Peer reviewed article

Haematopoietic stem cell transplantation in Switzerland: a comprehensive quality control report on centre effect

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Summary

Questions under study/principles: Interest groups advocate centre-specific outcome data as a useful tool for patients in choosing a hospital for their treatment and for decision-making by politicians and the insurance industry. Haematopoietic stem cell transplantation (HSCT) requires significant infrastructure and represents a cost-intensive procedure. It therefore qualifies as a prime target for such a policy.

Methods: We made use of the comprehensive database of the Swiss Blood Stem Cells Transplant Group (SBST) to evaluate potential use of mortality rates. Nine institutions reported a total of 4717 HSCT – 1427 allogeneic (30.3%), 3290 autologous (69.7%) – in 3808 patients between the years 1997 and 2008. Data were analysed for survival- and transplantation-related mortality (TRM) at day 100 and at 5 years.

Results: The data showed marked and significant differences between centres in unadjusted analyses. These differences were absent or marginal when the results were adjusted for disease, year of transplant and the EBMT risk score (a score incorporating patient age, disease stage, time interval between diagnosis and transplantation, and, for allogeneic transplants, donor type and donor-recipient gender combination) in a multivariable analysis.

Conclusions: These data indicate comparable quality among centres in Switzerland. They show that comparison of crude centre-specific outcome data without adjustment for the patient mix may be misleading. Mandatory data collection and systematic review of all cases within a comprehensive quality management system might, in contrast, serve as a model to ascertain the quality of other cost-intensive therapies in Switzerland.

Key words: haematopoietic stem cell transplantation; outcome; quality management; centre-specific data

Introduction

The first reports of successful haematopoietic stem cell (HSCT) transplantation date back more than fifty years [1]. After a long experimental phase, HSCT has become standard care for many patients with nonmalignant congenital or acquired disorders of the haematopoietic system or with haematological malignancies. HSCT has undergone rapid expansion and constant development in technology of use over the last two decades. Novel indications such as autoimmune disorders or single enzyme deficiencies are currently under evaluation. Bone marrow, peripheral blood and cord blood are available as stem cell sources. More than 13 million typed volunteer donors worldwide (www.worldmarrow.org) provide stem cells for patients without family donors. Novel conditioning regimens have extended the use of HSCT to older patients or to those with comorbidities [1–6].

No conflict of interest in relation to this article.

Major progress in supportive care measures and transplant application has significantly improved results over time. Nonetheless, HSCT remains associated with significant morbidity and mortality. Also, HSCT is a prototype for high cost, highly specialised medicine. It requires significant infrastructure and a network of specialists [7–10]. It is understandable that quality and cost issues are of major concern to transplant teams, patients, advocacy groups, referring physicians, health care providers, hospitals and politicians. The desire to obtain high quality treatment at reasonable cost, while ensuring access to transplant centres for patients, contrasts with the reality of limited resources and the need for a minimal volume of workload to ascertain quality. It is understandable that the provision of funds is linked to the request for outcome reporting. The C.W. Bill Young Transplantation act in the USA (www.hrsa.gov) has set an example.

Even though the utility of data on outcome is undeniable when deciding on allocation of funds, the reality is more complex. Many systems for analysis and reporting of data have been proposed, coming primarily from the field of surgical innovations [11–15]. All approaches discuss the publication of mortality rates as one possible way to improve outcome, to guide patients in their selection of medical care providers and to aid decision-making at the political level. While all stress the need for standardised evaluation, no single measure has been recognised as valid for all situations [16–19]. Public reporting is accepted as a standard during early introduction of new methods in fields with previously inadequate access [20, 21] or for some high volume procedures [11–15]. Its value in organ transplantation or HSCT remains a matter of debate. The same applies to the minimal number of procedures required for safe application. There is universal agreement that "learning curves" apply to manual as well as complex intellectual procedures, and that higher case loads accelerate and facilitate learning [22–28]. It is also generally accepted that differences in outcome exist between centres. Whether these differences are due to the volume of procedures or to "centre effects" reflecting local policies remains controversial [29–33]. In most of the recent evaluations of centre effects from different fields of medicine, differences between centres were primarily the consequence of variations in case mix [34–45].

