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Haematopoietic stem cell transplantation in Switzerland

Report from the Swiss Transplant Working Group for Blood and Marrow Transplantation (STABMT) Registry 1997–2003

J. Passweg[b], H. Baldomero[a], B. Chapuis[b], K. Leibundgut[c], U. Schanz[d], A. Gratwohl[a], for the STABMT Board

[a] Division of Haematology, University Hospital, Basel, Switzerland
[b] Division of Haematology, University Hospital, Geneva, Switzerland
[c] Division of Haematology/Oncology, Department of Paediatrics, University Hospital, Berne, Switzerland
[d] Division of Haematology, University Hospital, Zurich, Switzerland

Summary

In 1997, the Swiss Transplant Working Group Blood and Marrow Transplantation (STABMT) initiated a mandatory national registry for all haematopoietic stem cell transplants (HSCT) in Switzerland. As of 2003, information was collected of 2010 patients with a first HSCT (577 allogeneic (29%) and 1433 autologous (71%) HSCT) and 616 additional re-transplants. This included 1167 male and 843 female patients with a median age of 42.4 years (range 0.2–76.6 years). Main indications were leukaemias (592; 29%) lymphoproliferative disorders (1,061; 53%), solid tumours (295; 15%) and non-malignant disorders (62; 3%). At the time of analysis 1,263 patients were alive (63%), 747 had died (37%). Probability of survival, transplant related mortality or relapse at 5 years was 52%, 21%, 36% for allogeneic and 54%, 5%, 60% for autologous HSCT. Outcome depended on indication, donor type, stem cell source and age of patient. HSCT is an established therapy in Switzerland. These data describe current practice and outcome.

Key words: haematopoietic stem cell transplantation; Switzerland; outcome

Introduction

Transplantation of haematopoietic stem cells (HSCT) is an established therapy today and has seen rapid expansion over the last decade. It is applied for many severe acquired or congenital disorders of the haematopoietic system and for chemo-sensitive, radio-sensitive or immunosensitive malignancies. Stem cells from bone marrow, peripheral blood or cord blood are used and include stem cells derived from the patients themselves for autologous HSCT or stem cells from siblings, other family members or from unrelated donors for allogeneic HSCT [1–5]. The goals of HSCT are manifold. HSCT can be applied to restore bone marrow function in a patient with congenital deficiencies or acquired malfunction. It can be used to shorten the period of severe pancytopenia in the context of high dose chemo-/radiotherapy in autologous transplants. Allogeneic HSCT provides a powerful targeted anti-tumour effect in the context of a graft-versus-host or graft-versus-tumour reaction for the treatment of haematological or non-haematological malignancies. HSCT can induce tolerance to donor tissue in combination with solid organ transplantation and, last but not least, HSCT can reset ontogenesis of the immune system in the treatment of autoimmune diseases [6–13]. HSCT has a longstanding history in Switzerland [14–22].

HSCT is a complex, cost intensive, therapeutic procedure. In Switzerland, costs of the procedure are covered by health insurance based on the guidance of the Federal Office for Social Insurance. In this guidance (http://www.bag.admin.ch/kv/gesetze/d/KLV.Mod.1.1.2005.de%2029.11.04.pdf) diseases are listed as "established", "in evaluation with full payment", "in evaluation without payment" or as "not established". On the occasion of the last revision (2002), the Federal Office requested an analysis of this therapeutic instrument and asked for an evaluation registry. In anticipation of this requirement, the Swiss Transplant Working Group for Blood and Marrow Transplantation (STABMT) established a central registry for all HSCT in Switzerland. A preliminary analysis after six years with a minimum follow up of one year for all patients is presented in this report. It summarises the whole Swiss HSCT experience.

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Patients and methods

Data collection

Data collection was based on the Minimal Essential Data sets (Med-A; www.EBMT.org) of the European Group for Blood and Marrow Transplantation (EBMT) and as a minimal requirement requested information on patient age, sex, disease, disease stage, stem cell source, donor type, conditioning, days of hospitalisation and outcome. Data were collected on paper form or via the EBMT internet based Promise data catcher system. Patient data are updated annually. Included were all patients transplanted from 1997 to December 31, 2003. All updates were as of December 31, 2004, eg with a minimum follow up of all patients of one year.

