Changes in the use of hematopoietic stem cell transplantation: a model for diffusion of medical technology

Alois Gratwohl,[1] Alvin Schwendener,[2] Helen Baldomero,[3] Michael Gratwohl,[2] Jane Apperley,[4] Dietger Niederwieser,[5] and Karl Frauendorfer[2]

[1]Hematology, Department of Medicine, University Hospital, University of Basel, Switzerland; [2]Institute for Operations Research and Computational Finance, University of St. Gallen, 9000, Switzerland; [3]EBMT Activity Survey Office, University Hospital, Basel, Switzerland; [4]Department of Haematology, Imperial College, London, United Kingdom, and [5]Hematology & Oncology, University Hospital Leipzig, Germany

Acknowledgments: the authors thank S. Stöckli for excellent secretarial assistance.

Funding: this work was supported in part by the European Leukaemia Net LSH-2002-2.2.0-3, by a grant from the Swiss National Research Foundation, 3200B0-118176 the Swiss Cancer League, the Regional Cancer League and the Horton Foundation. The EBMT is supported by grants from the corporate members: Amgen Europe GmbH, ViroPharma Europe, Celegene International SARL, Genzyme Europe B.V., Gilead Sciences Europe Ltd, Miltenyl Biotec GmbH, F. Hoffmann-La Roche, Schering-Plough International Inc., Bristol Myers Squibb, CaridianBCT Europe NV, Cephalon Europe, Fresenius Biotech GmbH, Therakos Inc, Alexion Europe, Chugai Sanofi-Aventis, Merck Sharp and Dohme, Novartis, Pfizer, Pierre Fabre Médicament

Manuscript received on August 11, 2009. Revised version arrived on September 16, 2009. Manuscript accepted on September 16, 2009.

Correspondence:
Alois Gratwohl,
Hematology University Hospital
Basel Petersgraben 4
CH-4031 Basel, Switzerland.
E-mail: hematology@uhbs.ch

The online version of this article has a Supplementary Appendix.

ABSTRACT

Background

Innovations in hematology spread rapidly. Factors affecting the speed of introduction, international diffusion, and durability of use of innovations are, however, poorly understood.

Design and Methods

We used data on 251,106 hematopoietic stem cell transplants from 591 teams in 36 European countries to analyze the increase and decrease in such transplants for breast cancer and chronic myeloid leukemia and the replacement of bone marrow by peripheral blood as the source of stem cells as processes of diffusion. Regression analyses were used to measure the quantitative impact of defined macro- and microeconomic factors, to look for significant associations (t-test), and to describe the coefficient of determination or *explanatory content* (R^2).

Results

Gross national income per capita, World Bank category, team density, team distribution, team size, team experience and, team innovator status were all significantly associated with some or all of the changes. The analyses revealed different patterns of associations and a wide range of *explanatory content*. Macro- and micro-economic factors were sufficient to explain the increase of allogeneic hematopoietic stem cell transplants in general (R^2 = 78.41%) and for chronic myeloid leukemia in particular (R^2 = 79.39%). They were insufficient to explain the changes in stem cell source (R^2 =26.79% autologous hematopoietic stem cell transplants; R^2 = 9.67% allogeneic hematopoietic stem cell transplants) or the decreases in hematopoietic stem cell transplants (R^2 =10.22% breast cancer; R^2=33.17% chronic myeloid leukemia).

Conclusions

The diffusion of hematopoietic stem cell transplants is more complex than previously thought. Availability of resources, evidence, external regulations and, expectations were identified as key determinants. These data might serve as a model for diffusion of medical technology in general.

Key words: hematopoietic stem cell transplantation, diffusion of medical technology economics, evidence.

Citation: Gratwohl A, Schwendener A, Baldomero H, Gratwohl M, Apperley J, Niederwieser D, and Frauendorfer K. Changes in the use of hematopoietic stem cell transplantation: a model for diffusion of medical technology . Haematologica. 2010;95:637-643. doi:10.3324/haematol.2009.015586

Introduction

Innovations in modern medicine spread rapidly. Information has become available on a global level and there is little doubt about the benefit of modern medicine in general. Insight into molecular mechanisms of disease, novel diagnostic tools, new drugs, and better surgical techniques have increased life span and improved quality of life. The concept of evidence-based medicine has become accepted as a framework to measure the validity and benefit of new concepts, new drugs, or new technologies. Still, little is known about the mechanism of the spread of new medical technologies.[1-4] Rogers described adoption of a new medical intervention as a process of diffusion with five stages in an S-shaped process.[5] He introduced the concept of innovators, early adopters, early majority, late majority, and laggards. He stipulated the general applicability of this pattern but gave little information on the factors associated with the five subgroups or with the change itself.