In response to a relevant comment from the reviewer we have phrased the statement with greater care and balance. Publication of mortality rates is proposed by some as a criterion for quality control, despite its limited evidence [9–12]. Centre-specific mortality rates have also been requested by the recently established commission for highly specialised medicine in Switzerland. Outcome could be one of several criteria in this commission's decision making process (www.gdk-cds.ch/fileadmin/pdf/Themen/Gesundheitsversorgung/Hochspezialisierte_Medizin/Geschregl-CICOMS-1–7–d.pdf). The stem cell transplant collaborative group (SBST) in Switzerland was confronted with the same question more than 10 years ago. The decision made at that time was to commit all centres to the standardised European quality management system JACIE (www.jacie.org) [46–48] and to mandatory reporting of all procedures to an evaluation registry. The availability of this comprehensive database with sufficient follow-up provides the opportunity to test the value of centre-specific outcome reporting within one country.

Patients and methods

Study design

This is a retrospective observational data analysis based on the prospective evaluation registry of the Swiss Blood Stem Cells Transplant Group (SBST). The registry has been operational since 1997 and is based on the electronic database management system PROMISE of the European Group for Blood and Marrow Transplantation EBMT (http://www.ebmt.org). All teams performing HSCT in Switzerland (table 1) have committed themselves to reporting to the SBST database. They are required by law to report all transplant outcomes and to adhere to the comprehensive quality management system JACIE (www. Jacie.org). Hence the SBST data registry is unique in capturing 100% of all HSCT in Switzerland performed in public institutions.

All patients were required to give informed consent and all teams were required to have institutional review board approval for their transplant protocols.

Data collection and data validation

Data collection included basic information on disease, disease stage, patient and donor characteristics, donor type, stem cell source, date of transplant and outcome. Data were submitted at the time of transplant, either electronically or in paper form, and updated annually. Basic information on outcome included time of last follow-up, survival status, presence or absence of relapse and, if the patient died, cause of death.

Data were validated by different independent systems; through confirmation by the reporting team, which received a computer printout of the entered data, by selective comparison with the EBMT activity survey [27], by the regular JACIE audits or by selected on-site visits through the EBMT quality control programme (www.ebmt.org).

Table 1

Key characteristics of 4717 HSCT performed in Switzerland from 1997 to 2008.

	Allogeneic		Autologous		Total	
	N	% */**	N	%	N	%
N						
1st HSCT (patients)	1273	33.4**	2535	66.6**	3808	80.7*
Total HSCT	1427	30.3**	3290	69.7**	4717	100
Gender						
Male N (%)	871	61*	2045	62*	2916	61.8*
Female N (%)	556	39*	1245	38*	1801	38.2*
Age						
Median (range)	39.9		51.5		48	
range	(0.16–69.9)		(0.66–76.6)		(0.16–76.6)	
Centres**						
Aarau	–		280	100	280	5.9
Basel	619	63.6	355	36.4	974	20.6
Bellinzona	–		202	100	202	4.3
Bern	–		591	100	591	12.5
Geneva	344	94.2	21	5.8	365	7.7
Lausanne	–		888	100	888	18.8
St. Gallen	–		207	100	207	4.4
Zurich adult	316	31.3	695	68.7	1011	21.4
Zurich paediatrics	148	74.4	51	25.6	199	4.2
Main disease indications**						
Leukaemias	1084	79.4	281	20.6	1365	28.9
Lymphomas	193	7.7	2320	92.3	2513	53.3
Nonmalignant disorders	140	92.1	12	7.9	152	3.2
Solid tumours	10	1.5	677	98.5	687	14.6
Stem cell source**						
Bone marrow	368	94.6	21	5.4	389	8.2
Peripheral blood	1022	23.8	3269	76.2	4291	91.0
Cord blood	37	100	0	0	37	0.8
Donor type*						
Syngeneic	28	2.0				
HLA-identical sibling	790	55.4	n.a.	n.a.	n.a.	n.a.
Other family donor	143	10.0				
Unrelated donor	466	32.7				
Year of transplant**						
1997–2003	708	28.1	1810	71.9	2518	
2004–2008	719	32.7	1480	67.3	2199	
EBMT risk score*						
0	39	2.7	12	0.4		
1	155	10.9	93	2.8		
2	324	22.7	587	17.8		
3	317	22.2	1309	39.8	n.a.	n.a.
4	297	20.8	986	30.0		
5	220	15.4	303	9.2		
6	70	4.9				
7	5	0.4				
Days in hospital (SVK)***						
N HSCT	656		1571		2227	
75 percentile	26–70		15–28		15–49	

