Severe events in donors after allogeneic hematopoietic stem cell donation

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ABSTRACT

Background

The risk for donors of allogeneic hematopoietic stem cells transplants is generally considered negligible. Scattered reports of severe complications and a recent controversy on hematopoietic malignancies after granulocyte colony-stimulating factor administration have challenged this opinion.

Design and Methods

Three hundred and thirty-eight allogeneic transplant teams from 35 primarily European countries were asked to report numbers of fatalities, severe adverse events and hematologic malignancies occurring among their hematopoietic stem cell donors.

Results

Two hundred and sixty-two of the 338 teams (77.5%) responded to a first survey (1993-2002) and 169 of the 262 responder teams (65%) to a second survey (2003-2005). They had performed a total of 51,024 first allogeneic hematopoietic stem cell transplantations, of which 27,770 were bone marrow and 23,254 peripheral blood. They observed five donor fatalities, one after a bone marrow donation and four after peripheral blood donation (incidence 0.98 per 10,000 donations; 95% CI 0.32-2.29), 37 severe adverse events (7.25/10,000; 95% CI 5.11-9.99), of which 12 in bone marrow donors (4.32/10,000; 95% CI 2.24-7.75) and 25 in peripheral blood donors (10.76/10,000; 95% CI 6.97-15.85; $p<0.05$) and 20 hematologic malignancies (3.92/10,000; 95% CI 2.39-6.05), of which 8 after donating bone marrow and 12 after donating peripheral blood stem cells. The observed incidence rate of hematologic malignancies did not exceed the expected incidence in an age- and sex-adjusted general population.

Conclusions

Hematopoietic stem cell donation is associated with a small but definite risk of fatalities and serious adverse events. True incidences might be higher, due to potential underreporting by study design. A continuous, standardized donor follow-up is needed to define donor risk groups and to monitor intermediate and long-term sequelae.

Key words: hematopoietic stem cell donation, adverse event, hematologic malignancies, donor fatality.

Citation: Halter J, Kodera Y, Urbano Ispizua A, Greinix HT, Schmitz N, Favre G, Baldomero H, Niederwieser D, Apperley JF, and Gratwohl A, for the European Group for Blood and Marrow Transplantation (EBMT) activity survey office. Severe events in donors after allogeneic hematopoietic stem cell donation. Haematologica 2009; 94:94-101. doi: 10.3324/haematol.13668

Funding: this work was supported in part by the European Leukemia 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. EBMT is supported by grants from the corporate members: Amgen Europe GmbH, F. Hoffmann-La Roche, Gilead Sciences, Miltenyl Biotec GmbH, Schering-Plough International Inc., Celegene International SARL, Chugai Sanofi – Aventis SNC, Fresenius Biotech GmbH, Gambro BCT, Genzyme, Pfizer, Berlex AG (Schering AG Germany), Therakos, Bristol Myers Squibb, Novartis, Cephalon, Laboratoires Pierre Fabre and GE Healthcare.

Manuscript received July 15, 2008. Revised version arrived September 8, 2008. Manuscript accepted September 16, 2008.

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The online version of this article contains a supplementary appendix.

Introduction

Over the last two decades, allogeneic hematopoietic stem cell transplantation (HSCT) has become an established therapy and the numbers of such procedures increase year by year.[1] HSCT is still associated with significant morbidity and mortality for the patients. These risks are well defined. In contrast to the situation for the recipients, hematopoietic stem cell donation is considered a relatively safe procedure for the donor[2,3] and life-threatening complications are deemed exceedingly rare.