This process of diffusion is receiving renewed interest in medicine. Understanding the mechanisms appears essential for health care planning.[4] Too frequently, novel concepts are avidly adopted, spread rapidly but are as quickly abandoned when objective examination fails to show benefits.[6,7] A recent review summarized the main concerns: enthusiasm frequently outstripped evidence, adoption before proven efficacy wasted resources and harmed patients, easy-to-use technology was more likely to be adopted without evidence, and, confirming Roger's concept, adoption followed an S-shaped curve.[8] In this review, Wilson used "revascularization" of the brain by connecting the temporal artery with the middle cerebral artery as an example. The technology was rapidly adopted in the 1970s but as rapidly abandoned, when a randomized controlled trial showed no benefit.[8] The focus of this and other recent reviews was, however, on the characteristics of the new technologies and the dynamics of adoption. There was little or no analysis of the factors associated with the diffusion process itself. Availability of resources and evidence were considered as the key objective elements to enhance diffusion, lack of evidence or lack of resources as the key elements for disappearance of a new technology. The main concern was on inequity in health for populations with limited resources or absent health care coverage. None of these analyses could explain the process or the differences between countries of similar economic status.[9-12]

Hematopoietic stem cell transplantation (HSCT) represents an example of medical innovation which has seen rapid expansion and changes over the last two decades.[13-15] It is a complex, high-cost procedure and depends on a well established institutional infrastructure network.[16] Earlier observations showed a clear correlation between gross national income *per capita* (GNI/cap) and transplant rates in Europe.[17] Transplant rates (i.e. the number of transplants per number of inhabitants) were higher and increased more rapidly in countries with a higher GNI/cap. Furthermore, transplant rates were higher in countries with more transplant teams per number of its inhabitants (team density) or compared to its size in square kilometres (team distribution).[18] Still, unexplained differences between countries with similar economic backgrounds were observed. We were, therefore, interested in exploring further the factors associated with the spread of HSCT and with changes in its use. The availability of near complete information on all HSCT in Europe and data on a series of macro- and microeconomic factors in all participating countries provides a unique opportunity to study the process of diffusion.

Design and Methods

Study design

Data from the Annual Activity Survey of the European Group for Blood and Marrow Transplantation (EBMT) (*http://www.ebmt.org*) form the basis for this retrospective analysis.[19] Since 1990, all EBMT members and affiliated teams have been requested to report the numbers of patients with HSCT in the previous year by indication, stem cell source, and donor type. Data were validated by the reporting team and by cross checking with national registries. Quality control included onsite visits of randomly selected teams.

Participating teams and countries

This report is based on data contributed by 591 teams in 36 European countries on 251,106 patients who received their first transplant (83,187 allogeneic HSCT; 167,919 autologous HSCT) in Europe between 1991 and 2006.

Personal contacts, reviews with health care agencies, and cross checks with national registries indicate that the reported transplants comprise more than 80% of all autologous and more than 95% of all allogeneic HSCT in Europe. Participating teams are listed in the online appendix in alphabetical order according to country, city, and EBMT center code.

Changes of hematopoietic stem cell transplant technology use as a model for the process of diffusion

The analysis included the overall increase in allogeneic HSCT (Figure 1A), the change from bone marrow to peripheral blood as the source of stem cells in autologous (Figure 1B) and allogeneic HSCT (Figure 1C), the increase and decrease in autologous HSCT for breast cancer (Figure 1D), and the increase and decrease in allogeneic HSCT for chronic myeloid leukemia (Figure 1E).

Definitions and factors analyzed

Transplant rates

Transplant rates were defined as the number of HSCT per 10 million inhabitants. Population data were obtained from the World Bank (*http://www.worldbank.org*).

Macroeconomic factors

Macroeconomic factors included in the analysis were: GNI/cap, World Bank category, team density (number of transplant teams per 10 million inhabitants), and team distribution (number of transplant teams per 10,000 km^2). GNI/cap (according to World Bank definitions, *http//www.worldbank.org*) was used to classify the participating countries into *high income* (Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, and United Kingdom), *middle income* (Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, and Slovakia) and *low income* countries (Azerbaijan, Belarus, Bosnia, Herzegovina, Bulgaria, Macedonia, Romania, Russia, Serbia Montenegro, Ukraine, and Turkey).

Microeconomic factors

Microeconomic factors included in the analysis were team size, team experience, and innovator status. Team size was defined for the overall activity as the number of transplants per year; for the

analysis of breast cancer and chronic myeloid leukemia, as the number of transplants per year for the given indication. Team experience was defined as the number of years of HSCT activity of the team. Innovators were defined according to Roger's definition,[5] and included the first 2.5% of the teams to introduce or to abandon a technology.