Definitions for HSCT

HSCT were defined according to the criteria of the EBMT [23]. A HSCT is the infusion of haematopoietic stem cells given with the intention to replace the pretransplant recipient haematopoietic system. The report focused on first HSCT for individual patients. A re-transplant was defined as HSCT given after a previous (either autologous or allogeneic) HSCT for treatment of relapse or rejection. Multiple transplants were defined as subsequent infusions of stem cells in the context of planned double or triple transplant protocols.

Participating teams

HSCT were performed during the defined observation period in Aarau (Kantonsspital), Basel (University Hospitals), Bellinzona (Kantonsspital), Berne (University Hospital), Geneva (University Hospital [and Hospital "De la Tour" for a limited period]), Lausanne (University Hospital [and Clinic "La Source" for a limited period]), Neuchatel (Hôpital des Cadolles for a limited period), St. Gallen (Kantonsspital) and Zurich (University Hospital, University Children's Hospital and Clinic "Im Park") as listed in detail in the Appendix. Allogeneic HSCT were restricted to Basel, Geneva, Zurich University Hospital and Zurich University Children's Hospital; autologous transplants were performed at all centres. Since 1997, autologous HSCT in the 'Romandie' were performed primarily in Lausanne, allogeneic HSCT primarily in Geneva. Paediatric transplants were performed in Basel (allogeneic and autologous), Berne (autologous), Geneva (allogeneic and autologous), Lausanne (autologous) and Zurich (allogeneic and autologous).

All teams were required to have Ethics committee approval and all patients gave written informed consent before the transplant.

Statistical analysis

Mean, median and standard deviations of numerical variables were calculated on an Excel spread sheet. Outcomes measured were overall survival, done using the Kaplan-Meier estimator and treatment related mortality and relapse incidence using cumulative incidence curves adjusting for competing risks as appropriate. Comparisons were made by the log-rank test. Treatment related mortality was defined as death without relapse. This definition may also be termed non-relapse mortality and assumes that all deaths after intensive treatment prior to disease relapse may be attributable to the treatment itself.

Results

Numbers of HSCT

In total there were 2010 first transplants, 577 (29%) allogeneic and 1433 (71%) autologous, as illustrated in table 1. 616 additional re-transplants or multiple transplants (131 allogeneic/485 autologous) were performed during the same time period. Together there were 2626 transplants, 708 allogeneic and 1918 autologous.

Indications for first transplants and donor type

The indications for HSCT are listed by donor type and stem cell source in table 1. Main indications were lymphoproliferative disorders with 1,061 patients (53%; 55 patients (5%) with allogeneic HSCT, 1006 patients (95%) with autologous HSCT); leukaemias with 592 patients (29%; 460 patients (78%) with allogeneic and 132 patients (22%) with autologous HSCT); solid tumours with 295 patients (15%; 6 patients (2%) with allogeneic and 289 patients (98%) with autologous HSCT) and non-malignant disorders with 62 patients (3%; 56 patients (90%) with allogeneic and 6 patients (10%) with autologous HSCT. Patients with non-malignant disorders suffered predominantly from autoimmune disorders (6 patients), aplastic anaemia (28 patients) or congenital disease (28 patients).

For the 577 allogeneic HSCT recipients, 349 (61%) donors were HLA-identical siblings, 66 (11%) other family members, 11 (2%) syngeneic twins and 151 (26%) unrelated volunteer donors.

Stem cell source

The majority of HSCT were peripheral blood stem cell transplants. Of the autologous HSCT, there were 12 (1%) bone marrow and 1421 (99%) peripheral blood stem cell transplants. Of the allogeneic HSCT, there were 222 (38%) bone marrow, 349 (61%) peripheral blood and 6 (1%) cord blood transplants.

Changes over time

Table 2 illustrates the numbers of HSCT during the observation period. There was an increase of allogeneic HSCT for all indications with some exceptions, eg for chronic myeloid leukaemia. There was a continuous increase of autologous HSCT for lymphoproliferative disorders and a continuous decline of autologous HSCT for solid tumours.

Table 3 illustrates the repartition of the patients to the participating centres and shows the range from small to large centres.

Table 1

Numbers of patients with a first HSCT in Switzerland from 1997 to 2003 by disease, donor type and stem cell source. Indications are marked according to their insurance status.