Detailed information on the risks associated with harvesting hematopoietic stem cells comes from prospective, randomized studies comparing bone marrow (BM) and peripheral blood (PB) donations and from unrelated donor registry reports. Both procedures are accompanied by inconvenience for the donor. Adverse events before, during and after donation are frequent but most of them are transient, self-limited and without long-term consequences.[4] Careful donor selection and evaluation have become prerequisites and have been recommended for many years.[5,6]

Sporadic reports of severe or even life-threatening adverse events have been published. These reports define potential areas of risk, such as death, vascular events, bleeding, splenic rupture, triggering of inflammatory disease, transient respiratory disturbances, acute lung injury or sickle cell crises as well as hematologic malignancies but give no estimate of the magnitude of the risk.[7-12] Nevertheless, they document a potential hazard for the donor, which appears to be small but real. Concerns regarding the safety of stem cell donation were recently increased by the debate on potential long-term adverse effects of granulocyte colony-stimulating factor (G-CSF), which is required to mobilize PB stem cells. Experimental data and observational reports raised concern about an elevated risk of hematologic malignancies after G-CSF administration.[13,14] All these data were based on small series of donors;[7,8,15,16] long-term studies or collaborative surveys are still lacking. Careful observation and monitoring of at least 2,000 donors for a minimum of 10 years after G-CSF administration has been postulated to define sufficiently the risk of a hematopoietic malignancy in this group.[17]

Based on the need for such data, the European Group for Blood and Marrow Transplantation (EBMT) attempted to gather information on severe events in donors on a large scale, making use of its activity survey's infrastructure. The data of this survey are reported in adherence with the guidelines of the STROBE statement.[18]

Design and Methods

Study design and participating teams

This is a retrospective analysis of data collected in the EBMT activity survey network. Since 1990, all EBMT members and affiliated teams have been asked to report the numbers of patients undergoing a first HSCT in their centers and provide information on the indication, donor type and stem cell source. In 2003 all 338 teams performing allogeneic HSCT in 30 European and five affiliated countries, outlined in the appendix, were asked to report events occurring in donors; 262 (78%) replied. The 262 teams responding to the 2003 survey were recontacted in 2006, informed about the preliminary data of the first survey and asked again to report events in their donors. One hundred and sixty-nine of these teams responded to the second survey (65%), hence 50% of the initial cohort.

The first survey covered the years 1993-2002, corresponding to a 10-year period starting from the first allogeneic PB HSCT,[19] while the second survey covered the years 2003 to 2005.

Responding and non-responding teams did not differ with respect to years of practising HSCT, numbers of allogeneic HSCT or World Bank category of the team's country of origin.[1]

Transplant numbers

The 262 teams responding to the first survey performed a total of 39,210 first allogeneic HSCT of which 24,099 used BM (77% from related donors) and 15,111 PB (80% from related donors) during this first period. These transplants correspond to 78% of the total of 50,580 reported first allogeneic HSCT during that time period within the EBMT activity survey. The fact that the responding teams performed 77% of BM-HSCT and 78% of PB-HSCT during that period is another indication that the distribution of the two harvest procedures between teams reporting to the donor survey and those not responding must have been similar.

The 169 of 262 (65%) teams responding to the second survey (2003-2005) treated a total of 11,814 patients with a first allogeneic HSCT during the second time period, of whom 3,671 underwent BM HSCT (48% of them from related donors) and 8,143 PB HSCT (49% of them from related donors). This corresponds to 50% of the total of 23,417 allogeneic HSCT reported during the same time period within the EBMT activity survey.

In total, the present analysis covers 51,024 first allogeneic hematopoietic stem cell donations, of which 27,770 were BM (73% from related donors) and 23,254 PB (67% from related donors). This corresponds to 69% of the 73,997 first allogeneic HSCT reported between 1993 and 2005 to the EBMT activity survey.

Because fewer teams responded to the questionnaire covering the period from 2003 to 2005, when more PB HSCT were performed in general,[19] the present analysis is based on significantly more BM harvests (72%) than PB harvests (65%); furthermore, the observation time span was longer for BM donors than for PB donors. Thus, the observation time was 200,786 person-years for BM donors and 99,875 person-years for PB donors.