Statistical analysis

The trends of the seven diffusion processes were computed with regression analyses, using the ordinary least squares estimation method in order to define the coefficient of determination (R-squared, R^2) and the 95% confidence intervals. The relations of the macro- and micro-economic factors to the technology changes were also estimated by ordinary least squares-regressions. The corresponding t-statistics were used to confirm a significant positive or negative relation at the 1% (++, --) or 5% (+, -) level. R^2 describes the extent to which a single macro- or micro-economic factor could explain the individual process of diffusion, and, therefore, gives a quantitative aspect for the *explanatory content*. Finally, multiple regression analyses were used to describe this *explanatory content* of several macro- or micro-economic factors combined and to summarize to what extent (by R^2) the individual factors jointly explain the respective diffusion process.

Results

Increase in allogeneic hematopoietic stem cell transplantation

Annual numbers of transplants increased from 2,100 in 1991 to nearly 10,000 in 2006 in an almost linear manner (Figure 1A). Chronic myeloid leukemia was not included in this analysis, because of its biphasic development as outlined separately below. All macroeconomic factors had a significant association with this increase in HSCT, with a greater increase in countries with higher incomes (GNI/cap $P<0.01$; $R^2 = 56.07\%$; World Bank category $P<0.01$; $R^2 = 52.15\%$, Figure 2A). Team density provided the highest *explanatory content* ($P<0.01$; $R^2 = 69.85\%$) of the macroeconomic factors, team size the highest *explanatory*

