Clinical outcomes after peripheral blood stem cell donation by related donors: a Dutch single-center cohort study

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BACKGROUND: Relatives donating peripheral blood stem cells (PBSCs) may be accepted for donation on less strict criteria than unrelated donors. We evaluated the occurrence of adverse events during procedure and follow-up, with a special focus on donors who would have been deferred as unrelated donors.

STUDY DESIGN AND METHODS: All 268 related PBSC donors at our center (1996-2006) were included. Data were retrospectively collected from medical reports and standard follow-up. Health questionnaires were sent from 2007. Medical outcomes of donors, deferrable or eligible according to international criteria for unrelated donation, were compared.

RESULTS: Forty donors (15%) would have been deferred for unrelated donation. Short-term adverse events occurred in 2% of procedures. Questionnaires were returned by 162 (60%) donors on average 7.5 years after donation, bringing total person-years of follow-up to 1278 (177 in deferrable donors). Nine malignancies and 14 cardiovascular events were reported. The incidence rate of cardiovascular events in eligible donors was 6.5 (95% confidence interval [CI], 2.5-12.3) per 1000 person-years compared to 44.9 (95% CI, 17.4-85.2) in deferrable donors; incidence rates of malignancies were 4.6 (1.4-9.6) and 24.0 (6.0-53.9) per 1000 person-years, respectively, in eligible and deferrable donors. All incidence rates were within the range of age- and sex-matched general population. No autoimmune disorders were reported.

CONCLUSION: In both the eligible and the deferrable related donors treated with granulocyte–colony-stimulating factor there are few short-term and long-term problems. The occurrence of post-PBSC cardiovascular events and malignant disease in related donors appears to be within the range of the general population.

Recombinant human granulocyte–colony-stimulating factor (G-CSF) is increasingly used to mobilize peripheral blood stem cells (PBSCs) from healthy donors for allogeneic hematopoietic transplantation. In the Netherlands, PBSC collection has been performed in related donors since 1995. Counseling, collection, and formal follow-up evaluations of unrelated donors conducted since 2004 are performed in accordance with national policies that conform to the World Marrow Donor Association standards.[1] Although related donors are screened by independent physicians not involved in care of the patient, many of these donors are accepted for PBSC donation despite the presence of conditions for which they would be deferred if they were unrelated donors.

There is ample information about the short-term effects of the PBSC procedure in related and unrelated donors, indicating an acceptable safety profile in

ABBREVIATIONS: BMI = body mass index; CVC = central venous catheter; CVD = cardiovascular disease; IQR(s) = interquartile range(s); NMDP = National Marrow Donor Program; PBSC(s) = peripheral blood stem cell(s); SAE(s) = serious adverse event(s); SMR = standardized morbidity ratio.

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comparison to marrow donation under general anesthetic.[2,3] Nevertheless, some serious and potentially life-threatening complications have been described in allogeneic PBSC donation procedures, including splenic rupture,[4,5] anaphylaxis, vasculitis, and acute lung injury.[6] Myocardial infarctions,[7] thromboembolic events, subarachnoid hemorrhage, and cardiac arrests have been reported in at least 13 cases either during G-CSF mobilization or within 30 days after PBSC harvest.[8,9] Careful donor selection and observation might mitigate but not completely abolish these risks.

Potential long-term complications are, however, less well known. There are some reports suggesting that administration of G-CSF may enhance malignant transformation in patients.[10-12] Some have reported the occurrence of hematologic and solid malignancies in healthy donors after donation of G-CSF–mobilized PBSCs. Furthermore, there are concerns about the potential development or exacerbation of autoimmune or systemic inflammatory diseases.[3,8]

These considerations regarding possible long-term effects have stimulated investigators to report on long-term follow-up of PBSC donors.[13-15] However, long-term data concerning this topic in related donors are relatively scarce. Leitner and colleagues[16] observed a cohort of 171 related donors; de la Rubia and coworkers[17] described findings from a voluntary national registry of donation and follow-up of predominantly related donors; Halter and colleagues[8] reported international survey data from the European Group for Blood and Marrow Transplantation concerning both related and unrelated donors. None of these investigators found an increased incidence of malignancies; all authors mentioned the higher age of related donors as a relevant issue and called for systematic long-term follow-up.