Questions and definitions

The questionnaire included questions about the presence of a policy for active donor follow-up, about the numbers of serious adverse events (SAE) or donor fatal-

ities and about the development of hematologic malignancies in donors. Teams were also asked to report whether they felt confident about their data or not and whether they were willing to provide additional information. SAE were defined and restricted to any cardiovascular event or splenic rupture occurring within 30 days of donation and necessitating hospitalization. Fatality was defined as any death within 30 days of donation. Hematologic malignancies were defined as any hematologic malignancy (myeloid or lymphoid) which occurred at any time post-donation and was not present at the time of the initial assessment of the donor. The teams that reported events and agreed to provide more information were contacted again by e-mail, telephone or written letter to obtain the information. All teams were guaranteed strict confidentiality. All replies were sent to a defined mail or fax address with restricted access.

Statistics

Incidence of events and the approximate relative risks of donation were calculated as the incidence of donor events per 10,000 first allogeneic transplants. This approach was based on the assumption that each first transplant came from a different individual donor. It did not take into account that about 15% of all patients received more than one transplant, either because of rejection or relapse or within the framework of a planned double transplant program. Detailed information on this aspect was not available from the survey data. Since there were more donations than first transplants, the true incidence of events per donation is probably slightly lower than those reported here.

The results from BM and PB donors were compared using Fisher's exact test and the χ^2 test (Instant Biostatistics version 3.0, GraphPad Software Inc. San Diego, CA, USA).

The incidences of hematologic malignancies in BM and PB donors were compared by calculating the respective incidence per 10,000 person-years of follow-up. Calculated incidence rates were compared with age-specific (crude) incidence rates in the general white population of leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma and myeloma, obtained from the US Surveillance, Epidemiology, and End Results (SEER) Program.[20] Because the true age and sex distribution of our donor population is not known, information on the gender and age of donors was obtained from the EBMT ProMISe (Project Manager Internet Server) database which contains data from 72,548 donors who donated during the period 1993-2005: 57% were male and 43% were female. For the same period, the age of 19,503 donors was registered. The median age of related BM donors was 32.5 years, of unrelated BM donors 35.9 years, of related PB donors 43.7 years and of unrelated PB donors 34.6 years. Hence, unrelated BM and PB donors had the same age distribution, while related BM donors were significantly younger (p<0.001) than related PB donors (Figure 1) and 30.2% of all BM donors were 20 years or younger compared to 6.5% of PB donors. These results were compared with the corresponding age groups in the SEER program.

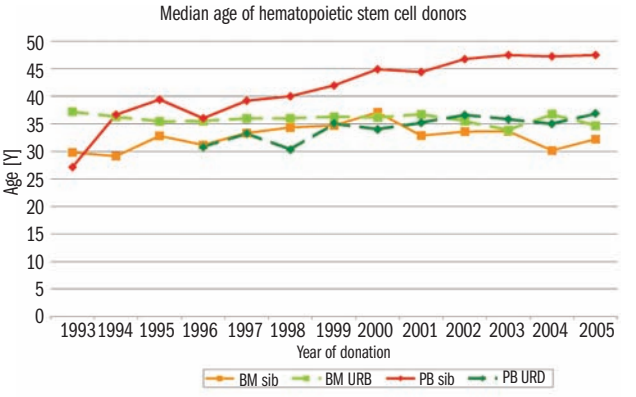

Figure 1. Median age of donors donating from 1993 – 2005 registered in the EBMT ProMISe database (n=19,503) by donor type and stem cell source. Peripheral blood stem cell-transplants from matched unrelated donors started in 1996 only. BM sib = sibling bone marrow donor; BM URD = unrelated bone marrow donor; PB sib = sibling donor of peripheral blood stem cells; PB URD = unrelated donor of peripheral blood stem cells.

Results

Follow-up policies

Of the 262 responding teams in 2003, 146 (55.7%) reported having an active donor follow-up system, 104 (39.7%) indicated that they did not have an active donor follow-up and 12 (4.6%) did not answer this question. The proportion of teams with an active donor follow-up system (60.4%) was slightly higher amongst the 169 teams responding to the second survey in 2006 (34.3% without follow-up, 5.3% with no reply). Donor follow-up in most centers was linked with the follow-up of the recipient and, therefore, ceased with the patient's death. Despite the limited formal donor follow-up, 244 teams (93%) of the first survey and 157 teams (93%) of the second survey responded that they felt confident about their data.