Year = 1997–2003	DONOR SOURCE													
	No. of patients													
	Allogeneic								Autologous			Total		
	Family						Unrelated							
	HLA-id		non-id		Twin									
	BM	PBPC	BM	PBPC	BM	PBPC	BM	PBPC	BM only	PBPC only	BM + PBPC	Allo	Auto	Total
Leukaemias	**86**	**187**	**5**	**47**	**0**	**4**	**84**	**47**	**5**	**126**	**1**	**460**	**132**	**592**
Acute myeloid leukaemia	26	76	1	17		2	24	15	1	91	1	161	93	254
Acute lymphoblastic leukaemia	24	41	1	19		1	14	11	3	17		111	20	131
Chronic myeloid leukaemia	27	43	1	6		1	35	8	1	7		121	8	129
Myelodysplastic syndrome	9	27	2	5			11	13		11		67	11	78
Lymphoproliferative disorders	**3**	**40**	**0**	**2**	**1**	**5**	**1**	**3**	**4**	**997**	**5**	**55**	**1006**	**1061**
Chronic lymphocytic leukaemia		13						1		14		14	14	28
Plasma cell disorders	1	11		2		2			1	454		16	455	471
Hodgkin's lymphoma		1				1			2	110	2	2	114	116
Non-Hodgkin's lymphoma	2	15			1	2	1	2	1	419	3	23	423	446
Solid tumours	**0**	**5**	**0**	**0**	**1**	**0**	**0**	**0**	**3**	**286**	**0**	**6**	**289**	**295**
Neuro/medulla/PNET/ Pinealoblastoma									1	49		0	50	50
Breast cancer										83		0	83	83
Germinal tumours									2	78		0	80	80
Ovarian cancer										5		0	5	5
Ewing's sarcoma					1					24		1	24	25
Soft tissue/rhabdomyo/ angiosarcoma										8		0	8	8
Lung cancer										16		0	16	16
Renal cancer		5								1		5	1	6
Melanoma												0	0	0
Other solid tumours										22		0	22	22
Non-malignant disorders	**21**	**7**	**7**	**5**	**0**	**0**	**13**	**3**	**0**	**6**	**0**	**56**	**6**	**62**
BM aplasia	9	5	3	1			7	2		1		27	1	28
Haemoglobinopathies	4	1	1									6	0	6
Immune deficiencies	6	1		4			5					16	0	16
Inherited disorders of metabolism	1		3				1	1				6	0	6
Autoimmune disease	1									5		1	5	6
Others												0	0	0
TOTAL	**110**	**239**	**12**	**54**	**2**	**9**	**98**	**53**	**12**	**1415**	**6**	**577**	**1433**	**2010**

Accepted in evaluation – yes in evaluation - no

BM = bone marrow; PBPC = peripheral blood precursor cells; Allo = allogeneic; Auto = autologous

Outcome

At the time of analysis 1263 patients were alive (63%), 747 had died (37%). Cause of death was transplant related mortality in 213 (28%) and relapse after transplant in 534 (72%).

Five year survival, transplant related mortality and relapse incidence differed for allogeneic and autologous HSCT (figure 1). Probability of survival, transplant related mortality or relapse at 5 years were 52%, 21%, 36% for allogeneic and 54%, 5%, 60% for autologous HSCT. Survival and transplant related mortality after allogeneic HSCT differed by donor type, with best survival and lowest TRM for patients with an HLA-identical sibling donor (figure 2).

Survival, transplant related mortality and relapse incidence were different for the main disease categories after allogeneic and also autologous HSCT with best survival for patients with non-malignant disorders (figure 3).

Table 2

Total number of HSCT in Switzerland by year from 1997–2003 and by main indication
2a: Allogeneic HSCT
2b: Autologous HSCT

Table 2a: Stern cell source in allogeneic HSCT 1997–2003

Transplants		1997	1998	1999	2000	2001	2002	2003	Total
Leukemias	BM	38	33	28	29	18	16	19	181
	PB	25	28	38	58	56	57	85	347
Lymphoproliferative disorders	BM	3	2	1		1	4		11
	PB	3	5	11	13	19	23	23	97
Solid tumors	BM			1					1
	PB					1	2	2	5
Non malignant disorders	BM	6	1	5	7	6	11	8	44
	PB	1	5	3	3	4		6	22
Total	BM	47	36	35	36	25	31	27	237
	PB	29	38	52	74	80	82	116	471

Table 2b: Stern cell source in allogeneic HSCT 1997–2003

Transplants		1997	1998	1999	2000	2001	2002	2003	Total
Leukemias	BM	2		2			1	1	6
	PB	12	17	15	24	22	22	20	132
Lymphoproliferative disorders	BM	1			1	1		1	4
	PB	128	136	153	175	191	187	250	1220
Solid tumors	BM	1			2				3
	PB	124	113	80	65	59	56	50	547
Non malignant disorders	BM								0
	PB	1	2		1		2		6
Total	BM	4	6	2	3	1	1	2	13
	PB	265	268	248	265	272	267	320	1905

Leukemias include acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia and myeloproliferative disorders.
Lymphoproliferative disorders include plasma cell disorders, chronic lymphocytic leukemia, Hodgkin's disease and non Hodgkin's lymphoma.
Solid tumours include all indications.
Non malignant disorders include bone marrow aplasias, hemoglobinopathies, immune deficiencies, inherited disorders of metabolism and autoimmune disorders.