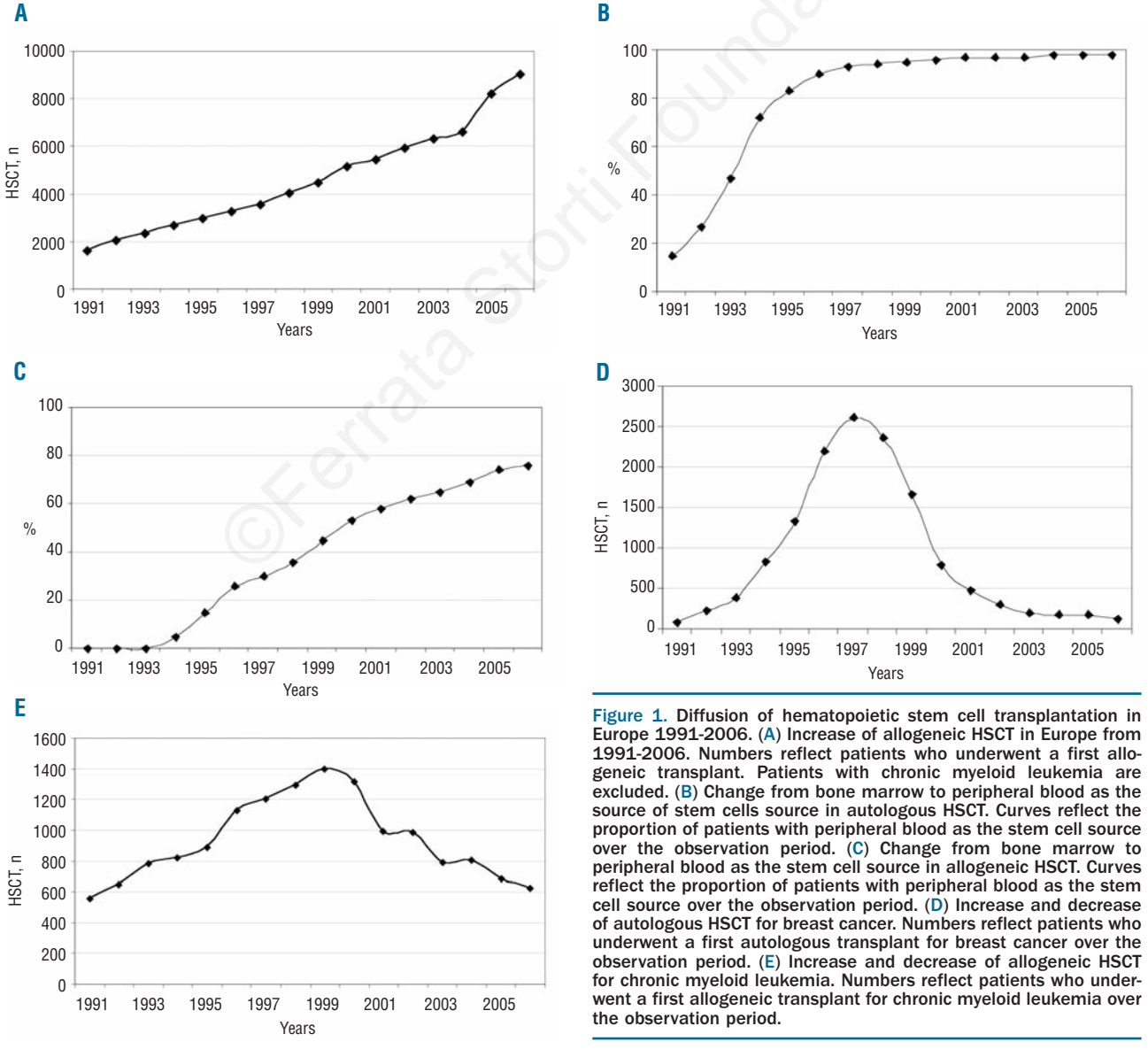

Figure 1. Diffusion of hematopoietic stem cell transplantation in Europe 1991-2006. (A) Increase of allogeneic HSCT in Europe from 1991-2006. Numbers reflect patients who underwent a first allogeneic transplant. Patients with chronic myeloid leukemia are excluded. (B) Change from bone marrow to peripheral blood as the source of stem cells source in autologous HSCT. Curves reflect the proportion of patients with peripheral blood as the stem cell source over the observation period. (C) Change from bone marrow to peripheral blood as the stem cell source in allogeneic HSCT. Curves reflect the proportion of patients with peripheral blood as the stem cell source over the observation period. (D) Increase and decrease of autologous HSCT for breast cancer. Numbers reflect patients who underwent a first autologous transplant for breast cancer over the observation period. (E) Increase and decrease of allogeneic HSCT for chronic myeloid leukemia. Numbers reflect patients who underwent a first allogeneic transplant for chronic myeloid leukemia over the observation period.

content of the microeconomic factors ($P<0.01$; $R^2 = 77.78$). Overall, macroeconomic factors could explain 76.25% of the increase and microeconomic factors 78.41% of the increase.

In order to analyze the interaction between team density and team size as a factor for adoption, rather than as a consequence of adoption, we performed a panel analysis by keeping the years fixed for the estimation of the variable factors. Irrespective of their past, larger teams were more likely to adopt or abandon the new technologies.

Change from bone marrow to peripheral blood as stem cell source

Stem cell source changed rapidly and completely from bone marrow to peripheral blood for autologous HSCT within a very narrow time span, exhibiting the classical S-shaped adaptation curve (Figure 1B). The change in allogeneic HSCT followed 3 years later, more slowly and so far without a plateau and without the S-shaped configuration (Figure 1C). The correlation with macro- and micro-economic factors was similar for both diffusion processes (Table 1), with innovator status of the teams providing the highest *explanatory content* ($P<0.01$; $R^2 = 25.15\%$ for autologous HSCT, $P<0.01$; $R^2 = 9.29\%$ for allogeneic HSCT).

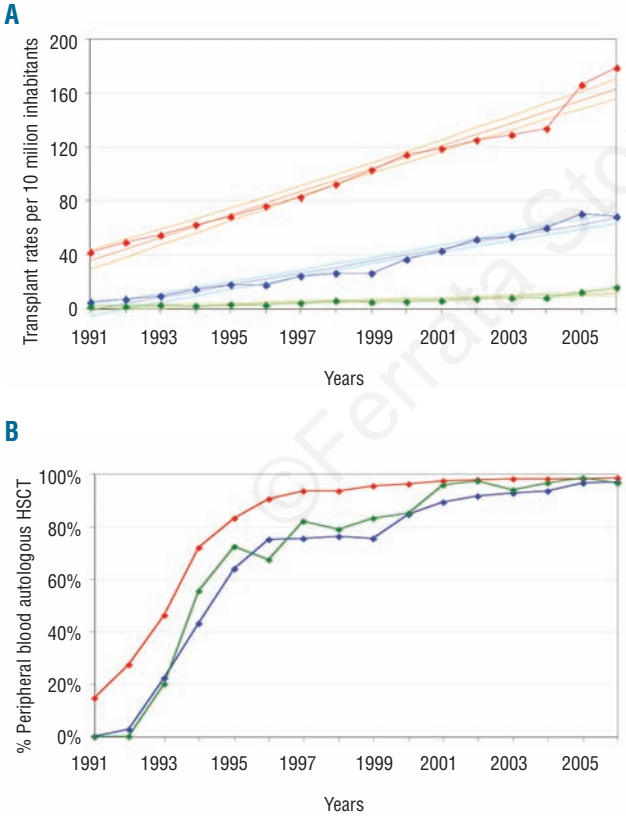

Figure 2. Impact of macroeconomic factors on the diffusion of HSCT in Europe. (A) Transplant rates (country-weighted) for allogeneic HSCT (excluding chronic myeloid leukemia) in Europe from 1991 to 2006 in countries with high (red), medium (blue) or low (green) income by World Bank category. (B) Proportion of autologous HSCT carried out with peripheral blood as the source of stem cells in Europe from 1991 to 2006 in countries with high (red), medium (blue) or low (green) income by World Bank category.