Donor fatalities

A total of five deaths, one in a BM donor and four in PB donors were reported (Table 1), which corresponds to an incidence of 0.98 per 10,000 first transplants (0.32-2.29/10,000 95% confidence interval [CI]) with a wide overlap of the 95% CI between BM (0.36; 0.01-2.01/10,000 95% CI) and PB (1.72; 0.05-4.40/10,000 95% CI) donations. All fatalities occurred in males between 27 and 67 years of age. All were related family donors. Of these five deaths, one (number 5) was due to an error during the donation procedure because of confusion of two infusion solutions. One donor (number 1) died from pulmonary embolism 15 days after BM harvest. He complained of pain in both legs. After two consultations during the first week after donation the diagnosis of deep venous thrombosis in both legs and in the vena cava inferior accompanied by pulmonary embolism was made on day 7. He died from massive pulmonary embolism 1 week later. A relationship with the harvest procedure is probable. Hereditary antithrombin III deficiency was later diagnosed within the family. It is possible, but unconfirmed, that the donor also suffered from

this deficiency. A third donor (number 2) developed a subarachnoid hematoma 1 day after the donation and died on day 29 from it. A minimal platelet count of 82×10^9/L after apheresis together with the patient's concurrent treatment with aspirin because of coronary heart disease might have contributed to the event. In two donors, the relationship between stem cell harvest and death remains unclear. Both died from cardiac arrest within 2 weeks after donation.

Severe adverse events

There were a total of 37 SAE, 12 in BM and 25 in PB donors as outlined in Table 2. The incidence was, therefore, 7.25 per 10,000 first transplants (95% CI 5.11-9.99) with significantly fewer SAE among the BM donors (4.32 per 10,000 first transplants; 95% CI 2.24-7.55) than among the PB donors (10.76 per 10,000 first transplants; 95% CI 6.97-15.85) ($p<0.05$). The types of events differed between the two groups. Cardiac events consisted of four cardiac arrests in the BM donor group and two myocardial infarctions in the PB donor group. Three of the former occurred during anesthesia monitoring in the operating room. Pulmonary embolism and deep venous thrombosis were more frequent in PB donors. One of

Table 1. Characteristics of donors who died within 30 days after stem cell donation.

Donor number	Age (years)	Sex	Mode of harvest	Mobilization	Number of harvest days	Died on day	Donor-recipient relationship	Cause of death
1	38	Male	BM	n.a.	1	15	Related	Massive pulmonary embolism after diagnosis of deep vein thrombosis and pulmonary embolism on day 7. Antithrombin III deficiency was later diagnosed in the family but was unknown at the time of donation
2	67	Male	PB	G-CSF	2	29	Related	Subarachnoid hematoma on day 1. Died on day 29.
3	43	Male	PB	G-CSF	2	15	Related	Cardiac arrest (no autopsy). Risk factors: arterial hypertension, heavy smoker
4	52	Male	PB	G-CSF	2	17	Related	Cardiac arrest Risk factor: smoker
5	27	Male	PB	G-CSF	1	0	Related	Cardiac arrest after human error (see text). Resuscitation unsuccessful

Table 2. Severe adverse events among 51,024 stem cell donations.

Stem cell source event	Bone marrow N.	Bone marrow Comment	Peripheral blood N.	Peripheral blood Comment
Cardiovascular				
Myocardial infarction			2	
Cardiac arrest	4	All during or shortly after harvest		
Supraventricular arrhythmia			1	Probably related to catheter. Needed transesophageal stimulation
Severe hypertension	2	Former normotensive donors	1	Required treatment for 1 month post-donation in a former normotensive donor
Thromboembolic				
PE/DVT			7	Between day –2 and day 30 of harvest. Three events occurred before day 0
Stroke	1	Due to HIT antibodies		
Pulmonary complications				
TRALI			1	Due to priming the cell separator with erythrocyte concentrates (pediatric donor)
Lung edema	1	At the end of anesthesia after two donations within 1 month. Needed mechanical ventilation for 24h.		
Hemorrhage				
Subdural hematoma			1	Day 21 after donation
Unspecified	1	Recovered after transfusion of four units of red blood cells	1	Hemorrhage from femoral artery after insertion of central venous catheter
Seizures			1	Due to severe electrolyte disorder during apheresis
Splenic rupture			5	
Unspecified	3		5	
Total	12		25	