* Column percentage, ** Row percentage, *** For years 2003–2008 only

Patient population

The analysis includes all patients receiving an HSCT in Switzerland in one of the nine institutions (table 1) between 1997, when the SBST database was established, and 2008. Consequently, a minimum follow-up of three months is available. Some patients received more than one transplant and some received both autologous and allogeneic transplants. A few patients have received a transplant for different diseases during the evolution over time. By design of the database, patients with a first allogeneic or first autologous HSCT were counted as patients, all subsequent procedures as additional transplants: by definition, there were more procedures than transplants and more "patients" with a first transplant than patients.

There were 4717 HSCT in 3656 patients. Of these, 152 received both a first autologous and a first allogeneic HSCT. Hence a total of 3808 patients received a first allogeneic (1273) or first autologous (2535) HSCT. There were 1061 additional transplants (306 allogeneic, 755 autologous HSCT). Of these 864 received a 2nd HSCT (237 allogeneic and 627 autologous HSCT), 189 a 3rd HSCT (65 allogeneic and 124 autologous HSCT) and 8 a 4th HSCT (4 allogeneic and 4 autologous HSCT). The basic characteristics of the 4717 HSCT are listed in table 1. There were significantly more male patients with a transplant (2916, 61.8%). The median age of all patients was 48 years (range 0.16–76.6 years). Patients with autologous HSCT were significantly older (median 51.5 years, range 0.66 to 76.6 years) than patients with an allogeneic HSCT (median 39.9 years, range 0.16 to 69.9 years; p = 0.0001).

Of the total of 4717 transplants, 1427 (30.3%) were allogeneic and 3290 (69.7%) autologous. Main indications for a transplant were *lymphoproliferative disorders* with 2513 transplants (53%), 193 patients with allogeneic HSCT (8%), 2320 with autologous HSCT (92%); *leukaemias* with 1365 transplants (28.9%), 1084 patients with allogeneic (79%), 281 with autologous (21%) HSCT; *solid tumours* with 687 transplants (14.5%), 10 with allogeneic HSCT (1%), 677 with autologous HSCT (99%) and *nonmalignant disorders* with 152 transplants (3.2%), 140 with allogeneic HSCT (92%) and 12 with autologous HSCT (8%).

The most frequent indication for an allogeneic HSCT for a malignancy was acute myeloid leukaemia, with 369 HSCT for this disease (33% of all allogeneic HSCT). The most frequent indication for an allogeneic HSCT for nonmalignant disease was a bone marrow failure syndrome with 54 HSCT (5% of all allogeneic HSCT). In contrast, the most frequent indication for an autologous HSCT was a plasma cell disorder with 922 patients (36% of all autologous HSCT). Autologous HSCT for nonmalignant indications were 12 in number and primarily restricted to autoimmune disorders (N = 11).

Statistical analysis

Differences in patient population between centres were analysed by the Kruskal Wallis test for continuous and the chi-squared for categorical variables. Survival was analysed by the Kaplan Meier estimator. Transplantation-related mortality was defined as death before relapse and was assessed as cumulative incidence, competing with the risk of relapse. Backward stepwise Cox regression models were used for the multivariable analyses, forcing in transplant centre and retaining EBMT risk score (composed of patient of patient, disease stage, time interval from diagnosis to transplant for all HSCT; donor type and in addition donor recipient gender combination for allogeneic HSCT) (49, 50), and year of transplant if significantly associated with the outcome under study. Given multiple comparisons a p value of <0.01 was considered statistically significant.

Results

Differences in patient population between centres

There were significant differences in the patient population between the nine transplant centres (table 2). Four centres performed allogeneic HSCT, one of them allogeneic HSCT exclusively. Autologous HSCT were performed in eight centres, in three combined with allogeneic HSCT. Paediatric transplants, defined as HSCT in patients under 18 years, were performed in five centres, allogeneic paediatric HSCT in 3, autologous paediatric HSCT in 3; hence age distribution differed significantly between the centres, with a median age range from 7 years to 51 years and an absolute range from 0.2 to 77 years.