There was one exception between the two groups: GNI/cap had a significant impact on the diffusion of peripheral blood as the source of stem cells in autologous HSCT ($P<0.01$; $R^2 = 18.53\%$, Figure 2B) but not in allogeneic HSCT ($P>0.05$; $R^2 = 1.0\%$). Overall, macro- and micro-economic factors did not provided a satisfactory *explanatory content* for this process of diffusion ($R^2 = 26.79\%$ for autologous HSCT, $R^2 = 7.75\%$ for allogeneic HSCT, Table 1).

Increase and decrease of autologous hematopoietic stem cell transplantation for breast cancer

The numbers of autologous HSCT for breast cancer increased rapidly from 1992 to a peak of 2,570 HSCT in 1997, followed by an equally rapid decline in a typical bell-shaped process to less than 300 HSCT (Figure 1D). The increase and decrease showed different patterns of associations. Team density ($P<0.01$; $R^2 = 69.62\%$) and team size ($P<0.01$; $R^2 = 61.76\%$) provided the highest *explanatory content* for the increase. The increase was also greater in countries with a higher GNI/cap ($P<0.01$; $R^2 = 26.43\%$) and occurred earlier in the high income World Bank category countries. In contrast, innovator status provided the highest *explanatory content* for the decrease ($P<0.01$; $R^2 = 9.67\%$) with larger teams stopping earlier than smaller teams ($P<0.01$; $R^2 = 5.55\%$). The *explanatory content* for the decrease was low. It is of interest to note that teams beginning their overall HSCT activity in 1997 only, at the time of peak activity of autologous HSCT for breast cancer, showed the same rate of decline as those who had started earlier ($P>0.05$; $R^2 = 0.0\%$). The increase in HSCT for breast cancer could be reasonably explained by macroeconomic factors (overall $R^2 = 75.69\%$), whereas the decrease could not ($R^2 = 8.14\%$ for macroeconomic factors, $R^2 = 10.22\%$ for microeconomic factors; Table 1).

Increase and decrease of allogeneic hematopoietic stem cell transplants for chronic myeloid leukemia

Allogeneic HSCT for chronic myeloid leukemia increased steadily over the observation period such that by 1999 chronic myeloid leukemia was the most frequent indication for an allogeneic HSCT (Figure 1E). Team size ($P<0.01$; $R^2 = 78.87\%$) and GNI/cap ($P<0.01$; $R^2 = 47.89\%$) provided the highest *explanatory content* for the increase. From 1999, transplants decreased rapidly. The decrease was most strongly associated with GNI/cap ($P<0.01$; $R^2 = 31.29\%$), with countries with a high GNI/cap stopping earlier and more rapidly. Team size was also associated with the decrease ($P<0.01$; $R^2 = 4.33\%$), with a more rapid decrease in larger teams. All microeconomic factors were significantly ($P<0.05$) associated with the decrease but had only marginal *explanatory content*. In contrast to the increase and decrease of HSCT for breast cancer, microeconomic factors provided the higher *explanatory content* for the increase ($R^2=79.39\%$) and macroeconomic factors the higher *explanatory content* for the decrease ($R^2=33.17\%$) of HSCT for chronic myeloid leukemia (Table 1).

Discussion

The present data give a quantitative element to a series of factors associated with the processes of adoption and diffusion of a technology within one field of innovative medicine, HSCT. They show a unique pattern for each of

the seven processes analyzed. They document that diffusion of a cost-intensive, complex technical process depends on more than availability of resources even though transplant rates were lower in low and middle income countries. The change from bone marrow to peripheral blood exemplifies the complexity. Infrastructure was required for the collection of peripheral blood stem cells instead of bone marrow, granulocyte colony-stimulating factor and cell separators were needed to collect peripheral stem cells. As these are expensive items, it would be reasonable to predict that GNI/cap would be significantly associated with the change from bone marrow to peripheral blood as the source of stem cells for autologous HSCT, which occurred first. This would not be the case for the more recent change from bone marrow to peripheral blood in allogeneic HSCT as the infrastructure and cell separators were already in place. This was indeed the case. However, macro- and micro-economic factors explained only a small part of the change from bone marrow to peripheral blood in allogeneic HSCT. Factors other than resources were apparently more important. Regulatory aspects restricted the use of growth factors for stem cell mobilization in healthy donors in some countries; access to transplants was centrally regulated in Norway during the observation period. These were external factors identified beyond availability of resources.[20,21]

Economic strength was the driving factor in the increase of transplant rates in general as well as specifically for breast cancer or chronic myeloid leukemia: GNI/cap provides a high *explanatory content*. An analysis of the individual macro- and micro-economic factors is hampered by the fact that all correlate with GNI/cap. Still, some distinctions could be made. Team density and team distribution were more closely correlated with the increase than was GNI/cap. Transplant rates were higher in countries with more transplant teams. This indicates that patients within a given country need to have access to a transplant team. Team size had a strong impact on the increase of HSCT for breast cancer. Larger transplant teams apparently tended to adopt new technologies and to recruit patients more rapidly. A reciprocal interaction that adoption increased team size and team density cannot be completely excluded. Interestingly, the duration of team experience had a marginal impact, if any. Teams starting a new transplant program followed the same transplant policy as programs

Table 1. Impact of macro- and micro-economic factors on the diffusion of HSCT technology in Europe 1991-2006.

