British Journal of Haematology, 2002, **117**, 451–468

Economics, health care systems and utilization of haematopoietic stem cell transplants in Europe

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Received 15 August 2001; accepted for publication 15 November 2001

Summary. Transplantation of haematopoietic stem cells from blood or bone marrow (HSCT) has seen rapid expansion. Increased costs and quality concerns present a challenge for health care providers. Information on factors influencing HSCT utilization is necessary. Data on 113 827 patients (37 761 allogeneic HSCT and 76 066 autologous HSCT), collected from 580 centres in 35 European countries between 1990 and 1999, were used. Economic factors, e.g. gross national product per capita, health care expenditure per capita and type of health care system were correlated with transplant rates (numbers of HSCT per 10 million inhabitants), team density (numbers of transplant teams per 10 million inhabitants) and increase in transplant numbers for each country. Annual numbers of HSCT increased in all European countries from 4234 in 1990 to 18 720 in 1999 irrespective of health care system. Economic strength and team density were the main determinants for transplant rate. This report reflects changes over the last decade and current status of HSCT in Europe. Economic strength, team density and hitherto unknown factors influence dissemination of the technology within Europe. These data provide a basis for health care planning, regulatory aspects and future research.

Keywords: haematopoietic stem cell, transplantation, transplant activity, countries, Europe.

Transplantation of haematopoietic stem cells (haematopoietic stem cell transplantation, HSCT) has increased considerably over the last decade. It is established therapy for congenital or acquired severe disorders of the haematopoietic system and chemo- or radiosensitive malignancies (Forman *et al*, 1998; Lennard & Jackson, 2000). Autologous or allogeneic transplants of haematopoietic stem cells from bone marrow, peripheral blood or cord blood are used. Donors for allogeneic transplants include human leucocyte antigen (HLA)-identical siblings, other family members or unrelated volunteers from the remarkably expanded donor pools. Risks and benefits of the different procedures have been defined (Confer, 1997; Gluckman *et al*, 1997; Gratwohl *et al*, 1998, Fischer, 1999; Bensinger *et al*, 2001). Currently, one in 2000 persons per 10 years is likely to be treated with HSCT in western European countries. Most practitioners will be confronted with a patient who has received an autologous or allogeneic HSCT (Duncombe, 1997). Availability of general information on the procedure has become a necessity.

This development began with the first reports on correction of severe congenital immune deficiencies by bone marrow transplants from HLA-compatible siblings in the late 1960s (Bach *et al*, 1968; Gathi *et al*, 1968). Correction of severe aplastic anaemia and eradication of leukaemias proved the concept that bone marrow from normal healthy donors could replace failing organ function independent of the cause. These early results stimulated groups worldwide to gather together, share their experience and spread the technology. The annual numbers of HSCT in Europe increased from 18 in 1973, when the European Group for Blood and Marrow Transplantation (EBMT) was founded, to 4234 HSCT in 1990, when the EBMT activity survey was introduced (Gratwohl, 1991), and to an estimated number of more than 20 000 patients in the year 2000. Successful treatment of many patients with various diseases forms the basis of the continuing ambition and enthusiasm of the transplant community. Reduction in transplant-related mortality and standardization of procedures have fostered

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its expansion. Patient and donor selection and fine tuning of supportive care during the aplastic phase are part of this improvement. It has opened up new indications. With introduction of low-intensity conditioning programmes (Barrett & Childs, 2000), patient age as a limiting factor has been abandoned. Today, HSCT are part of the treatment programme in most university hospitals and larger clinics in Europe. They are integrated in the therapeutic plan for many disease categories right from diagnosis (Goldman *et al*, 1998).

Rapid development and the high costs associated with HSCT have put pressure on health care agencies (Jacobs *et al*, 2000). Temptations to restrict transplant activity parallel awareness of quality control. Recent data indicate that annual numbers of transplants performed by an institution affect outcome (Apperley *et al*, 2000). Such correlations between numbers of procedures and outcome have been documented for many medical or surgical interventions, including organ transplantation (Opelz *et al*, 1975; Hosenpud *et al*, 1994; Lin *et al*, 1998; Edwards *et al*, 1999; Schurman *et al*, 1999; Frassoni *et al*, 2000). As a consequence, quality assurance programmes for centres of excellence, such as the Foundation for Accreditation of Haematopoietic Cell Therapy and Graft Engineering (FAHCT) (http://www.edu/community/fahct.org) and JACIE (Joint Accreditation Committee of the International Society for Haematotherapy and Graft Engineering (ISHAGE)-Europe and EBMT) (http://www.EBMT.org), stipulate a minimum number of 10 transplants per year. Defining a minimum number of transplants for institutions might improve outcome; the optimal number still needs to be determined. Furthermore, no data are available to define optimal dissemination within a country. Focusing on outcome, quality control and economic aspects might favour a concept of concentration of the technology on a few teams and neglect aspects of availability for the population at large. The annual surveys of the EBMT on HSCT activity monitor changes in activity for individual indications and observe trends (Gratwohl, 1991; Gratwohl *et al*, 2001). They allow comparisons between the individual participating European countries. As such, they provide a tool for the preparation of recommendations for health care agencies.

PATIENTS AND METHODS

Data collection and validation. The present report is based on the EBMT activity surveys introduced in 1990 (Gratwohl, 1991). Since then, all European centres known to the investigators to be performing transplants are requested annually to report on a survey sheet the numbers of new patients by indication, stem cell source and donor type. This survey was adopted by the General Assembly of EBMT as a mandatory self-reporting system and now forms an integral part of a prospective quality assurance programme. Details of the procedure have been published (Gratwohl, 1991). Transplants were defined as the infusion of haematopoietic stem cells following a conditioning regimen, with the intention of replacing the existing haematopoesis by injected stem cells.