There were significant differences in the distribution of the main indications. Lymphoproliferative disorders were the main indications in centres with autologous HSCT, leukaemia in centres with allogeneic HSCT and nonmalignant, mainly congenital disorders in the only exclusively paediatric centre. There were significant differences in the EBMT risk score among centres performing allogeneic HSCT (p <0.0001). There was a significant difference in the duration of hospital stay, with a median hospitalisation of 19 days (range 0–438 days) for autologous and of 42 days (range 0–389 days) for allogeneic HSCT. It is of interest to note that paediatric patients (median 56 days, range 5–247 days) were in hospital significantly longer than adult patients (median 21 days, range 0–438 days).

Survival and transplantation-related mortality

At the time of analysis (July 2009), 2287 of the 3808 patients were alive (60.1%), 1420 had died (37.3%), in 344 mortality was transplantation-related (24%), in 1076 patients (76%) the cause was relapse of malignant disease. Ninety-three patients (2.4%) were lost to follow-up, in 8 (0.2%)

Table 2

Main indications and HSCT characteristics by transplant centre.

	Aarau	Basel	Bellinzona	Bern	Geneva	Lausanne	St. Gallen	Zurich adult	Zürich paed.
Total transplants									
Total	280	974	202	591	365	888	207	1011	199
Allo	0	619	0	0	344	0	0	316	148
Auto	280	355	202	591	21	888	207	695	51
N male	162	592	139	386	229	537	105	639	127
%	57.9	60.8	68.8	65.3	62.7	60.5	50.7	63.2	63.8
Age: Allogeneic									
median		40			44			44	7
(range)		0.74–69.6			2.75–69.9			16.7–68	0.16–23.3
Age: autologous									
median	50	44	51	47	25	49	49	48	7.6
(range)	17.3–70.7	1.8–73.2	11.1–73	1.5–73.3	5.0–69.3	1.5–76.6	17.9–68.7	14.7–75.3	0.7–17.1
Main indication*									
Leukaemia	39 (14%)	544 (56%)	18 (9%)	69 (12%)	264 (72%)	62 (7%)	7 (4%)	292 (29%)	69 (35%)
Lymphoma	196 (70%)	300 (31%)	171 (85%)	393 (66%)	69 (19%)	623 (70%)	170 (82%)	583 (58%)	8 (4%)
Nonmalignant	0	43 (4%)	0	0	17 (5%)	0	0	9 (1%)	83 (42%)
Solid tumour	45 (16%)	86 (9%)	13 (6%)	129 (22%)	15 (4%)	203 (23%)	30 (14%)	127 (12%)	38 (19)
EBMT risk score									
0	2	13	3	1	9	3	0	2	18
1	12	58	9	16	28	26	6	40	53
2	51	185	34	116	74	177	33	158	83
3	106	290	61	255	85	353	80	360	36
4	76	243	72	167	85	256	67	310	7
5	33	147	23	36	56	73	21	132	2
6		34			27			9	
7		4			1				
Paediatric patients**									
Allogeneic	0	98	0	0	34	0	0	5	141
Autologous	1	48	2	42	6	26	1	10	51