Table 3

Numbers of patients with a first HSCT in Switzerland from 1997–2003 by centre and main indication.

Patients	Autologous				Allogeneic			
	Leukemia	Lymphoproliferative disorders	Solid tumors	Non malignant disorders	Leukemia	Lymphoproliferative disorders	Solid tumors	Non malignant disorders
Aarau	19	70	12					
Basel	23	84	42	5	200	34	1	11
Bellinzona	8	63	4					
Bern	19	157	47					
Geneva	4	8	6		110	14	3	6
Lausanne	37	286	76					
St. Gallen	3	57	10					
Zurich adults	9	233	54		126	7	2	6
Zurich pediatrics	5		18	1	24			33
Meyrin	2	7	13					
Neuchatel		6						
Pully		2	2					
Zurich Hirslanden	3	33	5					
Total	132	1006	289	6	460	55	6	56

Survival was also influenced by disease stage with higher transplant related mortality and higher relapse rate in patients with advanced disease compared to patients transplanted in early disease. Due to an increase in transplant related mortality with increasing age, survival was better in younger patients (data not shown).

There was no difference in TRM in patients with "established indications" compared to patients with "indications under evaluation" (fig. 4). In this comparison of outcome between patients transplanted for established or for non-established indications with respect to health care funding, we showed equivalent outcomes for allo-