Data quality is assured through cross-checking with national transplant registries and by on-site visits according to the EBMT quality assurance programme.

Participating teams. Data are based on 610 teams in 35 European countries known to the investigators to be transplant teams. Five hundred and eighty (95% return) replied in 1999 (Gratwohl et al, 2001). This includes all 470 EBMT member teams. No major transplant team in Europe is missing from this list. One hundred and forty-two teams responded in 1990. The contacted teams are listed in the Appendix in alphabetical order according to country, city and EBMT centre code. We received personal communications that, in 1999, no blood or marrow transplants were performed in the following European countries: Albania, Andorra, Armenia, Azerbaijan, Bosnia-Herzegovina, Georgia, Latvia, Liechtenstein, Malta, Macedonia, Moldavia, Monaco, Romania, San Marino and the Vatican.

Data for 1973 and 1983 are based on a retrospective survey conducted in 1993.

Transplant rates and team density. Transplant rates were computerized for each participating country and defined as the division of transplant numbers of a given country by its population, with adjustment to 10 million inhabitants. Transplant rates were calculated for each year for all HSCT, separately for autologous, allogeneic and unrelated HSCT, and for each main indication. Similarly, team density was defined as number of teams per 10 million inhabitants. Population data since 1996 were obtained from the US census office (http://www.census.gov/cgi-bin/ipc/idbrank.pl) and for previous years from the annual Fischer's Weltalmanach.

Economic evaluation. For each country and year, information was obtained on gross national product (GNP) per capita in US$, growth rate of GNP, health care expenditures (HCE) per capita in US$ and HCE as a percentage of GNP. Information on GNP was obtained from http://www.worldbank.org, information on HCE from the European Observatory on Health Care Systems (http://www.observatory.dk) and from literature (Hoffmeyer & McCarthy, 1994). Countries were grouped into three categories of health care systems: (a) social insurance-based health care systems or Bismarckian type (Austria, Belgium, France, Germany, the Netherlands and Switzerland) (Group 1); (b) tax-funded health care systems or Beveridge type (Denmark, Finland, Greece, Ireland, Italy, Norway, Spain, Swedena and the UK) (Group 2); and (c) centralized health care systems or Semashko-type [includes all countries from the former USSR or Council on Mutual Economic Assistance (CMEA)] (Group 3) (Majnoni d'Intignano, 1992).

Transplant efficiency was then calculated by dividing the transplant rate of each country by its HCE. Transplant efficiency was grouped by health care system.

Statistical analysis. Mean, median and standard deviations of numerical variables were calculated on an EXCEL spreadsheet. Groups were compared with chi-square tests.

In order to assess trends, increases in transplant rates were computerized for donor types, stem cell source and main disease indications for each individual country and by health care system group.

Regression analyses were used to estimate the relationship of transplant rates and team density with GNP per capita, annual growth rate of GNP, HCE per capita and HCE percentage of GNP in individual countries. Analyses were performed for each year. The presented data refer to the latest that are available (1998/1999).

RESULTS

Development of transplant activity

The evolution of HSCT in Europe from 1973 to 1999 is illustrated in Fig 1. There has been a steady increase in HSCT activity for allogeneic transplants. Autologous HSCT began later with a more rapid increase. In 1991, equal numbers were reported for both technologies. Autologous HSCT showed a marked increase after 1993, culminating in 1998 with almost 13 000 patients and a decline thereafter. In total, there were 18 720 first transplants, including 5879 (31%) allogeneic and 12 841 (69%) autologous HSCT in 1999.

Increase in transplant activity during the last decade was based both on increase in teams and on increase in transplants within participating teams. Teams increased from eight in 1973 to 143 in 1990 and 610 in 1999. Of those, 580 responded and 50% perform allogeneic and autologous transplants; 48% restrict their activity to autologous and 2% to allogeneic transplants only.

There is a wide variation in activity between teams. One hundred and fifty-two (26%) teams performed less than 10 transplants, 122 (21%) teams between 10 and 20 HSCT, 180 (31%) between 20 and 50 HSCT, 99 (17%) between 50 and 100 HSCT and 27 teams (5%) more than 100 HSCT in 1999.

Indications for HSCT, donor type and stem cell source

Numbers of patients treated with HSCT over the last decade are listed in Table I, according to disease indication and donor type. Overall, there were 113 827 first transplants; 37 761 (33%) were allogeneic and 76 066 (67%) were autologous HSCT. They are grouped into four main disease categories, lymphoproliferative disorders with 43 529 patients (38·2%), leukaemias with 42 144 patients (37%), solid tumours with 21 898 patients (19·2%) and non-malignant disorders with 5216 patients (4·6%).

There are distinct differences between these groups with regard to donor type. Solid tumour patients were almost exclusively treated with autologous HSCT (99·2%). In contrast, patients with aplastic anaemia, haemoglobinopathies, immunodeficiency disorders or in-born errors, in the group of non-malignant disorders, were almost exclusively treated with allogeneic HSCT (98·7–100%). The few patients with congenital disorders treated using autologous HSCT are those given genetically modified autologous HSCT. Patients with lymphoproliferative disorders were treated predominantly with autologous HSCT (92·9%). Similarly, patients with autoimmune disorders were primarily treated with autologous HSCT (92·3%). Patients with leukaemias were mainly treated with allogeneic HSCT (68·5%), even though for some subgroups, such as acute myeloid leukaemia, numbers of autologous HSCT equalled those for allogeneic procedures.

Of the 37 761 allogeneic HSCT, 27 046 (72%) recipients received cells from an HLA-identical sibling donor, 2551 (7%) recipients had other family members as a donor, 401 (1%) recipients had a syngeneic twin as donor and 7763 (21%) recipients had an unrelated volunteer donor.