PE/DVT: pulmonary edema/deep vein thrombosis; HIT: heparin-iduced thrombocytopenia; TRALI: transfusion-related acute lung injury.

the thrombo-embolic events was due to heparin-induced thrombocytopenia (HIT). HIT was also associated with a stroke in an unrelated BM donor. Other SAE, such as splenic rupture, transfusion-related acute lung injury (TRALI), local hemorrhage or catheter-related infections were mainly procedure-related, as indicated in Table 2.

Three pediatric donors with severe adverse events were reported, two BM (cardiac arrest, lung edema) and one PB donor (TRALI). Because age was not available for all donors reported we were not able to calculate the incidence of SAE for pediatric donors separately.

Hematologic malignancies

Overall 20 hematologic malignancies were reported, 8 among BM donors and 12 amongst PB donors (Table 3). Neoplasms of both myeloid and lymphoid origin occurred with a wide range of latency from donation to diagnosis in donors of any age at the time of donation.

The incidence rates for developing a hematologic malignancy were 0.40 per 10,000 person-years for BM and 1.20 per 10,000 person-years for PB donation.

An exact comparison with the general population was not possible because of missing individual information on age and sex of the donors.

As reported above, sibling donor age was significantly higher for PB donors and increased over time (Figure 1). This higher age of PB donors might be a factor accounting for the higher incidence of SAE and the higher incidence rate of late hematologic malignancies in PB donors compared to BM donors. The observed incidence rate in both BM and PB donors was compared with that in the general population using the expected age-specific (crude) SEER incidence rates for hematologic malignancies (leukemia, lymphoma and myeloma) for both sexes.[20] The expected rates ranged from 0.9/10,000 individuals for the age group from 20 to 24 years old up to 6.3/10,000 for the age group from 55 to 59 years old with values of 1.3-1.6/10,000 for the age group from 30 to 39 years old and 1.6-2-2.8/10,000 for the age group from 35 to 45 years old. Considering these data, the observed incidence rates of hematologic malignancies in donors in our survey were not significantly different from the expected range.

Table 3. Hematologic malignancies observed in 51,024 stem cell donors.

Donor number	Age	Sex	Relationship	Mode of harvest	Mode of mobilization	Number of donations	Diagnosis	Interval between donation and diagnosis	Treatment	Outcome	Duration of follow-up
06	20	F	Unrelated	BM	–	1	AML M2	1y6m	Allogeneic HSCT	Alive in CR	2y
07	n.r.	F	Syngenic twin	BM	–	1	AML M1	12y	n.r.	n.r.	n.r.
08	n.r.	M	Sibling	BM	–	1	T-ALL	12y2m	n.r.	Died	n.a.
09	1	M	Sibling	BM	–	1	B-ALL	10m	Chemotherapy	Alive in CR	6y
10	n.r.	n.r.	Sibling	BM	–	1	NHL low grade (follicular)	6y	Radiotherapy	Alive in CR	n.r.
11	53	M	Sibling	BM	–	1	DLBCL	4m	Chemo-/ radiotherapy	Died from lymphoma	8y
12	n.r.	n.r.	n.r.	BM	–	n.r.	Lymphoma	n.r.	n.r.	n.r.	n.r.
13	57	F	Sibling	BM	–	1	Nasopharyngeal plasmacytoma	7m	Radiation, surgical resection	Alive in CR	10y
14	34	F	Sibling	PB	G-CSF	1x2	AML	2y8m	Chemotherapy/ allogeneic HSCT	Alive in CR	1y
15	38	F	Sibling	PB	G-CSF	1x2	ALL	1y5m	Chemotherapy	Died in induction	na.
16	47	F	Sibling	PB	G-CSF	1	MPN	4y3m	n.r.	n.r.	n.r.
17	n.r.	n.r.	Sibling	PB	n.r.	n.r.	CLL (familial?)	several years	n.r.	n.r.	n.r.
18	25	n.r.	Sibling	PB	n.r.	1	NHL low grade	9m	Chlorambucil	Alive in CR	3y3m
19	45	F	Sibling	PB	G-CSF	1(BM)*	NHL low grade	7y3m	Chemotherapy	Alive in CR	9m
20	41	M	Sibling	PB	G-CSF	1x2	DLBCL	4y3m	Chemotherapy	Alive in CR	4y
21	28	M	Sibling	PB	G-CSF	1	HD	1y	Chemotherapy	Alive	2y
22	68	M	Sibling	PB	G-CSF	1	Splenic maginal zone lymphoma	7y	none	Alive	1y
23	n.r.	n.r.	n.r.	PB	n.r.	n.r.	Malignancy not specified	n.r.	n.r.	n.r.	n.r.
24	n.r.	n.r.	n.r.	PB	n.r.	n.r.	Malignancy not specified	n.r.	n.r.	n.r.	n.r.
25	n.r.	n.r.	n.r.	PB	n.r.	n.r.	Malignancy not specified	n.r.	n.r.	n.r.	n.r.