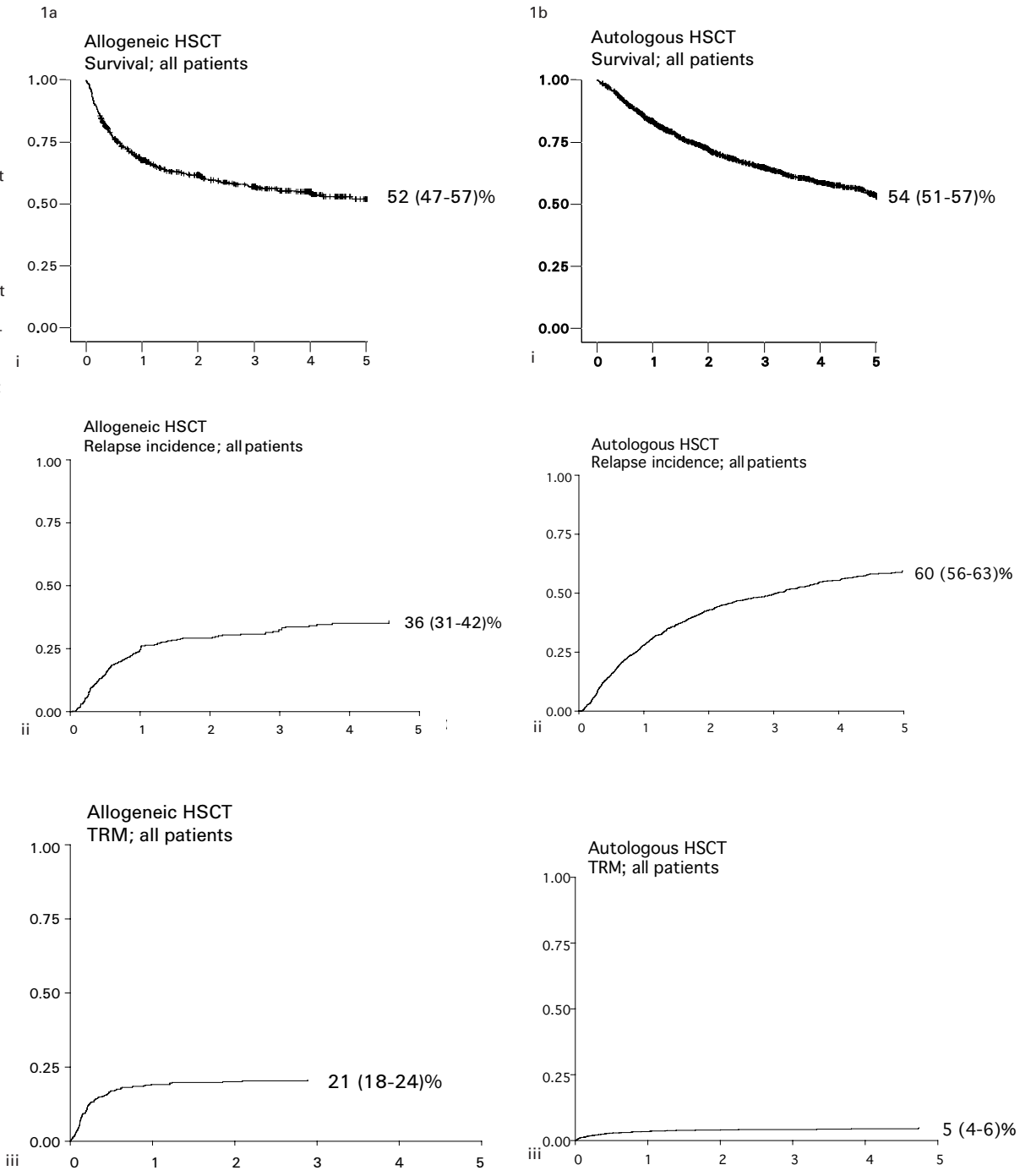


Figure 1

Main outcome of 2010 patients with HSCT in Switzerland between 1997 and 2003.
1a: Survival (i) relapse incidence (ii) and transplant related mortality (iii) in 577 allogeneic HSCT.
1b: Survival (i) relapse incidence (ii) and transplant related mortality (iii) in 1433 autologous HSCT

TRM = transplant related mortality

geneic HSCT. In autologous HSCT survival in patients receiving transplant for non-established indications was slightly lower. This difference was due to a difference in relapse rate; transplant related mortality was not different in the two cohorts. We do not have data on outcome of non-treated patients; this was not within the design of this project. Hence we cannot give an estimate on the cost-effectiveness.

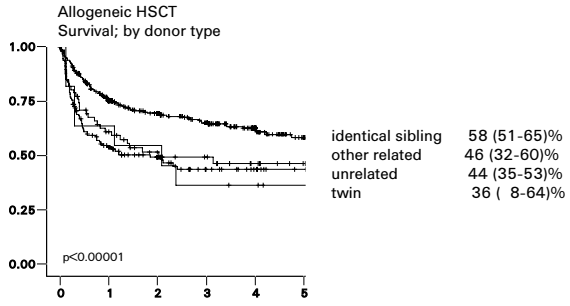
Discussion

This report illustrates experience with HSCT in Switzerland from 1997 to 2003 and it describes the current status. It documents the feasibility of a national registry for haematopoietic stem cell transplantation and gives some valuable information on outcome.

The data showed that HSCT is an accepted therapy in Switzerland, which is used increasingly. The rise in autologous transplants for lymphoproliferative disorders was the consequence of prospective randomised controlled studies, which have shown an advantage of autologous HSCT over conventional chemotherapy for patients with non-Hodgkin's lymphoma, multiple myeloma and for children with neuroblastoma. The decreased use of autologous HSCT for solid tumours in par-

Figure 2

Influence of donor type in 577 allogeneic HSCT.
2a: Survival of allogeneic HSCT by donor type. HLA-identical sibling transplants, other family member transplants, unrelated donor transplants and twin transplants.
2b: Relapse incidence of allogeneic HSCT by donor type. HLA-identical sibling transplants, other family member transplants, unrelated donor transplants and twin transplants.
2c: Transplant related mortality of allogeneic HSCT by donor type. HLA-identical sibling transplants, other family member transplants, unrelated donor transplants and twin transplants.



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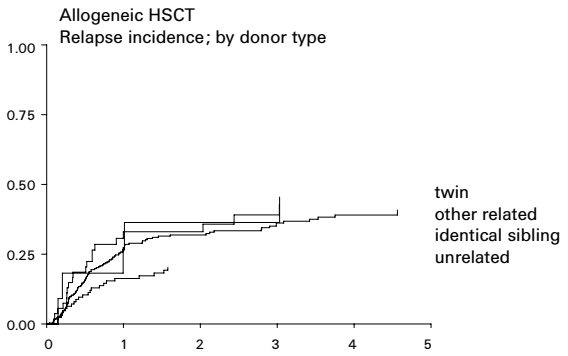