Over the decade, the percentage of twin donors has remained stable; the percentage of unrelated donors has increased from less than 10% to over 30% in 1999 (see details in Gratwohl *et al*, 2001).

Of the 113 827 HSCT, 45 758 (40%) were bone marrow derived; 68 069 (60%) were from peripheral blood stem cells or combined bone marrow and peripheral blood stem cell transplants. There were differences between autologous and allogeneic HSCT. Of the 37 761 allogeneic HSCT, 29 820 (79%) were bone marrow and 7941 (21%) were peripheral blood stem cell transplants. Of the 76 066 autologous HSCT, 15 938 (21%) were bone marrow and 60 128 (79%) were peripheral blood stem cell transplants. The proportion of peripheral blood as stem cell source varied over time and depended on donor type. Almost all HSCT in 1990 were bone marrow derived. It has changed within the decade to 95% of cases using peripheral blood as the stem cell source for autologous HSCT, to 50% for HLA-identical sibling donor transplants, to 77% for HSCT from other family members, to 63% for twin donors and to 27% for unrelated donors in 1999.

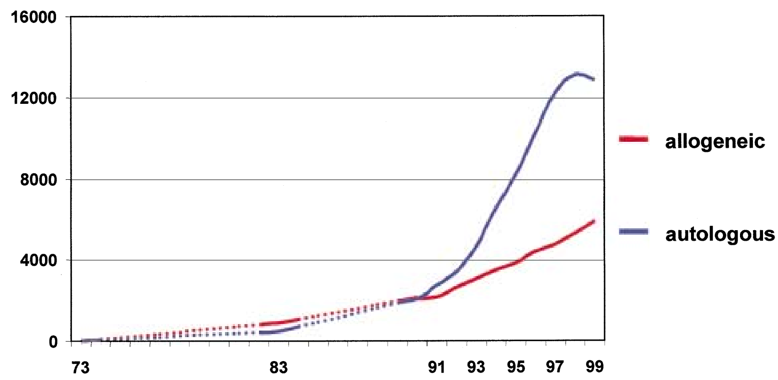

Fig 1. Evolution of HSCT in Europe from 1973 to 1999. Graphs reflect annual numbers of patients treated with autologous or allogeneic HSCT. Numbers for 1973, 1983 and 1990–1999 are derived from the EBMT activity surveys.

Table I. Numbers of patients treated in Europe from 1990 to 1999 with a first haematopoietic stem cell transplant, according to disease indication and donor type. The proportion of allogeneic transplants and the 95% confidence limits are given for all main indications and subgroups.

	Indications for HSCT in Europe 1990–1999			
	Number of patients			Percentage of allogeneic HSCT (95% CI)
	Allogeneic	Autologous	Total	
Leukaemias	28856 (76·4%)	13288 (17·5%)	42144 (37·0%)	68·5 (68–68·9)
Acute myeloid leukaemia	9363 (32·4%)	7082 (53·3%)	16445 (39·0%)	56·9 (56·2–57·7)
Acute lymphocytic leukaemia	7736 (26·8%)	3463 (26·1%)	11199 (26·6%)	69·1 (68·2–69·9)
Chronic myeloid leukaemia	9244 (32·0%)	1819 (13·7%)	11063 (26·3%)	83·6 (82·9–84·2)
Myelodysplastic syndromes	2226 (7·7%)	247 (1·9%)	2473 (5·9%)	90·0 (88·7–91·2)
Chronic lymphocytic leukaemia	287 (1·0%)	677 (5·1%)	964 (2·3%)	29·8 (26·9–32·8)
Lymphoproliferative disorders	3110 (8·2%)	40419 (53·1%)	43529 (38·2%)	7·1 (6·9–7·4)
Multiple myeloma	1175 (37·8%)	12818 (31·7%)	13993 (32·1%)	8·4 (7·9–8·9)
Hodgkin's disease	252 (8·1%)	7852 (19·4%)	8104 (18·6%)	3·1 (2·7–3·5)
Non Hodgkin's lymphoma	1683 (54·1%)	19749 (48·9%)	21432 (49·2%)	7·9 (7·5–8·2)
Solid tumours	168 (0·4%)	21730 (28·6%)	21898 (19·2%)	0·8 (0·7–0·9)
Neuroblastoma	29 (17·3%)	1650 (7·6%)	1679 (7·7%)	1·7 (1·2–2·5)
Glioma	1 (0·6%)	471 (2·2%)	472 (2·2%)	0·2 (0–1·4)
Soft tissue sarcoma	8 (4·8%)	869 (4·0%)	877 (4·0%)	0·9 (0·4–1·9)
Germinal tumours	7 (4·2%)	2354 (10·8%)	2361 (10·8%)	0·3 (0·1–0·6)
Breast cancer	41 (24·4%)	11817 (54·4%)	11858 (54·2%)	0·3 (0·3–0·5)
Ewing's sarcoma	24 (14·3%)	1157 (5·3%)	1181 (5·4%)	2·0 (1·3–3·1)
Lung cancer	1 (0·6%)	256 (1·2%)	257 (1·2%)	0·4 (0–2·5)
Ovarian cancer	4 (2·4%)	528 (2·4%)	532 (2·4%)	0·8 (0·2–2·1)
Other solid tumours	53 (31·5%)	2628 (12·1%)	2681 (12·2%)	2·0 (1·5–2·6)
Non malignant disorders	4995 (13·2%)	221 (0·3%)	5216 (4·6%)	95·8 (95·2–96·3)
Aplastic anaemia + Fanconi	2196 (44·0%)	6 (2·7%)	2202 (42·2%)	99·7 (99·4–99·9)
Thalassaemia	1202 (24·1%)	0 (0·0%)	1202 (23·0%)	100 (99·6–100)
Combined immune deficiencies	621 (12·4%)	8 (3·6%)	629 (12·1%)	98·7 (97·4–99·4)
Inborn errors	959 (19·2%)	4 (1·8%)	963 (18·5%)	99·6 (98·9–99·9)
Auto immune diseases	17 (0·3%)	203 (91·9%)	220 (4·2%)	7·7 (4·7–12·3)
Others	632 (1·7%)	408 (0·5%)	1040 (0·9%)	60·8 (57·7–63·7)
Total	37761	76066	113827	33·2 (32·9–33·4)