* Column percentage

** Defined as <18 years old at time of HSCT

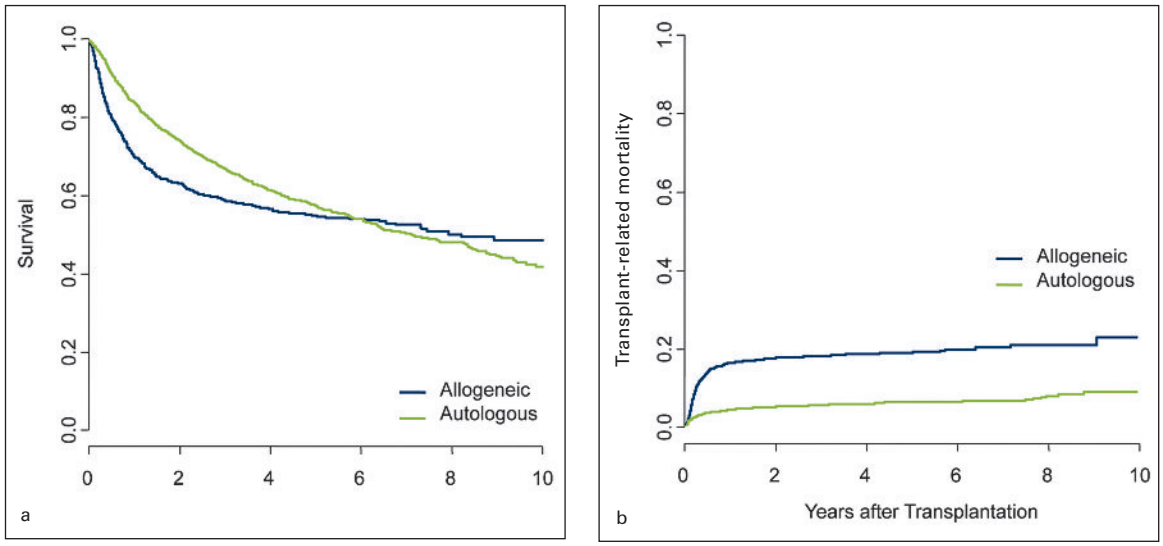

Figure 1

Survival- and transplantation-related mortality of 3808 patients with a first HSCT from 1997 to 2008 in Switzerland.
a) Probability of survival by donor type; b) Cumulative incidence of transplantation-related mortality. Survival estimates according to Kaplan and Meier
Autologous = autologous (green) HSCT (N = 2535)
Allogeneic = allogeneic (blue) HSCT (N = 1273).

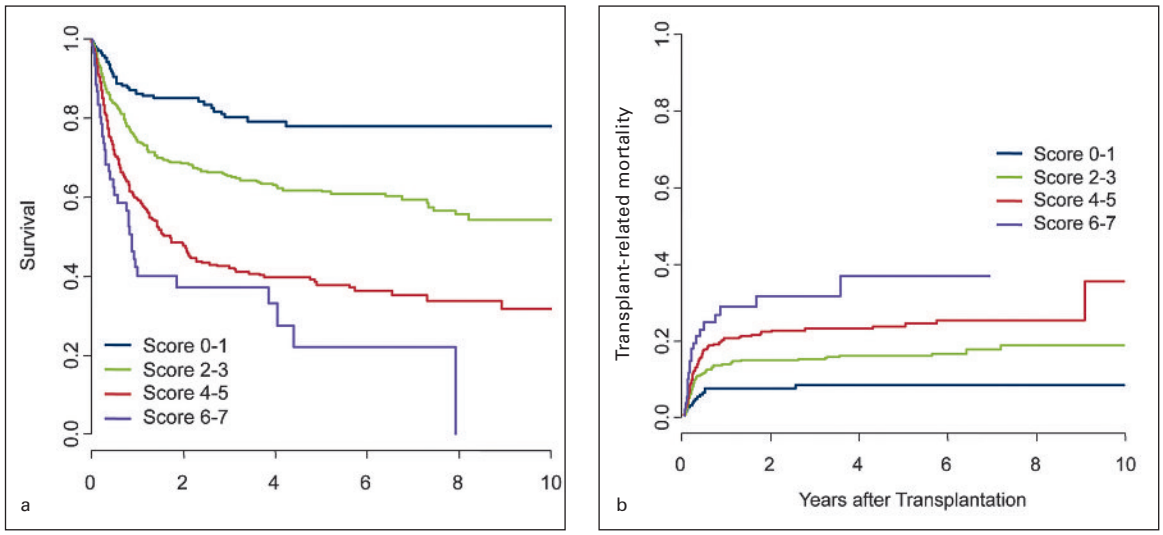

Figure 2

Survival and transplantation-related mortality of 1273 patients with an allogeneic HSCT from 1997 to 2008 in Switzerland by EBMT risk score.
Risk score 0–1, 2–3, 4–5, 6–7 (for definition see patients and methods)
a) Probability of survival.
b) Probability of transplantation-related mortality.