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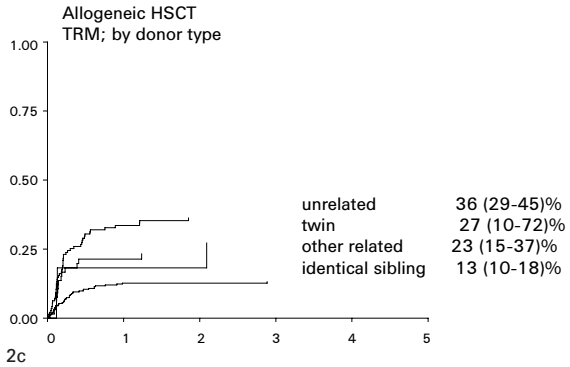
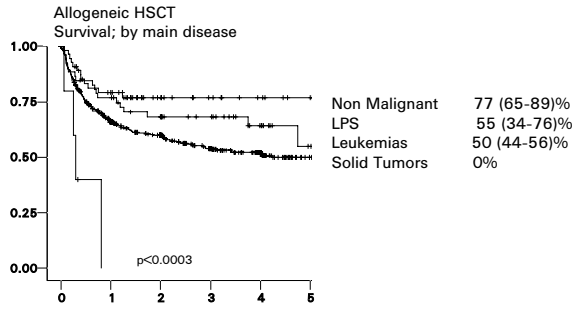


2c

Figure 3

Outcome of HSCT according to main disease category.
3a: Survival according to main disease category for 577 allogeneic HSCT (Leukaemias, lymphoproliferative syndromes, solid tumours and non malignant disorders).
3b: Survival according to main disease category for 1433 autologous HSCT(Leukaemia, lymphoproliferative syndromes, solid tumours and non malignant disorders).

LPS = lymphoproliferative syndromes



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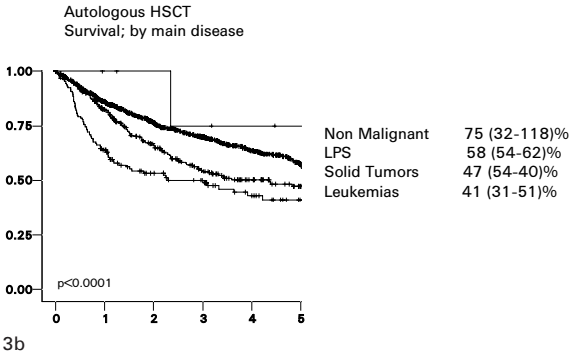