**No apheresis due to intolerance after completion of G-CSF mobilization, donor finally underwent BM harvest. AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin's lymphoma; DLBCL: diffuse large B-cell lymphoma; MPN: myelo-proliferative neoplasm; CLL: chronic lymphocytic leukemia; HD: Hodgkin's disease; CR: complete remission.*

Discussion

This report illustrates the quantitative and qualitative aspects of severe events in donors of hematopoietic stem cells for allogeneic HSCT. It adds to the detailed information on minor and transient side effects of the harvest procedure. Despite several limitations due to the retrospective nature of the present survey, we estimate that about 1 in 10,000 donors had a fatal complication, about 1 in 1,500 donors had a severe complication leading to hospitalization and at least 1 in 3,000 developed a hematologic malignancy. The risk of death was not different between BM or PB donors, but there was a two-fold higher risk of SAE (1 in 1,000) after PB donation than after BM donation (1 in 2,500). Having focused on cardiovascular events and splenic rupture we cannot exclude that other important SAE were missed. Furthermore, given the retrospective nature of the survey and the lack of donor follow-up in some centers, underreporting must be assumed and *true* incidences are likely to be higher. Prospective studies which include all SAE are needed to define the risk more precisely and to enable the identification of potential risk factors. Most of the reported events occurred in related donors. The data do not allow definition of the relative impact of age, donor type (related/unrelated) or the harvest procedure on the events reported. However the higher average age of related PB donors as an important imbalance between the different groups of donors must be kept in mind when interpreting the data. Hematologic malignancies were observed after both BM and PB donation with incidence rates within the expected ranges for an age and sex-adjusted general population. Again, for the same reasons as stated above, underreporting is likely and *true* incidences may be higher.

These data contradict in part observations from carefully conducted surveys of data in unrelated donor registries. In a nation-wide prospective survey of the Japan Society for Hematopoietic Cell Transplantation (JSHCT) no death within 30 days after donation was reported among 2,784 donors [*Y. Kodera, personal communication*]. Likewise, no harvest-related death was reported in a survey conducted by the National Marrow Donor Program (NMDP) among 5,165 donors and the German Deutsche Knochenmarkspender Datei (DKMS) registry among 10,949 donors [*D. Confer and A. Schmidt, personal communications, presented at the EBMT meeting 2007*]. None of these reports covered a number of donations comparable to that in our survey. Moreover, these data came from unrelated donors and no comparable data are available for related donors. These discrepancies between the registry data and the data reported here may explain why stem cell harvesting in healthy donors has been deemed absolutely safe. The scattered publications of fatal complications and SAE in donors do, however, fit with our report. There are literature reports of nine deaths among stem cell donors, six in BM-donors (two of which occurred before the donation procedure could be done) and three in PB-donors.[7] An internal company report (which remains unpublished but was made available to Y. Kodera; *personal communication*) revealed seven additional deaths of donors of both genders between 1998 and 2001 from all over the world. Just one of them is listed in our survey. Hence, an estimate of one fatal event in 10,000 donations is likely to reflect the reality. For obvious reasons eligibility criteria for donor clearance might have been less strict for related donors than for unrelated donors, among whom no donation-related deaths have been reported so far.