Diffusion Process (single Regression)		Macroeconomic factors					Microeconomic factors			
		GNI/cap	World bank class.	Team density	Team distribution	Cumulative R^2	Team size	Team experience	Innovator status	Cumulative R^2
Increase in HSCT	R^2	56.07%	52.15%	69.85%	37.52%	76.25%	77.78%	21.56%	27.65%	78.41%
	t-statistic	20.59	22.86	33.59	13.59		82.53	33.55	39.61	
	Ranking	II	-	I	III		I	II	III	
	Sign. (*P* value)	++	++	++	++		++	++	++	
BM-PB autologous	R^2	18.53%	11.08%	15.53%	7.75%	20.70%	0.00%	0.00%	25.15%	26.79%
	t-statistic	5.45	3.67	6.38	4.56		2.49	-5.96	10.40	
	Ranking	II	-	II	-		II	-	I	
	Sign. (*P* value)	++	++	++	++		+	- -	++	
BM-PB allogeneic	R^2	1.00%	0.12%	0.56%	3.36%	7.75%	0.50%	1.08%	9.29%	9.67%
	t-statistic	-1.86	-0.65	1.41	5.14		4.77	-6.95	6.10	
	Ranking	II	-	-	I		-	II	I	
	Sign. (*P* value)	0	0	0	++		++	- -	++	
Breast cancer autologous	R^2	26.43%	17.07%	69.62%	39.04%	75.69%	61.76%	0.00%	1.56%	61.88%
	increase t-statistic	7.33	8.83	13.34	6.38		19.17	1.06	4.43	
	Ranking	II	-	I	III		I	-	III	
	Sign. (*P* value)	++	++	++		++	++	0	++	
Breast cancer autologous	R^2	1.47%	2.82%	7.29%	2.59%	8.14%	5.55%	0.00%	9.67%	10.22%
	decrease t-statistic	-2.72	-3.41	-4.18	-3.11		-5.15	-1.86	-8.65	
	Ranking	-	-	I	-		-	-	I	
	Sign. (*P* value)	- -	- -	- -	- -		- -	0	- -	
CML allogeneic increase	R^2	47.89%	43.38%	42.14%	14.93%	56.01%	78.87%	10.73%	41.46%	79.39%
	t-statistic	11.94	13.46	12.93	5.80		31.58	14.11	12.50	
	Ranking	II	III	II	-		I	III	III	
	Sign. (*P* value)	++	++	++	++		++	++	++	
CML allogeneic decrease	R^2	31.29%*	2.00%	2.43%	0.00%	33.17%	4.33%	0.86%	1.28%	4.51%
	t-statistic	-8.62	-2.45	1.31	1.04		-4.35	-4.72	-4.71	
	Ranking	II	-	-	-	-	I	-	-	
	Sign. (*P* value)	- -	-	0	0		- -	- -	- -	

Single and multiple regression analyses. Numbers (e.g. 56.07%) indicate the explanatory content R^2 of the seven examined macro- and micro-economic factors for each process of diffusion. The ranking indicates the factor with the highest explanatory content (Ranking I); ranking II and III represent factors with additional explanatory content when analyzed in a multiple regression analysis by combining significant factors. Cumulative R^2 gives the combined total explanatory content when all significant factors are analyzed together. Team size refers to the total number of HSCT in a given year for the evaluation of all allogeneic HSCT; to the numbers of autologous HSCT for breast cancer or allogeneic HSCT for chronic myeloid leukemia for the respective analysis for these indications. BM: bone marrow; PB: peripheral blood; CML: chronic myeloid leukemia; R^2: coefficient of determination or explanatory content as defined in the text; Sign = +/- represent a positive/negative correlation by t statistics at the <0.05 level (P value) + +/– – represent a positive/negative correlation by t statistics at the <0.01 level; for definition of GNI/cap, World Bank classification, team density, team distribution, team size, team experience: see text.

established for a long time.

Innovators, as defined by Rogers,[5] were identified for the changes from bone marrow to peripheral blood. A few teams introduced the new technology; they were followed by others. This was best shown, with the highest *explanatory content* for innovators concerning the change from bone marrow to peripheral blood in autologous HSCT. Findings were different and unexpected for the decrease. The higher *explanatory content* for the innovators of the decrease in autologous HSCT for breast cancer suggests that an unproven technology is abandoned more rapidly and with more thoroughness by a few leaders in the field than it is adopted.