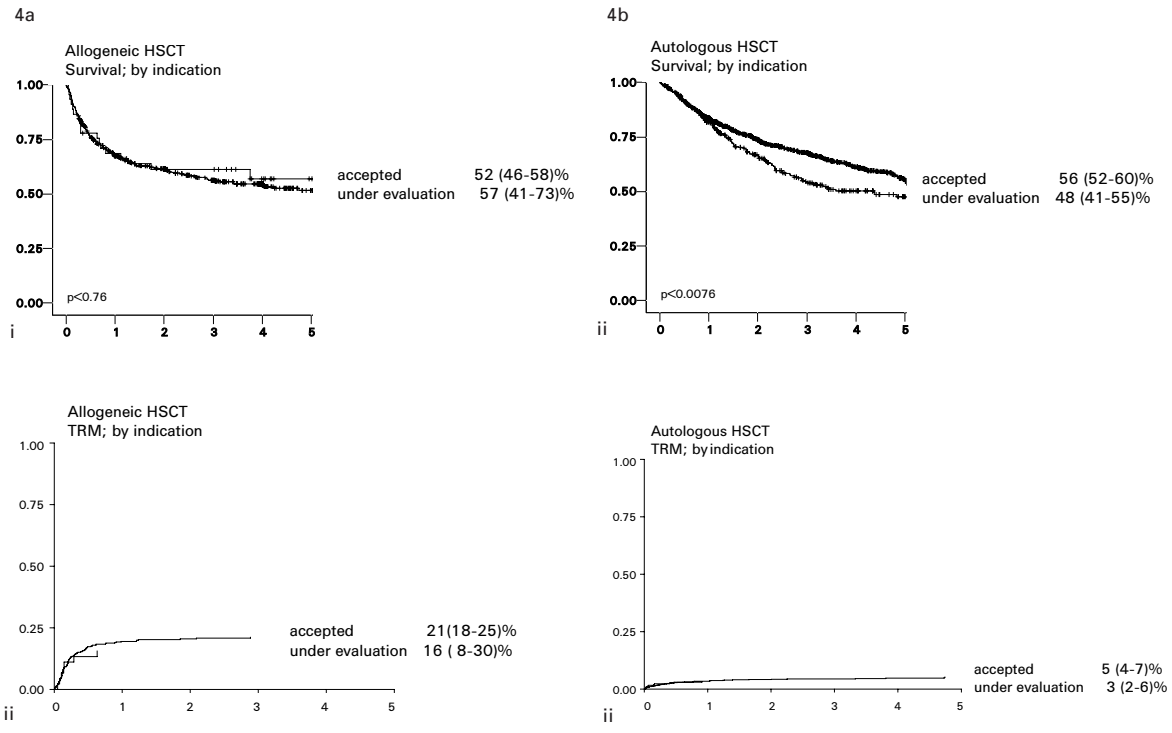
3b

allel was the consequence of prospective randomised studies, which failed to show an advantage of HSCT for patients with breast cancer. The decrease in allogeneic HSCT for chronic myeloid leukaemia was the consequence of the introduction of imatinib mesylate, a targeted inhibitor of the BCR/ABL tyrosine kinase, which is the responsible, acquired genetic defect in this disease [23–32]. In all these increases and decreases, Swiss centres followed the same trends as elsewhere in Europe [5]. Total transplant rates, eg the numbers of transplants to number of inhabitants in Switzerland, were within the average of transplant rates within Western Europe [32].

The data on outcome reflects the current situation. Outcome varied according to indications and clinical situations. It was dependent on disease, disease stage, donor type, and histocompatibility between donor and recipient in allogeneic HSCT and on main pretransplant risk factors, as previously described by the international transplant registries [33]. As such, data in Switzerland do not differ from international data. Autologous and allogeneic HSCT had a different pattern of outcome. Transplant related mortality was lower with autologous HSCT compared to allogeneic HSCT. On the other hand, relapse rate was higher with autologous HSCT and survival curves indicated an ongoing risk of relapse over time. Outcome of HSCT was better, when transplants were performed at an early stage of the disease. Transplant related mortality as well as risk of relapse increased in patients transplanted in advanced disease stage. Outcome was different depending on main disease categories. Mainly, risk of relapse was lower in non-malignant diseases and the need for tumour reduction, hence need for intensive pretransplant conditioning, was absent in these categories. Age is a risk factor. Younger patients had a lower risk for transplant related mortality than older patients.However, median age of patients increased over time. New modalities, such as reduced intensity conditioning transplants, offer the possibility of allogeneic HSCT for patients at a higher age or

Figure 4

Outcome of HSCT according to state of insurance.
4a: Survival (i) TRM (ii) of 577 allogeneic HSCT with accepted indications or indications under evaluation.
4b: Survival (i) TRM (ii) of 1433 autologous HSCT with accepted indications or indications under evaluation.



those with co-morbidities. As such, age is no longer considered the sole limit for HSCT; it is always considered in the disease context, alternative treatment possibilities and risk of co-morbidity [34, 35].

The current analysis has looked at two specific components of the evaluation registry. It is comforting to see, that transplant related mortality was not very different in patients treated with novel approaches. Early mortality was similar in patients with upfront allogeneic HSCT compared to patients with double transplant programmes, where a first autologous HSCT was given in order to reduce tumour burden, followed by an allogeneic HSCT with reduced intensity conditioning. Similarly, early mortality was not different in patients with autologous or allogeneic HSCT for established, as opposed to novel indications under evaluation.

Federal regulations in Switzerland made it mandatory to maintain an evaluation registry for continued reimbursement of these treatments. This lead to a valuable database that, as opposed to other international registries, includes all HSCT's performed in Switzerland during the period of observation. It constitutes a true observational registry that will be useful for quality assurance programmes, health care cost estimation and health care planning.

There are some caveats. The registry is not designed to compare outcome of patients with HSCT to patients with the same disease but no HSCT. The registry cannot prove the value of HSCT; other instruments are required; such answers have to be provided on an international level. The registry was not established to compare outcome data between individual centres. The heterogeneity of the patients and the multitude of factors influencing outcome makes direct comparison meaningless at the present time. Still, the fact that all centres participated and that all Swiss centres adhered to an international quality control system, JACIE, (www.JACIE.org) is a first, essential step. Quality will be assessed in the future not only at the organisational but also at the outcome level [36, 37]. It is satisfying to see that results in Switzerland compare very well to results at an international level [33].

