemia. Lancet. 359(9307): 712-3, 2002.
21. Gratwohl A, Baldomero H, Rosti G. High-dose chemotherapy for breast cancer. Bone Marrow Transplant. 26: 599, 2000.
22. Gratwohl A, Baldomero H, Horisberger B, et al. Current trends in hematopoietic stem cell transplantation in Europe. Blood 100: 2374-2386, 2002.