Transplant rates and team density

There were major differences between European countries in the total number of HSCT and transplant rates, as observed previously (Gratwohl *et al*, 1993) (illustrated in Fig 2 and Table II and as listed in the Appendix). Total numbers ranged from none in several countries to 3637 HSCT in Germany in 1999. Transplant rates varied from 0 HSCT per 10 million in several countries to a maximum of 1050 HSCT per 10 million in small countries such as Luxemburg. Median value was 184 HSCT per 10 million inhabitants.

There were differences between autologous and allogeneic HSCT. Transplant rates for allogeneic HSCT varied from 0 to 263 (median 70) per 10 million inhabitants, for autologous from 0 to 1050 (median 150) per 10 million inhabitants. Differences in transplant rates for individual indications were described earlier (Gratwohl *et al*, 1999).

The numbers of teams and team density varied in the European countries, from none to a maximum of 100 teams in Germany. Team density varied from 0 per 10 million inhabitants to 19·6 per 10 million inhabitants in Belgium (Iceland and Luxemburg excluded). There were a median 8·8 teams per 10 million inhabitants.

Transplant rates were closely correlated with team density ($R^2 = 0{\cdot}708$; F 70·17; $P < 0{\cdot}0001$) (excluding Iceland and Luxemburg), as an estimated increase of 28·2 HSCT per 10 million inhabitants has been suggested for each additional team per 10 million inhabitants (Fig 3). The correlation remained when countries with < 10 teams per 10 million inhabitants were analysed separately ($R^2 = 0{\cdot}699$; F 39·55; $P < 0{\cdot}0001$). Saturation appeared when countries with team density > 10 teams per 10 million inhabitants were analysed ($R^2 = 0{\cdot}222$; F 2·85; $P = 0{\cdot}122$).

Economic factors

Transplant rates and team density in part reflected the different economic situations in European countries. There was a clear correlation between transplant rates and the GNP per capita, as illustrated in Fig 4, based on data from

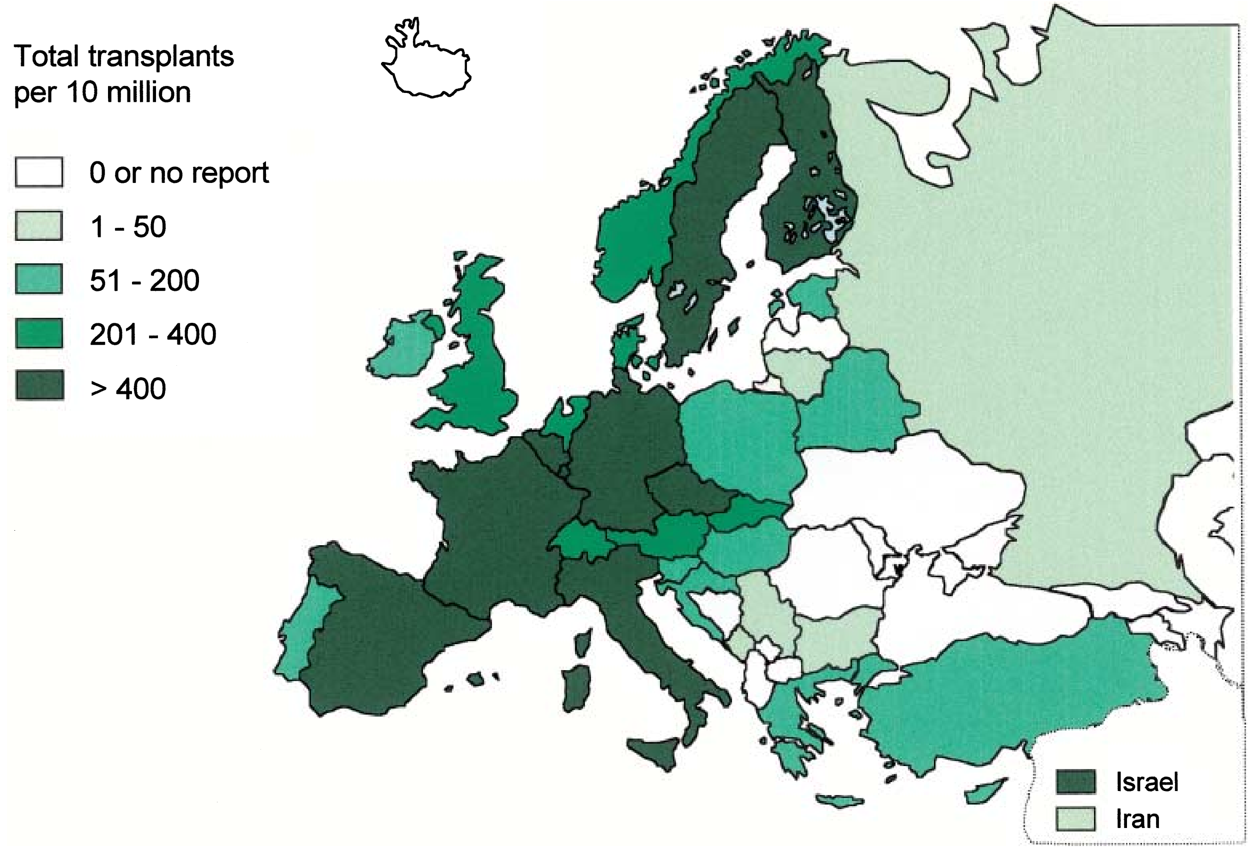

Fig 2. Transplant rates in participating European countries in 1999. Shades reflect total number of HSCT (autologous and allogeneic) per 10 million inhabitants.