The data of this survey illustrated current indications and results of HSCT in Switzerland and gave clear information to patients, referring physicians and health care officials.

Correspondence:
Prof. Dr. A. Gratwohl
Haematology
University Hospital Basel
CH-4031 Basel
E-Mail: hematology@uhbs.ch

Participating institutions

Aarau, Centre of Oncology/Haematology, Department of Internal Medicine, Centre for Laboratory Medicine, Aarau Blood Centre, Kantonsspital Aarau, CH-5001 Aarau: M. Bargetzi*, J. Burger, P. Fernandez, I. Heijnen, A. Huber, C. Langer, W. Mingrone, S. Schirlo, A. Schönenberger, M. Wernli

Basel, Stem cell transplant team University Hospital and the Children's University Hospital, CH-4031 Basel: A. Gratwohl*, H. Baldomero, S. Christen, A. Droll, G. Favre, D. Heim, T. Kühne, S. Meyer-Monard, J. Passweg, M. Paulussen, C. Stebler-Gysi, A. Tichelli

Bellinzona, Division of Haematology, Hospital San Giovanni, CH-6500 Bellinzona: M. Ghielmini*, F. Cavalli, L. Leoncini-Franscini

Berne, Division of Haematology/Oncology, Department of Paediatrics, University Hospital, CH-3010 Berne: Leibundgut K*

Department of Haematology, University Hospital, CH-3010 Berne: Zwicky C

Department of Oncology, University Hospital, CH-3010 Berne: Fey M, Papst T

Geneva, Division of Haematology, University Hospital, CH-1211 Geneva 14: B. Chapuis*, Y. Chalandon, C. Helg

Geneva, L'Hôpital de la Tour, Avenue J-D. Mallard 3-11, CH-1217 Meyrin-Geneva (1997–1999) C. Irlé*

Lausanne, Stem cell transplant team for autologous HSCT, University Hospital, CH-1011 Lausanne: M. Schapira*, A. Cairoli, T. Calandra, G. Canellini, V. Frossard, N. Ketterer, T. Kovacsovic, S. Leyvraz, A. Rosselet, J-D. Tissot, P. Schneider Neuchatel, Division of Oncology, Hôpital des Cadolles, CH-2000 Neuchatel (1997–1999) D. Piguet*

Pully, Division of Haematology/Oncology, Clinic "La Source" Ch. Des Roches 9, CH-1009 Pully (1998–1999): V. von Fliedner*

St. Gallen, Division of Haematology/Oncology, Department of Internal Medicine, Kantonsspital, CH-9007 St. Gallen: U. Hess*, M. Fopp

Zurich, Clinic of Oncology and Division ofHaematology, University Hospital, 8091 Zurich: U Schanz*, J. Halter, Ch. Taverna

Zurich, Division of Immunology/Haematology/Oncology, University Children's Hospital, Steinwiesstrasse 75, CH-8032 Zurich: R. Seger*, J.P. Bourquin, T. Güngor, F. Scherer, M. Schmugge.

Zurich, Division of Oncology/Haematology, Clinic "Im Park", Seestrasse 220, CH-8027 Zurich (until 31/12/03) J. Gmür*

* transplant team director (JACIE 2004)

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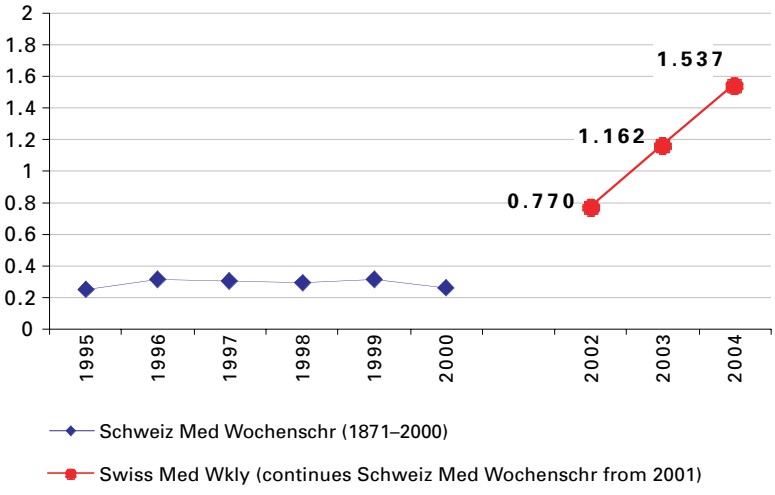

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