The five fatal events observed in our survey had different causes. All affected donors were adult, related donors. Fatal outcomes have been reported in both male and female donors[7] (*Y. Kodera, personal communication*). The fact that in our survey all the donors who died were males is, therefore, most likely to be by chance even if 57% of more than 72,000 donors registered to the EBMT ProMISe database from 1993-2005 were males. An unequivocal relationship to the donation can be established for one of the five deaths. Human error remains a risk factor, even if people are well organized and highly trained. In a second donor it is very likely that BM donation contributed to a fatal pulmonary embolism. Surgery is a well known risk factor for venous thromboembolism and the congenital antithrombin III deficiency which was diagnosed in the family after the donor's death and which the donor, may, therefore, have had could have been a co-factor. The moderate decrease of the platelet count after apheresis together with concomitant use of aspirin may have contributed to the subarachnoid hemorrhage that led to the death of a third donor. For the other two cases only a temporal relationship with the donation exists, as death occurred within 30 days after the donation. A causal link with donation cannot be excluded. Non-fatal myocardial infarcts were also reported.

The 37 reported SAE reflect the known risks of both procedures and reveal new findings. Splenic enlargement and splenic rupture are well-known complications in healthy PB donors. Three of the five cases in our series have already been published.[9,10,21] Four donors had a cardiac arrest during or shortly after BM harvest. This is a well-known, rare complication of anesthesia. The incidence of 1.44 events per 10,000 BM donations in our survey is compatible with the results of two large recent studies in which the risk of anesthesia contributing to cardiac arrest was 1.37 and 1.1 per 10,000 episodes of anesthesia.[22,23]

Thromboembolic events apart from catheter-associated thrombosis[16] were not reported in previous studies on G-CSF-mobilized donations. Seven cases were noted in this survey (incidence 3 in 10,000). Three occurred before stem cell harvest and the mobilization had to be stopped prematurely. Activation of the coagulation system during G-CSF mobilization has been repeatedly demonstrated.[13] The two cases of myocardial infarction in the PB group might reflect the pro-inflammatory effect of G-CSF on unstable atherosclerotic plaques. This fits with the report from a series of patients with severe coronary artery disease undergoing stem cell mobilization. Angina pectoris was precipitated during mobilization in almost 90% of cases.[24]

Of special interest is the question of hematologic malignancies after stem cell donation.[12] G-CSF has been

described to induce genetic alterations in mononuclear cells of normal donors. These effects were transient and their impact is not clear yet.[13] Recent reports about a doubling of the risk of acute myeloid leukemia or myelodysplastic syndrome in patients treated for breast cancer[25] as well as a few new cases in healthy donors[14] initiated a controversial debate about the risk of G-CSF. These observations must be set in the context of the known predisposition for hematologic malignancies within families.[26] That family members have an at least doubled incidence of hematologic malignancies is widely accepted and a case of acute leukemia found in a donor on the day of BM donation underlines this risk.[27]

Twenty hematologic malignancies were reported in this survey. They occurred with a latency of a few months to more than 10 years after the donation. Malignancies of myeloid and lymphoid origin were seen, with no relation to the type of hematologic malignancy in the recipient, i.e. donors donating for siblings with myeloid neoplasias developed lymphoma and vice versa (*data not shown*). Only one of the surviving recipients developed donor-type leukemia or lymphoma during the follow-up, a rare but well-known event.[28] Hematologic neoplasias developed in both BM and PB stem-cell donors. In both groups the incidence rates were below the age-specific crude incidence rates for a normal population. Bearing in mind that even a slightly higher rate than the age-specific incidence rate could be expected,[26] underreporting of hematologic neoplasias in our survey is likely.