The changes in technology occurred before formal evidence was published in the medical literature. The key study on the benefits of peripheral blood compared to bone marrow as the source of stem cells for autologous HSCT was published in 1996,[22] at a time when the saturation had already exceeded 90%. In allogeneic HSCT, the feasibility of peripheral blood as the stem cell source was reported in 1998, when more than 50% of all allogeneic HSCT were already being performed with peripheral blood.[23,24] Autologous HSCT for breast cancer was primarily driven by a few preliminary reports. The prospective randomized study that showed a benefit of autologous HSCT in breast cancer over conventional chemotherapy was published in 1995, close to the peak of activity. This paper was later found to be fraudulent and was withdrawn. A negative study followed in 2000, i.e. 3 years after the decline.[25] The decline in allogeneic HSCT for chronic myeloid leukemia began in 1999, 2 years before the first publication of the phase I study of imatinib,[26] a specific tyrosine kinase inhibitor. This was possible because chronic myeloid leukemia is a chronic disorder and physicians and patients could gamble on remaining in the chronic phase until the drug therapy was approved. This was not the case in countries with lower income where the costs of drug treatment could be expected to be higher than the costs of a transplant.[27,28] Hence, the process of diffusion started before evidence or lack of evidence was formally provided. Teams obtained their information from other sources, and were prepared to change practice before formal peer review.

In summary, diffusion of a new technology requires an economic background sufficient to provide the necessary infrastructure and to give patients access to the procedure.[4,8] Preliminary promising data, presented at scientific meetings, spread rapidly and trigger rational expectations.[29] Innovations are adopted if they fit current concepts and are easy to use.[3,7] They are maintained if evidence is confirmed and are abandoned if confirmation is not provided or new methods appear to be more promising. Last, the legal and regulatory environment must permit the introduction and adoption of the new technology. These findings are compatible with a concept that adoption of any new medical technology and its diffusion correlate with four main elements: economics, evidence, external regulations, and expectations. It is likely that these four factors form the principle basis for any process of diffusion.

Authorship and Disclosures

AG, JA, KF and MG designed the study concept. HB was responsible for data collection; AS, MG and KF performed the statistical analyses; AG, JA, DN and KF wrote the manuscript; all authors approved the final version; all researchers were independent from the funding sources.

The cooperation of all participating teams and their staff (listed in the Appendix), the EBMT Co-ordination office; Barcelona (F McDonald, E McGrath, SM Jones, EJ Mac Hale), Paris (V Chesnel, C Kenzey, NC Gorin), London (C Ruiz de Elvira, S Hewerdine, S de Souza), the Austrian Registry (ASCTR) (H Greinix, B Lindner), the Czech BMT Registry (K Benesova, M Trnkova), the French Registry (SFGM) (N Milpied, F Mesnil), the German Registry (DRST) (H Ottinger, K Fuchs, C Müller, H Neidlinger, U Feldmann), the Italian Registry (GITMO) (A Bosi, R Oneto, B Bruno), the Dutch Registry (HOVON) (A Schattenberg, M Groenendijk), Spanish BMT Registry (GETH), (E Carreras, I Espigado, J López, A Cedillo), the Swiss Registry (STABMT) (U Schanz, H Baldomero, E Buhrfeind), the Turkish BMT Registry (G Gurman, M Arat, F Arpaci, M Ertem) and the British Registry (BSBMT) (T Pagliuca, J Cornish, K Kirkland, J Lee, R Paul) is greatly appreciated. The manuscript is the sole responsibility of the authors.

The need for ethics approval and informed patient consent was waived by the Ethics Committee Beider Basel (EKBB).

No potential conflicts of interests relevant to this article were reported.