1999 ($R^2 = 0{\cdot}680$; F 57·45; $P < 0{\cdot}0001$) (Fig 4A). This observation was valid for the years between 1990 and 1999 (data not shown); it was not influenced by the economic growth rate (data not shown). The calculation showed a closer correlation for allogeneic transplant rates ($R^2 = 0{\cdot}790$; F 101·82; $P < 0{\cdot}0001$) than for autologous HSCT ($R^2 = 0{\cdot}543$; F 32·09; $P < 0{\cdot}0001$), and a closer correlation for 'established' indications (34), e.g. allogeneic HSCT for chronic myeloid leukaemia ($R^2 = 0{\cdot}68$; F 61·63; $P < 0{\cdot}0001$) than for autologous HSCT for breast cancer ($R^2 = 0{\cdot}188$; F 6·71; $P < 0{\cdot}015$). The correlation between rate and GNP per capita remained the same when countries with a GNP per capita < 14 000 US$ were analysed separately ($R^2 = 0{\cdot}488$; F 13·7; $P < 0{\cdot}003$); it disappeared when countries with a GNP per capita > 14 000 US$ were analysed ($R^2 = 0{\cdot}004$, F 0·05; $P = 0{\cdot}830$). The same results were observed when HCE per capita were compared with transplant rates ($R^2 = 0{\cdot}568$; F 26·34; $P < 0{\cdot}0001$) (Fig 4B). GNP per capita and HCE per capita show a very close correlation in Europe (data not shown in detail). Again, when countries with HCE per capita > 1400 US$ were compared separately, no correlation was found ($R^2 = 0{\cdot}012$; F 0·7115; $P = 0{\cdot}749$). There was also a weak correlation between GNP per capita, HCE per capita and team density (data not shown in detail).

In contrast to GNP per capita and HCE per capita, no correlation with transplant rate and team density was found for annual growth rate or percentage of HCE compared with GNP (data not shown in detail).

Transplant efficiency varied from 11·56 to 44·8 transplants per 10 million inhabitants for each 10 000 US$ spent on HCE per capita, with a similar distribution between insurance-based type (median 21·1; range 15·1–27·8), tax-funded type (median 26·0; 11·5–41·8) and centralized-type (32) (median 19·1; 14·9–44·8) health care systems (P = NS).

Increase in transplant rate

Transplant growth, i.e. increase of transplant rate, was observed in all European countries. Not all indications increased at the same rate, as reflected in Fig 5. Some indications appeared only recently, such as allogeneic HSCT for solid tumours or HSCT for autoimmune disorders. Concerning allogeneic HSCT, a marked increase was observed for leukaemias, and a relatively stable rate for non-malignant disorders, including aplastic anaemia (Fig 5A). In contrast, for lymphoproliferative disorders, a trend towards more allogeneic HSCT was observed for the last two years. For autologous HSCT, the pattern was different (Fig 5B). Breast cancer showed a marked increase after 1994, with a peak in 1997 and a continuous decline

Table II. Transplantation of haematopoietic stem cells and economics in European countries.*

Country	Code	Population	Teams	HSCT	TR	TD	GNP/C	GNP rate	HCE C	HCE %
Austria	A	8·1	14	1954	384	17·3	26·8	3·2	1793	7·9
Belarus	BY	10·4	3	190	54	1·9	2·2	10·8	NA	5·7
Belgium	B	10·2	25	3378	487	19·6	23·4	2·8	1747	7·6
Bulgaria	BG	7·9	1	20	13	1·3	1·2	5·1	NA	4·7
Croatia	HR	4·3	2	588	184	4·7	4·6	2·6	NA	9·0
Cyprus	CY	0·8	1	12	150	12·5	NA	NA	NA	NA
Czech Republic	CZ	10·3	10	1867	405	9·7	5·2	− 2·1	904	7·0
Denmark	DK	5·3	3	1200	355	5·7	330	2·4	1848	7·7
Estonia	EST	1·4	1	68	100	7·1	3·4	6·4	NA	6·0
Finland	SF	5·2	6	1398	425	11·5	24·3	6·5	1447	7·3
France	F	59·1	83	21018	486	12·5	24·2	2·8	2103	9·9
Germany	DK	82·6	100	18628	440	12·1	26·6	2·8	2339	10·4
Greece	GR	10·6	11	1093	181	10·4	11·7	3·1	974	7·1
Hungary	HR	10·2	4	398	101	3·9	4·5	4·6	602	6·5
Ireland	IRL	3·8	3	468	153	5·3	18·7	7·9	1324	7
Italy	I	57·6	95	16687	507	16·5	20·1	1·3	1589	7·6
Lithuania	LT	3·4	1	2	6	2·9	2·5	4·8	NA	5·1
Netherlands	NL	15·8	14	3716	380	8·9	24·8	2·7	1825	85
Norway	N	4·5	5	678	260	11·1	34·3	1·7	1814	7·4
Poland	PL	38·7	13	1466	106	3·1	3·9	4·4	371	5·3
Portugal	P	10·0	7	1293	181	6·0	10·7	3·7	1125	8·2
Russia	RUS	146·5	14	541	9	0·9	2·3	− 6·4	47	2·2
Slovakia	SK	5·4	4	491	207	7·4	3·7	4·1	NA	7·1
Slovenia	SLO	1·9	1	81	111	5·3	9·8	4·1	743	7·7
Spain	E	40·0	76	12975	489	17·0	14·1	3·6	1168	7·4
Sweden	S	8·9	10	2944	474	11·2	25·6	2·8	1728	8·5
Switzerland	CH	7·2	12	1877	385	16·7	40·0	1·5	2547	10·2
Turkey	TR	64·8	21	1113	51	3·1	3·2	2·3	232	3·5
United Kingdom	UK	59·4	55	14723	351	9·1	21·4	2·0	1347	6·7
Yugoslavia	YU	10·7	4	274	30	3·7	NA	NA	NA	NA

*This table excludes Iceland and Luxemburg, and also countries with no HSCT.