data were missing. Outcome was different for allogeneic and autologous HSCT. Of the 1273 patients with an allogeneic HSCT, 761 (60%) were alive, 480 (38%) had died, in 210 (44%) mortality was transplantation-related, in 270 (56%) the cause was relapse. 27 (2%) were lost to follow-up and 5 had missing data. Of the 761 patients still alive, 671 (88%) were alive without disease and 90 (12%) alive with relapse of disease. Of the 2535 patients with an autologous HSCT, 1526 (60%) were alive, 940 (37%) had died, in 134 (14%) mortality was transplantation-related, 806 (86%) had died from relapse. 66 (3%) were lost to follow-up and 3 had missing data. Of the 1526 patients still alive, 1092 (72%) were disease-free and 434 (28%) were in relapse of disease.

Despite the similarity of the absolute proportions of patients alive (60%) between autologous and allogeneic HSCT, probability of survival differs significantly between the two populations (fig. 1). The better early survival in patients with an autologous HSCT (fig. 1a) due to the lower transplantation-related mortality (fig. 1b) is offset later on by the increase in relapse and relapse deaths.

This difference in outcome due to donor type is further illustrated by the results of allogeneic HSCT. Survival is best for HLA identical sibling donor transplants due to the lower transplantation-related mortality compared to mismatched family donor or matched or mismatched unrelated donor transplants with their higher transplantation-related mortality (data not shown).

Survival, transplantation-related mortality and relapse were primarily influenced by the EBMT risk score (fig. 2). Survival at day 100 and at 5 years decreased with an increasing risk score.

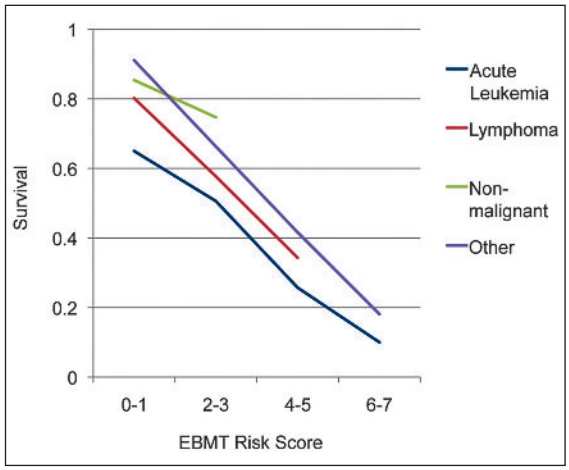

Figure 3

Survival probability at 5 years depending of the EBMT risk score in the different main disease categories.
Acute leukaemia, Lymphoma = lymphoproliferative disorders, Nonmalignant = nonmalignant diseases, Other = all other indications.

Figure 4

Survival- and transplantation-related mortality of 3808 patients with an autologous or allogeneic HSCT from 1997 to 2008 in Switzerland by EBMT risk score and transplant centre.

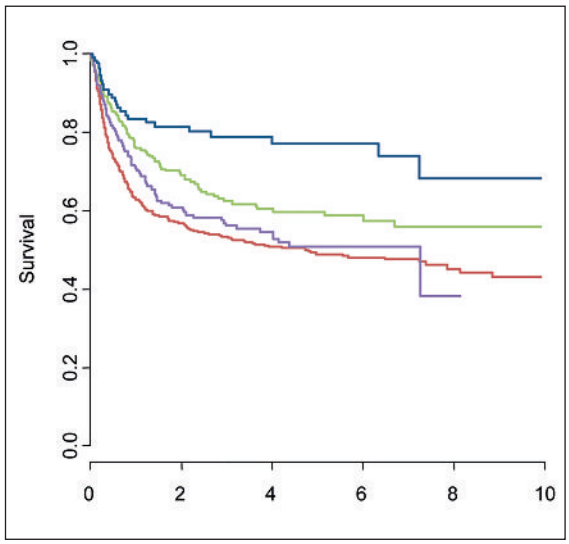

Figure 4a

Survival by centre, allogeneic HSCT.