References

1. Cajn M, Rittmann R. Diffusion of Innovation in Health Care. California Health Care Foundation Health Report; May 2002.
2. Yokota T, Kojima S, Yamauchi H, Hatori M. Evidence-based medicine in Japan. Lancet. 2005;366(9480):122.
3. Papageorgiou C, Savvides A, Zachariadis M. International medical technology diffusion. J Int Econom. 2007;72(2):409-27.
4. Ostfeld I, Tamir O, Hanin S, Vaknin S, Harai G, Abadi-Korek I, et al. What is influencing the adoption of new medical technologies by physicians? Handb Health Technol Assess. 2006;3:178.
5. Rogers E. Diffusion of Innovations. The Free Press, New York 2003, 5th edition.
6. Sharma B, Danjoux NM, Harnish JL, Urbach DR. How are decisions to introduce new surgical technologies made? Advanced laparoscopic surgery at a Canadian community hospital: a qualitative case study and evaluation. Surg Innov. 2006;13(4):250-6.
7. Toledo-Pereyra L. Surgical revolutions. J Invest Surg. 2008;21(4):165-8.
8. Wilson CB. Adoption of new surgical technology. Br Med J. 2006;332(7533): 112-4.
9. Oh EH, Imanaka Y, Evans E. Determinants of the diffusion of computed tomography and magnetic resonance imaging. Int J Technol Assess Health Care. 2005;21(1): 73-80.
10. Loureiro S, Simões B, Aragão E, Mota F, Moura H, Damasceno L. Diffusion of medical technology and equity in health in Brazil: an explanatory analysis. Eur J Develop Res. 2007;19(1):66-8.
11. Havighurst CC. Disruptive innovation: the demand side. Health Affairs. 2008;27(5): 1341-4.
12. Dearing JW. Evolution of diffusion and dissemination theory. J Public Health Manag Pract. 2008;14(2):99-108.
13. Nandakumar AK, Beswick J, Thomas CP, Wallack SS, Kress D. Pathways of health technology diffusion: the United States

and low-income countries. Health Affairs 2009;28(4):986-95.
14. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354(17): 1813-26.
15. Ljungman P, Urbano-Ispizua A, Cavazzana-Calvo M, Demirer T, Dini G, Einsele H, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: definitions and current practice in Europe. Bone Marrow Transplant. 2006; 37(5):439-49.
16. Tan SS, Uyl de-Groot CA, Huijgens PC, Fibbe WE. Stem cell transplantation in Europe: trends and prospects. Eur J Cancer. 2007;43(16):2359-65.
17. Gratwohl A, Passweg J, Baldomero H, Horisberger B, Urbano-Ispizua A for the Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT): economics, health care systems and utilisation of hematopoietic stem cell transplants in Europe. Br J Haematol. 2002;117(2):451-68.
18. Gratwohl A, Baldomero H, Schwendener A, Gratwohl M, Apperley J, Niederwieser D, et al. Joint Accreditation Committee of the International Society for Cellular Therapy, European Group for Blood and Marrow Transplantation, European Leukaemia Net. Predictability of hematopoietic stem cell transplantation rates. Haematologica. 2007;92(12):1679-86.
19. Gratwohl A. Bone marrow transplantation activity in Europe 1990. Report from the European Group for Bone Marrow Transplantation (EBMT). Bone Marrow Transplant. 1991;8(3):197-201.
20. Brinch L, Ljungman P, Sengelöv H, et al. Differences in the use of allogeneic hematopoietic stem cell transplants in the Nordic countries. Bone Marrow Transplant. 2008; 41 (Suppl 1): S340.
21. Goldman J. A special report: bone marrow transplants using volunteer donors-recommendations and requirements for a standardized practice throughout the world-1994 update. The WMDA Executive Committee. Blood. 1994;84(9):2833-9.
22. Schmitz N, Linch DC, Dreger P, Goldstone AH, Boogaerts MA, Ferrant A, et al. Randomised trial of filgrastim-mobilised peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients. Lancet. 1996;347(8998):353-7. Erratum in: Lancet 1996; 347(9005):914.
23. Schmitz N, Bacigalupo A, Hasenclever D, Nagler A, Gluckman E, Clark P, et al. Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 1998;21(10):995-1003.
24. Bensinger WI, Martin PJ, Storer B, Clift R, Forman SJ, Negrin R, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. N Engl J Med. 2001; 344(3):175-81.
25. Lippman ME. High-dose chemotherapy plus autologous bone marrow transplantation for metastatic breast cancer. N Engl J Med. 2000;342(15):1119-20.
26. Druker BJ, Talpaz M, Resta DJ, Peng B, Buchdunger E, Ford JM, et al. Efficacy and safety of a specific inhibitor of the BCR-ABL tyrosine kinase in chronic myeloid leukaemia. N Engl J Med. 2001 344(14): 1031-7.
27. Gratwohl A, Baldomero H, Schwendener A, Gratwohl M, Alvaro Urbano-Ispizua A, Frauendorfer K. Hematopoietic stem cell transplants for chronic myeloid leukaemia in Europe: impact of cost considerations. Leukaemia. 2007;21(3):383-6.
28. Gajewski JL, Robinson P. Do affluent societies have the only options for the best therapy? Leukaemia. 2007;21(3):387-8.
29. Muth J. Rational expectations and the theory of price movements. Econometrica. 1961;29:315-35.
30. Auerbach AD, Landefeld CS, Shojania KG. The tension between needing to improve care and knowing how to do it. N Engl J Med. 2007;357(6):608-13.
31. Makal A, Karan AK. Diffusion of medical technology: medical devices in India. Expert Rev Med Devices. 2009;6(2):197-205.