HSCT, total number of transplants reported for 1990–99; TR, transplant rate, as number of HSCT per 10 million inhabitants in 1999; TO, team density; GNP/C, gross national product per capita in US$; GNP rate, increase/decrease in GNP in the late nineties; HCE/C, health care expenditure per capita in US$; HCE%, health care expenditure as a percentage of GNP.

thereafter; other solid tumours continue to increase, as does multiple myeloma. Lymphoproliferative disorders (lymphoma) showed the most pronounced increase, with the beginning of a plateau for the last 2 years. The increase was similar within western European countries independent of health care system. There was a wide gap between eastern and western European countries, which is slowly becoming smaller.

DISCUSSION

This report provides an overview on current status of HSCT in Europe. Data on more than a 100 000 patients treated with this technology during the last decade document that HSCT has become an established therapy. There was a consistent trend towards increased use of this technology. Age is no longer considered a limiting factor. For many haematological malignancies, there is an increased incidence with increasing age. More patients in the higher-age categories will be treated for established indications (Goldman *et al*, 1998). New indications are being explored: the value of autologous HSCT is being examined for patients with severe autoimmune diseases (Tyndall & Gratwohl, 1997; Potter *et al*, 1999; Traynor *et al*, 2000) and the value of allogeneic HSCT for patients with certain malignancies, such as melanoma or renal cell carcinoma (Childs *et al*, 2000). Expansion of volunteer donor pools and cord blood banks increases the likelihood of finding a compatible unrelated allogeneic donor (Confer, 1997; Gluckman *et al*, 1997). Low-intensity conditioning approaches render the procedure more attractive for patients with previous exclusion criteria for an allogeneic HSCT (Barrett & Childs, 2000; Carella *et al*, 2000). It can be predicted that, in the immediate future, numbers of allogeneic and autologous HSCT will continue to increase.

Not all indications will increase at the same rate (Twombly, 2000). Breast cancer illustrates such an example for autologous HSCT (Gratwohl *et al*, 2000). Doubts about the value of HSCT have reversed the previous trend. It is difficult to predict what the numbers will be in a few years

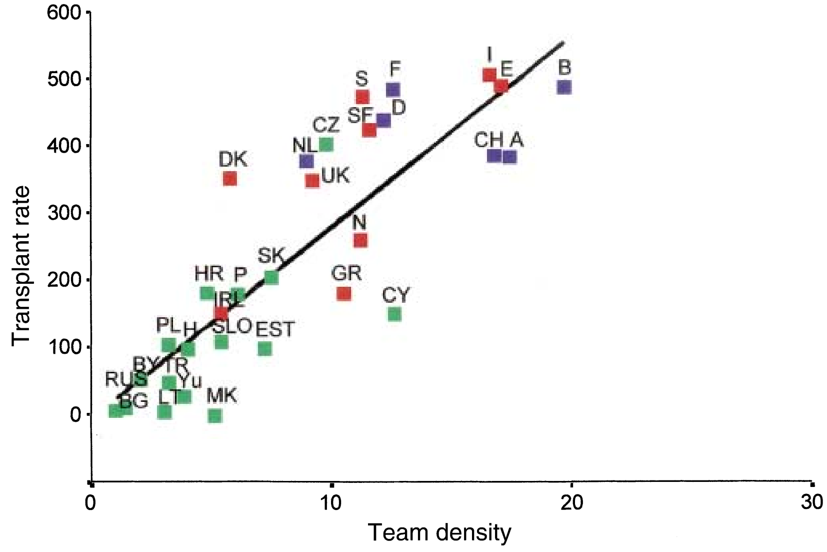

Fig 3. Correlation between transplant rate and team density per country in Europe (Iceland and Luxemburg are excluded from the analysis). Symbols correspond to health care systems: blue, insurance-based system; red, tax-funded system; green, centralized system.