Here we report follow-up data concerning a Dutch cohort of related donors. Because of the apparent difference in acceptance of related donors in comparison to unrelated donors, we also separately analyzed the data on the individuals who would not have been accepted under international screening criteria for unrelated donors.

MATERIALS AND METHODS

Study population and PBSC procedure

The study cohort consisted of all related donors who underwent G-CSF mobilization and PBSC harvesting at Leiden University Medical Center from May 1996 to May 2006; the recipients were all patients at the hospital's transplantation unit. The study was performed as part of a larger study that also comprised a prospectively enrolled group of donors and for which ethical approval was obtained from the hospital medical ethics committee.

Donor consent and medical clearance were performed by an independent physician. Subject to careful medical assessment, related donors could be accepted without upper age or body weight restrictions and sometimes in the presence of conditions which would constitute contraindications for unrelated stem cell donation. A short description of the procedures and reference criteria is given in Appendix S1, available as supporting information in the online version of this article.

Donors received 10 μg/kg G-CSF (filgrastim, Amgen, Inc., Thousand Oaks, CA) once daily. The white blood cell (WBC) count was checked on the fourth morning for dose adjustment (halving) to take place if there was an increase above 70×10^9/L. The fifth dose was administered at the end of the fourth day. PBSC apheresis (COBE Spectra, CaridianBCT, Lakewood, CO) was conducted on the fifth and, if necessary, sixth or subsequent day after an additional dose of G-CSF. If required, calcium was supplemented. Standard procedures allowed reinfusion of autologous platelets (PLTs) prepared from the stem cell product if there was a postapheresis PLT count below 50×10^9/L or if it was below 80×10^8/L and a second day of apheresis was needed. After completion of the procedure, follow-up visits were scheduled at both 1 month and 1 year after collection.

Data collection

We extracted data from medical records and hospital information systems concerning predonation examination, donation, and follow-up visits. Furthermore, we evaluated findings of medical screening and noted cases of acceptance where the donor would have been deferred under the criteria for unrelated donors. Mobilization and apheresis procedural data were extracted, including data on deviation from standard G-CSF schedule, use of a central venous catheter (CVC), the number of apheresis sessions, PBSC harvest, and reinfusion of autologous PLTs prepared from the stem cell product. We retrieved information on requested target stem cell dose and yield, as well as on second requests for hematopoietic stem cells and donor lymphocyte collections (donor lymphocyte infusion). Finally, we recorded serious adverse events (SAEs) during follow-up.

In November 2007 we sent all donors a standardized health questionnaire by post. It comprised 14 yes or no questions about medical diagnosis and treatment indicative of health problems since the donation; free-text explanation was to be added if there were any "yes" responses. If the information given was not clear, one of the investigators (JWO) contacted the donor by telephone or e-mail for clarification. When necessary medical details were requested from treating physicians with written consent from the donor. If the questionnaire was not returned, several attempts were made to check the address and find

the donor. In January 2011 we accessed the hospital patient database to ascertain whether the recipient was alive or retrieve the date of death.

Definitions

Donor eligibility status was retrospectively assessed according to the Assessment Tool at Workup from the National Marrow Donor Program (NMDP, 2009 version, Minneapolis, MN),[18] which was applied alongside general blood donation criteria. Broadly, unrelated donors must have no history of cardiovascular, diabetes, systemic autoimmune, eye, or thyroid disease; donation is permitted up to age 60 years and a body mass index (BMI) of 40 kg/m^2. Donors who would not have been eligible as unrelated donors are referred to as "deferrable donors."

All events requiring unscheduled medical examination or treatment from the start of mobilization until the 1-month follow-up were taken into consideration and categorized as procedure-related SAEs.

Follow-up period is defined as the period starting 1 month after start of G-CSF to the latest contact with the donor. Contacts from 30 up to 100 days were considered as early follow-up and contacts from 100 to 730 days as late follow-up.