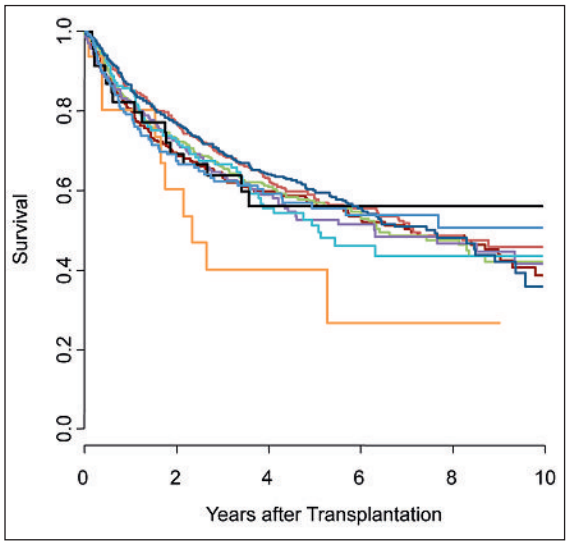

Figure 4b

Survival by centre, autologous HSCT.

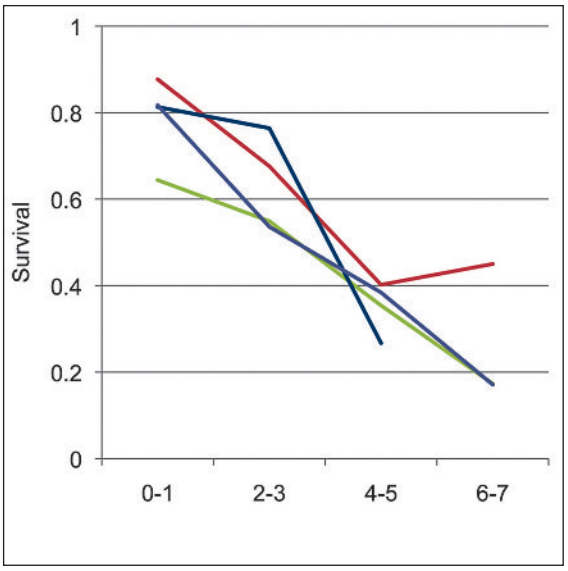

Figure 4c

Probability of survival at 5 years, depending on EBMT risk score and centre, allogeneic HSCT.

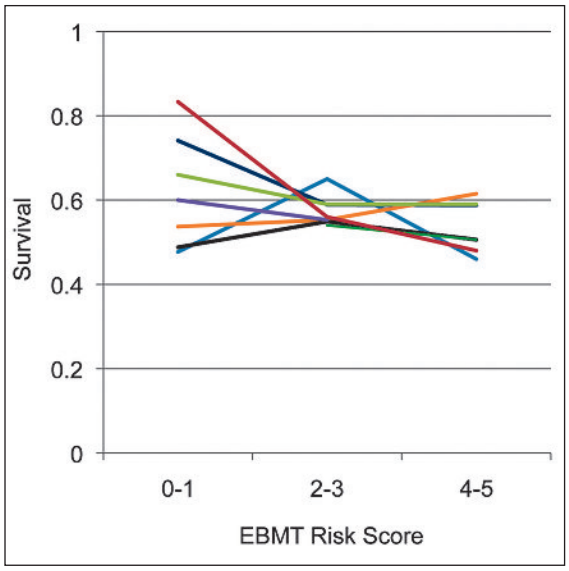

Figure 4d

Probability of survival at 5 years, depending on EBMT risk score and centre, autologous HSCT.

This was due to the growing risk of transplantation-related mortality and relapse with increasing risk score (fig. 2b). This effect of the EBMT risk score on survival and transplantation-related mortality was seen both for patients with allogeneic (fig. 2a) and those with autologous HSCT (data not shown). This effect of the EBMT risk score was seen for all main disease categories, with different impact in the different disease categories but a constant decrease in survival with increasing risk score, due to increasing transplantation-related mortality and relapse death (fig. 3). In autologous HSCT the effects of risk score were more pronounced for TRM than for survival.

Outcome by centre

Absolute and relative numbers of fatalities differed significantly between the nine participating centres. Similarly, probability of survival of allogeneic HSCT (fig. 4a) and autologous HSCT (fig. 4b) showed marked differences. These differences became minor when results were presented by EBMT risk score, for allogeneic (fig. 4c) or autologous HSCT (fig. 4d). Using a Cox model of centre effect there were highly significant differences in mortality among centres (p <0.0001) when studied univariately; this difference decreased considerably and was of borderline significance only (p = 0.046) after adjustment for EBMT risk score, underlying disease and year of transplant for allogeneic HSCT. There was no significant centre effect on overall mortality after autologous HSCT in univariate or multivariate regression models.