Information on related donors – who comprised the majority of donors in our survey – was highly dependent on survival of the recipient. Underreporting of data from donors whose recipients died, loss of follow-up of surviving recipients and donors, poor contact between donors and recipients and physicians not asking for donor health data might explain the fact that no excess incidence compared to that in a general population was observed. Since the overall survival for BM and PB recipients transplanted in responding centers from 1993-2005 was not significantly different (*data not shown*), the higher incidence rate of hematologic malignancies in PB donors is most likely to be explained by the fact that PB donors were older than BM donors, but a reporting bias or an effect of the method used for harvesting cannot be excluded.

There are additional limitations to this study. It was a retrospective analysis which relied on the team members' capacity for remembering such events. Only about half of the responding centers had a policy of active donor follow-up, which was rather heterogeneous. Considering patients' survival and its presumed impact on the quality of donor follow-up, we might have missed reliable long-term donor follow-up data for half of the related donor population. Only a selected group of teams reported the exact number of donors, their gender and age distribution was unknown and data on some of the SAE and hematologic malignancies were incomplete. Nevertheless, the large majority of centers felt confident about the data reported. In any case, the *true* incidence would be higher.

What are the consequences of this report? SAE and donor fatalities are likely to continue. With the increasing age of the recipients of HSCT, the number of older family donors with co-morbidities will increase. Efforts to improve training, safety and quality control systems by implementing the Joint Accreditation Committee-ISCT & EBMT (JACIE)[29] accreditation process (*www.jacie.org*) will further safeguard against errors but cannot prevent all of them. Harvest centers need to know about potential complications, need to inform donors about their risks and establish policies for insurance cover for donors and their families in the case of an event. Rules for standardized donor follow-up should be established by the international transplant and donor community, which would probably be best conducted within the framework of a global organization, such as the World Marrow Donor Association (*www.worldmarrow.org*), EBMT (*www.ebmt.org*), Center for International Blood and Marrow Transplant Research (*www.cibmtr.org*) or World Wide Group for Blood and Marrow Transplantation (*www.wbmt.org*). Even more importantly, rules and regulations covering legal aspects of events related to donation procedures must be established in order to protect the staff working at harvest centers.

This report demonstrates that SAE, including fatal events and hematologic malignancies do occur during follow-up in healthy donors. The incidence of these events can be estimated; it is small but real, in BM as well as in PB donors. Related PB donors are older than other donors and more frequently suffer severe adverse events during donation. Hematologic malignancies occur in both BM and PB donors. The estimation of the true incidence rates is limited by incomplete donor follow-up and significant underreporting is likely.

Donors must be informed about the potential risks of making a donation. Systematic follow-up is already well established for HSCT recipients. Such a follow-up should be extended to donors and should cover established mobilizing agents as well as new agents to come.[5,6,30]

Appendix

The co-operation of all participating teams and their staff (listed in the Online Appendix), at the EBMT Coordination Office Barcelona; EBMT Central Registry Office London, EBMT Data Office Paris, the Austrian Registry (ASCTR), the Czech Registry, the French Registry (SFGM-TC), the German Registry (DRST), the Italian Registry (GITMO), the Dutch Registry, the Spanish Registry (GETH), the Swiss Registry (STABMT), the Turkish Registry and the British Registry (BSBMT) is greatly appreciated. The authors also thank M. Stern for excellent statistical assistance, S. Stöckli for secretarial assistance, as well as L. John for technical assistance with data management.

Authorship and Disclosures

AG, JH and YK designed the current analysis. HB, GG and JH were primarily responsible for data collection.

AG and JH were primarily responsible for drafting the paper. All authors contributed to data collection, data analysis and interpretation and to the final version of the manuscript.

AG is member of a Novartis advisory committee and gets research support from AMGEN, Roche, Novartis, BMS and Pfizer. All other authors declared that they have no conflicts of interest.

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