The study outcomes were as follows:

1. Any malignancy (basal cell carcinoma excluded).
2. Cardiovascular disease (CVD) after the procedure: a combined outcome of medically diagnosed fatal or nonfatal myocardial infarction, newly diagnosed coronary disease treated by medication or ischemic vascular disease, cardiac intervention or vascular intervention, cerebrovascular event, medically diagnosed transient ischemic attack for which treatment was instituted, or venous thromboembolism.
3. (Systemic) autoimmune disease of any type.

Statistical analyses

Data for all donors are presented, with comment on completeness of information. Means, medians, and interquartile ranges (IQRs) were calculated as descriptive statistics. For each donor, the number of follow-up years was determined from the time of donation to the latest contact date. Annual disease-specific incidence rates were calculated as the number of events per 1000 person-years of follow-up, including all follow-up years until occurrence of the first event or until the latest contact date with donors without events. Confidence intervals (CIs) are given for the 95% level of statistical significance.

To compare incidence rates in our study group with those in the general population, age- and sex-specific incidence rates of CVD and for cancer within the Dutch general population were retrieved from the national statistics database (http://statline.cbs.nl/statweb/?LA=en) and from the national cancer registry (http://www.iknl.nl/). Using the number of follow-up years for male and female donors in each age band we calculated the numbers of cardiovascular events and malignancies which would be expected in the study population if they had the same rate as in the general population. The standardized morbidity ratio (SMR) was determined, the ratio of observed events to the number expected. (A SMR less than 1 means that there were fewer events in the study cohort than expected.) The SMR and 95% CI were calculated for the whole cohort and also separately for the deferrable versus eligible groups.

RESULTS

Population characteristics

The 268 related donors had a median age of 43 years (range, 14-70 years) at donation; the demographic characteristics of the cohort are shown in Table 1. Forty donors would have been deferred according to NMDP criteria; the reasons are summarized in Table 2. Apart from age over 60 years, BMI over 40 kg/m^2, and hypertension (>160/95 mmHg), medical contraindications were present in 10 donors: Factor V Leiden and/or previous deep venous thrombosis (n = 2), coronary atherosclerosis and medication or revascularization (n = 2; stable), aortic valve stenosis (stable), Parkinson's disease, past treatment for breast cancer (more than 5 years previously), diabetes mellitus Type 1 or 2 (n = 2), or low concentration monoclonal (M) protein.

All procedural data were complete for 262 donors. Data on both target and yield of CD34+ cells were available for 234 donors. A collection of PBSCs that was deemed

TABLE 1. Donor characteristics and medical history*

Donor characteristics	All donors (n = 268)	Deferrable (n = 40)
Female	115 (43)	18 (45)
Age at donation (years)	42.8 (34.6-51.2)	60.4 (46.9-63.5)
BMI† (kg/m^2)	24 (22-28)	27 (24-30)

* Data are reported as number (%) or median (IQR).
† BMI known for 242 donors.

TABLE 2. Deferral reasons of 40 deferrable donors*

Deferral reasons	Number
BMI (>40 kg/m^2)	2
Hypertension (>160/95 mmHg)	13
Other medical conditions	10
Age >60 years	21

* More than one reason may apply.

TABLE 3. Procedure-related SAEs

SAEs	Sex (M/F), age (years)	Deferral reason (if present)
Excessive tiredness, one night hospitalization after PBSC	M, 32	Hypertension
Chest pain; no explanation	F, 34	
Inpatient opiate pain control; G-CSF stopped on Day 3 with WBC count of 59.7×10^9/L	M, 39	
Inguinal venous thrombosis after CVC	F, 45	
Persistent pain symptoms at injection site	F, 24	
Potentially serious dose incidents		
Received incorrect G-CSF dose; no excessive increase in WBC count	F, 36	Previous DVT
No dose reduction on Day 3 (WBC count was 80×10^9/L); precollection WBC count of 107×10^9/L.	F, 55	Previous DVT

DVT = deep vein thrombosis.

adequate was achieved in all but three donors (1.1%; one female and two male donors deferrable for age over 60 years).

The collection was completed in one session in 176 donors (66%): 76% for male and 52% for female donors. Most of the remaining donors underwent 2 days of apheresis; more than two sessions were needed in five (three males). A CVC was used in 22 of 268 (8%, 16 females). Four females out of these 22 donors were deferrable (two for hypertension, one for age >60 years, and one for both BMI > 40 kg/m^2 and hypertension).