Discussion

These data summarise the current activity and outcome of HSCT in Switzerland. They document the fact that all centres achieve a high quality and that data compare favourably with concurrent outcome in the literature from other countries. They also illustrate the danger of centre-specific outcome reporting in a complex field such as HSCT. A simple comparison of mortality rates might suggest marked differences between the participating centres. This is not the case and can be easily explained. The main difference in early mortality in patients with HSCT is observed between autologous and allogeneic HSCT, due to the more complex situation of an allogeneic transplant with its associated early immunological complications of rejection, graft-versus-host disease and delayed immune reconstitution. Even though differences between centres remain, when the observation is restricted to either autologous or allogeneic HSCT the centre effect is most probably not due to "the centre" but the case mix. Differences begin to fade merely with integration of the EBMT risk score into the analysis [49, 50]. Five simple baseline pretransplant characteristics, pooled in a score from 0–7 (0–5 for autologous HSCT) – age of the patient, stage of the disease, time interval from diagnosis to transplant and (for allogeneic HSCT) donor type and donor recipient gender combination – to a large extent predict outcome.

This observation sends several independent messages. First, the data suggest that the most likely explanation for the differences observed are differences in the case mix. This is in line with several recent reports of outcome analyses in as different fields as HIV, stroke, surgery, or solid organ transplantation [15, 35–44]. Differences in case mix become obvious when centres with paediatric or adult patients are compared. It is more difficult when the treatment applies to apparently similar patient populations. The EBMT risk score provides only a rough estimate. Several other independent patient or disease risk factors have been identified in HSCT, such as minor histocompatibility antigen differences, cytokine polymorphisms, ABO barrier, cytomegalovirus status, Karnofski score, comorbidity index or molecular features of the disease [51–55]. They are all established risk factors with a well-defined impact on outcome, none were included in the analysis; information on these factors was not routinely collected. They could have had an impact on some of the still observed differences, as has been discussed in other comparative studies [56–58].

Similarly to these additional risk factors, treatment modalities or transplant techniques were not analysed in detail. There are differences between bone marrow, cord blood and peripheral blood stem cell products [3], and there are differences between specified conditioning regimens and graft-versus-host disease prevention or treatment methods. Again, this information was not collected in detail. However, as shown in large-scale studies, they are more likely to have an impact on short-term outcome with e.g. lower early TRM with reduced intensity conditioning regimens, at the expense of a higher relapse rate later on [50]. Considering only TRM at day 100 without integrating conditioning intensity would falsify the comparison. The absence of significant differences between centres illustrates the difficulties in assessing changes in use of transplant technologies. It is wholly possible that strategy A confers an advantage compared to strategy B. To test the validity of such an assumption goes beyond the available numbers of patients in a country as small as Switzerland. Comparison of crude mortality rates remains inadequate or might even be dangerous. It could prompt centres to refuse treatment for high-risk patients, to avoid falling below a predefined benchmark.

The second important and comforting message is that all centres in Switzerland provide a similar quality of care when measured by risk-adjusted outcome. This confirms the concept adopted by the group, that all centres should follow a strict and internationally recognised quality management system, JACIE. The number of transplants performed, beyond the priority minimum, defined by JACIE as 10 HSCT per year, should no longer be used as a criterion for political decisions on transplant allocation. This does not rule out the possibility that, for certain rare indications as postulated for paediatric transplants or HSCT for autoimmune disorders, numbers will remain associated with outcome [22, 23, 48] It remains an open question whether these few studies, e.g. HSCT for autoimmune disease, relate more to the learning curve or the volume.

Lastly, the data illustrate the feasibility of a mandatory data collection and data analysis system within a complex field of medicine. This provides a basis for a network for collaboration and exchange, a prime prerequisite for quality improvement [9, 15, 59–61]. As such, the HSCT database in Switzerland and its management by SBST may serve as a model for other fields of high-cost or complex medicine in the future.

The authors would like to thank all contributing teams, their data managers and their staff for the excellent work and their patient care.

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