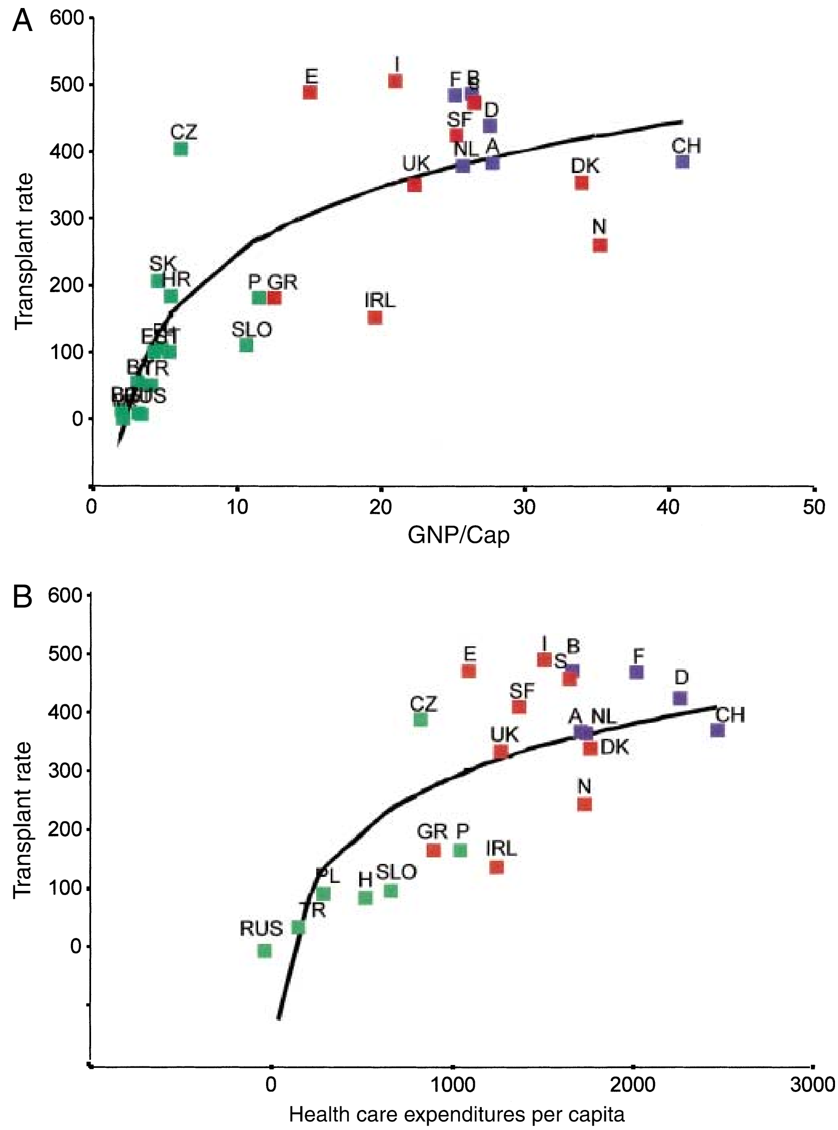

Fig 4. Economic factors. (A) Transplant rate and GNP per capita in Europe. (B) Transplant rate and HCE per capita in Europe. Symbols correspond to health care systems: blue, insurance-based system; red, tax-funded system; green, centralized system.

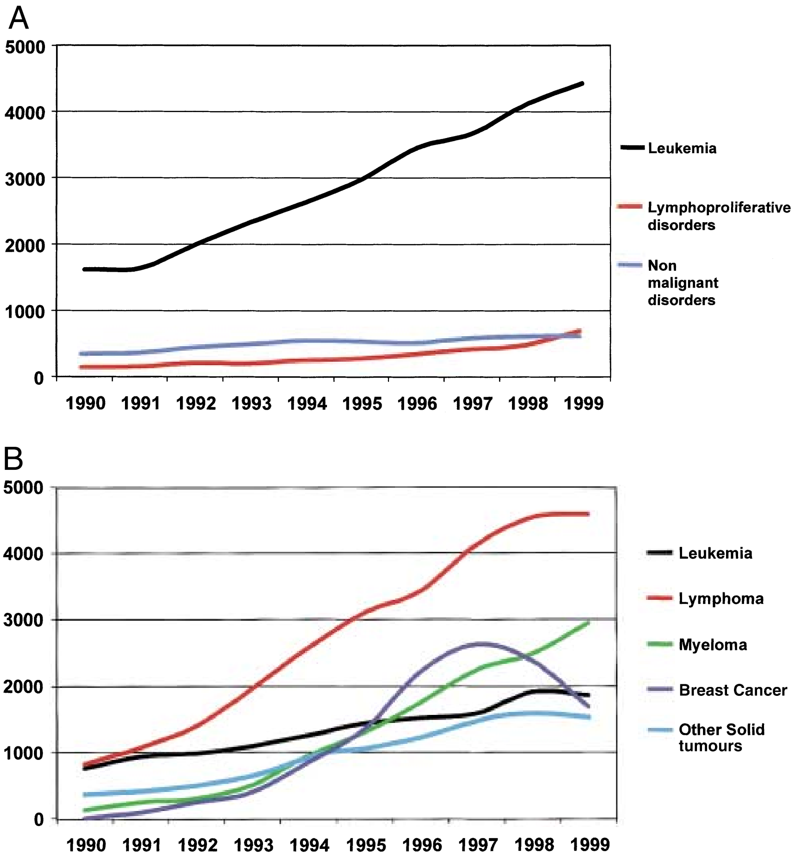

Fig 5. Absolute numbers of HSCT from 1990 to 1999 according to selected indications. (A) Allogeneic transplants grouped into leukaemias, lymphoproliferative disorders and non-malignant disorders. (B) Autologous transplants grouped into five groups, leukaemias, lymphomas, multiple myelomas, breast cancer and other solid tumours.

time. Results of the ongoing prospective randomized studies are awaited (Editorial, 1999). For other indications, a plateau has probably been reached. Most patients fulfilling entry criteria are already being treated with HSCT. For others, alternative treatments may improve and replace HSCT. Novel agents, such as tyrosine kinase inhibitors in chronic myeloid leukaemias or monoclonal antibodies in lymphoid malignancies, are examples that might obviate the need for HSCT (Druker & Lydon, 2000). Observational or cross-sectional studies (Liu *et al*, 2000), such as the EBMT activity surveys, provide a tool to capture trends early in this rapidly changing field. These rapid changes are best demonstrated by the shift from bone marrow to blood as the stem cell source within just a decade.