Follow-up visits are recorded for 230 donors (86%): 207 (77%) for early follow-up within 100 days and 156 (58%) for late follow-up approximately 1 year after collection, some because of subsequent donations. There was no correlation between this follow-up attendance and survival of the recipient in the first 6 months after transplantation. A total of 122 donors made subsequent donations: 113 donated lymphocytes (donor lymphocyte infusion) on one or more occasions, seven donors underwent a second PBSC collection, one donor donated granulocytes, and one donor donated marrow because of inadequate PBSC yield. The interval for subsequent donations was on average 329 days (IQR, 170-398 days; median, 248 days).

Procedure-related and short-term events

G-CSF led to changes in hematologic variables as expected. Eighty donors (30%) received autologous PLTs (60 donors once and 20 donors twice or more) separated from the PBSC product. No transfusion reactions to PLTs or serious biochemical changes were recorded. All of the mild elevations of LDH and bilirubin normalized within 6 weeks of harvest.

Table 3 shows the SAEs, one of which was related to the use of a CVC. In all, five donors (2%) required unscheduled medical attention and/or hospitalization during the period of G-CSF administration or harvest or during the direct follow-up period. We found no correlation between donor's eligibility status and the occurrence of short-term procedure-related SAEs. The table also details two potentially serious dosing incidents. A total of eight donors (3%) reported excessive tiredness in relation to the procedure, which lasted for longer than 1 week, persisting until 6 weeks postdonation in three cases.

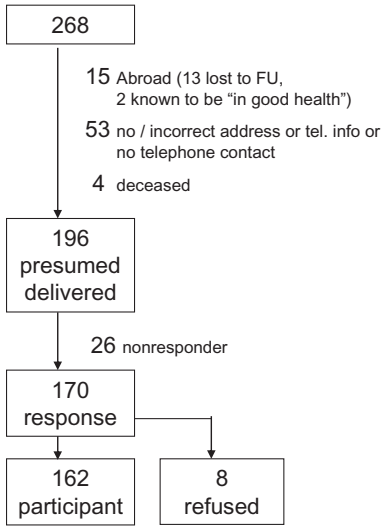

Fig. 1. Responses to the follow-up (FU) health questionnaire.

Follow-up

Figure 1 summarizes the response to the follow-up questionnaire. Of the 268 donors, 162 returned questionnaires giving a response rate of 60%. Responders were more likely to be female and older; there was no difference in proportion of responding donors according to death or survival of the recipient.

The total number of donor follow-up years was 1278. The median follow-up was 4.5 years (range, 0-13.6 years; IQR, 0.6-8.4 years). No autoimmune disorders had been diagnosed during the follow-up period. Table 4 shows the reported long-term morbidity and follow-up outcomes together with the eligibility status of the donors. Fourteen (new) cardiovascular events had occurred and nine malignancies were diagnosed (excluding two donors who had been treated for basal cell carcinoma). In all, four donors are known to have died: one of a

TABLE 4. Follow-up findings in donors

Sex (M/F), age (years) at donation	Interval (year)	Problem during follow-up	Deferral reason (if present)
F, 45 and 24		Persistent symptoms after procedure	
Cardiovascular total n = 14; interval median, 3.5 years (range, 6 weeks-10.5 years)			
F, 70	5.8	Pacemaker implantation	Age
M, 37	3.2	Dissecting aneurysm*	
M, 42	4.9	TIA	
M, 44	2.4	Myocardial infarction	Hypertension
M, 45	6.8	Myocardial infarction	Hypertension
M, 47	0.6	DVT	
M, 50	3.8	Peripheral vascular disease	Other
M, 52	3.7	Myocardial infarction	
M, 54	1.4	Angina pectoris diagnosed	
M, 55	4.9	Myocardial infarction	Hypertension
M, 57	1.5	Coronary revascularization	
M, 58	0.5	Vascular dementia	
M, 60	10.5	Cardioversion for atrial fibrillation	Age
M, 62	0.2	Myocardial infarction	Hypertension
Malignancies total n = 9; interval median, 4.2 years (range, 3.0-10.1 years)			
F, 16	4.1	Hodgkin's lymphoma	
F, 46	4.2	Breast cancer	
F, 51	7.6	Bowel cancer	
F, 52	7.5	Lung cancer*	
F, 55	8.6	Breast carcinoma in situ	
F, 70	3.9	Breast cancer	Age
M, 44	10.1	Glioblastoma	Hypertension
M, 60	3.1	Rectal cancer	Age
M, 66	3.0	Lung cancer*	Age

* Deceased; in addition a female donor in the eligible group, aged 56 at donation, is known to have died but the date and cause are unknown.
DVT = deep vein thrombosis; TIA = transient ischemic attack.

TABLE 5. Incidence rates (IRs) of cardiovascular events and malignancies in study cohort and comparison to general population rates

				Comparison with Dutch general population	
Study population	Events	Person-years at risk	Incidence rate* (95% CI)	Expected IR†	SMR (95% CI)
CVD					
Eligible	7	1080	6.5 (2.5-12.3)	11.5†	0.6 (0.2-1.1)
Deferrable	7	156	44.9 (17.4-85.2)	33.3†	1.3 (0.5-2.6)
Malignancy					
Eligible	5	1086	4.6 (1.4-9.6)	3.9‡	1.2 (0.4-2.5)
Deferrable	4	167	24.0 (6.0-53.9)	10.2‡	2.4 (0.6-5.3)

* Per 1000 person-years.
† Expected rate per 1000 person-years on the basis of age- and sex-specific population figures: "Hospital admission for disease of heart or circulation."
‡ Expected rate per 1000 person-years: incident cancer diagnoses.

cardiovascular event and two from lung cancer while a fourth donor is known to have died but the cause is unknown. Four donors had a new diagnosis of Type 2 diabetes and two, previously controlled on diet alone, had started taking oral antidiabetic agents; one of these six donors was in the deferrable group (for age >60 years). A donor who had suffered from persistent pain at the G-CSF injection site continued to be affected by fibromyalgia-like symptoms over 5 years after donation. The donor who had a femoral venous thrombosis still suffered from functional impairment in the leg and inability to work despite adequate anticoagulant treatment and resolution of the thrombus.

Table 5 shows the incidence rates of cardiovascular events and of malignancies in the study cohort and age- and sex-adjusted rates in the general population. The incidence rate of cardiovascular events in deferrable donors was 44.9 per 1000 person-years (95% CI, 17.4-85.2 per 1000 person-years) in comparison to 6.5 per 1000 person-years (95% CI, 2.5-12.3 per 1000 person-years) in eligible donors. The rates of cardiovascular events and malignancy in deferrable donors were in the range of the expected rates on the basis of age- and sex-specific rates in the general population; that of cardiovascular events in eligible donors was 0.6 times that of the general population (95% CI, 0.2-1.1).

DISCUSSION

In this cohort of related donors, 15% would have not been accepted according to international criteria for unrelated PBSC donation. The likelihood of procedure-related SAEs was similar in these deferrable donors compared to donors who would have qualified as unrelated volunteer donors. The overall incidence of 2% short-term procedure-related SAEs associated with mobilization and PBSC harvest is consistent with figures previously reported in larger series. For instance the Center for International Blood and Marrow Transplant Research and European Group for Blood and Marrow Transplantation reported 15 (1.1%) donation-related adverse events among 1337 allogeneic, mostly related PBSC donors, of which five were catheter-related.[19]

The use of autologous PLT transfusions was implemented in our institution to comply with the guidelines, which do not allow stem cell apheresis if the preapheresis count is below 80×10^9/L and which require daily monitoring until recovery of PLT counts if the postapheresis count is below 50×10^9/L. The procedure and its effect for the donor as well as for the stem cell product have been validated in our center. No adverse transfusion effects were observed.

In our long-term follow-up, the incidence rate of cardiovascular events in deferrable donors was 45 events per 1000 person-years (95% CI, 17-85 events per 1000 person-years) in comparison to 6.5 per 1000 person-years in eligible donors. Rates of malignancy as well as cardiovascular events in both deferrable and eligible donors were in the range of age- and sex-adjusted population rates. The point estimate of the SMR for malignancy in the deferrable group was 2.4; however, the 95% CI is very wide and our data cannot exclude an increased incidence up to 5.3-fold.