HSCT are a high-cost medicine. Continuing increases in utilization put a burden on health care providers and turn the focus to quality control aspects. Competent care for a specialized procedure, 24 h/d on a 7 d a week basis, can only be cost effective when a given number of procedures is performed at the same institution. There are many examples in several fields of medicine, including transplantation medicine, that experience is associated with outcome. Based on these data, quality control programmes for HSCT, by FAHCT in the US and JACIE in Europe, ask for at least 10 transplants per year to guarantee adequate quality standards. Based on considerations of simple cost-effectiveness, it may be advisable to restrict HSCT activity to a few centres in a country. Data from this report speak against this concept. This neglects the fact that additional factors influence availability of a procedure for the patient population at large.

There are major differences between European countries. Some can be explained. Transplant rates are correlated with economic factors. As presented earlier and shown in this report, GNP per capita and HCE per capita are the main determinants for transplant rates. Absolute expenditures are essential, rather than annual growth rates or percentages of GNP for HCE which are not. Still, this correlation is limited to countries with low economic strength. Above a certain GNP, more economic power no longer translates into more transplants. Economic factors are essential for initiating and promoting transplant programmes. Other factors become more important once countries have sufficient economic strength. This is exemplified by a similar transplant efficiency in different health care systems. In addition, these limited resources appear to be invested primarily in accepted indications. This is shown clearly by the correlation of transplant rates and GNP per capita with allogeneic HSCT and treatment for chronic myeloid leukaemia.

Besides GNP and HCE, team density influences transplant rates. Although weakly associated with economic factors itself, it needs to be considered separately. Optimal use of resources and experience, as well as quality concerns, might require a reduction of a technology to as few centres as possible. Optimal dissemination of a modern technology such as HSCT within a country requires expansion to several centres. It might therefore be wise to postulate that the number of teams should be expanded to allow dissemination of the technique, but be restricted to such an extent that sufficient experience at the individual centres remains. The present study gives some clues. An increase in team density above 10 teams per 10 million inhabitants is no longer associated with an increase in transplant rates.

There are some discrepancies between this study and early reports from the US on a general decline of HSCT (Twombly, 2000). Explanations remain speculative. The European survey captures almost all transplant teams in Europe. Still, some teams who previously reported or who were known to have performed transplants decided not to report or failed to answer the survey for unknown reasons, despite several attempts to reach them. Besides the usual arguments, such as an increase in workload, some participants personally communicated their reluctance to report to the bodies publishing transplant activity, for the reasons mentioned above and for fear of coercive action (Gratwohl & Baldomero, 2001). If this trend continues, novel approaches will be required to gather comprehensive transplant information.

Finally, for most of the differences between the economically strong European countries, we failed to define the factors influencing transplant rates. Differences in health care systems give inadequate explanations. Any form of grouping, such as comparing tax-funded or insurance-funded programmes, showed similar results. There are some indications that countries with strong national transplant regulations, such as France, Spain, Germany and Italy, have higher transplant rates. Financial incentives for participating institutions, as have been claimed for the rapid dissemination of HSCT for breast cancer alone, provide an inadequate explanation. Clearly, the data reveal a lack of knowledge in this field and a need for directed research.

This report highlights the current practice of HSCT in Europe during the last decade. It documents changes and trends, marking a break in the hitherto continuing rise in application. It gives some explanations about the differences in transplantation rates between the European countries and points to unanswered questions. As such, it should provide a basis for healthcare planning and interpretation of outcome data so that recommendations for the counselling of individual patients can be achieved.

ACKNOWLEDGMENTS

The co-operation of all participating teams and their staff (listed in the Appendix), the EBMT secretariat (A. Urbano-Ispizua, A. Bauer), the European EBMT Data Office in Paris (V. Chesnel, P. Palut, N. C. Gorin), the EBMT Registry Subcommittee (P. Ljungman, C. Ruiz de Elvira), the French Registry SFGM (J. P. Vernant, M.-L. Tanguy), the Dutch Registry (T. de Witte, A. v. Biezen, N. Tazelaar), the Austrian Registry (D. Niederwieser, B. Gritsch), the Italian Registry (M. Vignetti, A. Bacigalupo, R. Oneto, C. Palazzi), the German Registry (H. Ottinger, C. Müller, B. Kubanek, N. Schmitz, U. W. Schaefer), the Swiss Registry (J. Passweg, H. Baldomero), the British Registry (A. Eades), the Belgium Registry (Y. Beguin) and the Spanish Transplantation Office (ONT) (M. Naya) is greatly appreciated. The authors also wish to thank A. Maerki for secretarial assistance, L. John and O. Baldomero for technical assistance with data management, Michael Gratwohl for statistical expertise and A. Wodnar-Filipowicz for a careful review of the manuscript.

The work was supported in part by a grant from the Swiss National Research Foundation, 32-52756·97, the Swiss Cancer League, and the Horton Foundation. EBMT is supported by grants from corporate members: Hoffmann-La Roche Ltd, Amgen Europe, Chugai Rhone-Poulenc Rorer, Baxter, Astra, Cobe International, Nextar, Liposome Co., Imtix, Octapharma, Stem Cell Technologies, ICN Pharmaceuticals and Bristol-Meyers Squibb.

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Pavia, Fondazione Clinica del Lavoro, CIC 771, A. Zambelli, G. Robustelli della Cuna
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Perugia, Policlinico Monteluce, Università, CIC 794, M.F. Martelli, F. Aversa
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Pesaro, Ospedale, CIC 529, G. Lucarelli
Pescara, Ospedale Civile, CIC 248, P. di Bartolomeo
Pisa, University of Pisa (Ads hem, peds hem + onco), CIC 795, P. Macchia, M. Petrini
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Roma, Ospedale S. Camillo, CIC 287, I. Majolino, A. Locascivlli
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Latvia: no report

Liechtenstein: no report

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Malta: no report

Moldova: no report

Monaco: no report

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