A theoretical concern has always been that use of G-CSF might favor the development of malignancy which would only become apparent after several years' latency. The overall number of malignancies in our study was relatively high compared to other studies. Halter and coworkers[8] reported the survey of both related and unrelated donors by the European Group for Blood and Marrow Transplantation, which included almost 100,000 person-years of follow-up of more than 23,000 PBSC donors. A total of 12 hematologic malignancies occurred. While the rate of hematologic malignancy was higher in PBSC donors (1.2 vs. 0.4 in 27,770 former marrow donors) this is probably explained by the higher age of related PBSC donors. Pulsipher and coworkers[15] reported on follow-up findings ranging from 2 days to 99 months, with a median of 49 months, on 2408 unrelated donors (9% older than 50 years at donation) for recipients within the NMDP program; there were 21 nonhematologic malignancies excluding basal cell carcinoma and one case of chronic lymphocytic leukemia. Concerning solid malignancies in former PBSC donors, Hölig and coworkers[14] reported on 3928 unrelated donors in whom a total of eight nonhematologic and four hematologic malignancies occurred. All investigators made comparisons with data for the general population and found no indication of any increase. Our cohort was approximately 9 years older than the donors reported on by Hölig and coworkers who had a median age of 34 years; in our group only two malignancies occurred in donors aged below 40 at the time of donation. Although our data give no reason for concern that there might be a relevant increase in rate of malignancy, our cohort is small with a limited follow-up. More person-years of follow-up would be needed to reject the possibility even of an implausibly high 10-fold increase in rate of malignancies.[20]

The occurrence of autoimmune disease has less frequently been evaluated.[16,21] So far, no investigators have found any indication of an increase of autoimmune conditions. Even if we consider a worsening of existent Type 2 diabetes mellitus as a possible effect of G-CSF, the six cases of new or worsened Type 2 diabetes in our cohort are not in excess of what would be expected.

Our study benefits from the fact that it describes results from a single center using uniform standard procedures; however, the relatively small group of donors remains a limitation. Its retrospective design, in particular the impossibility to trace a large number of donors, is a further limitation. This leads to missing data and a risk of ascertainment bias. The SMR is calculated using age- and sex-specific population rates and the numbers of follow-up years in females and males in each 5-year age band. Hence the result is fully adjusted for the fact that responders tended to be female and older. However, any conclusions are based on the assumption that responders and nonresponders do not differ in their rate of the studied outcomes. In the observational setting the validity of this assumption cannot be tested. The difficulty of follow-up of related donors beyond a year after G-CSF exposure is encountered by other investigators.[16,22,23] In the Netherlands, the standard schedule ends after the 1-year attendance because the recipient's health insurance only reimburses such follow-up to 1 year after donation. In our study this lack of routine follow-up was addressed by postal health questionnaires. However, nearly one-fifth of donors could not be traced and the overall response of 60% is suboptimal.

A strength of the study is that it additionally captured data on CVD in the years after participation in the PBSC procedure. The incidence of late vascular events beyond 4 weeks has to our knowledge never been systematically recorded. The comparison with population data gives no indication of any excess morbidity. However, donors should normally constitute a lower-risk population, which is reflected in the incidence of CVD in the eligible group.

Importantly, the incidence rate of approximately 45 per 1000 person-years in the deferrable donors suggests that the safety margins in this group are smaller. Vascular disease is an important reason for deferring donors in view of the short-term risk of thrombotic complications. The survey by Halter and coworkers[8] describes clustering of cardiovascular events in the first weeks after the procedure. This was not seen in our study population although three cardiovascular events occurred in the 7 months after the procedure.

Raised and/or drug-controlled blood pressure and age were the most frequent reasons for which the related donors would not have been eligible for unrelated donation. Candidate-related donors, most of them being siblings of cancer patients, tend to be older than unrelated donors and age in itself brings increased risks of CVD. In our center the donor assessment is performed by a physician who is not involved with the treatment of the patient. While this prevents any conflict of loyalties and minimizes risk, it is not a strict policy to rigidly defer all donors with one or more characteristics, including age, that would have led to deferral of an unrelated donor. Our data are consistent with other observations and show that if screening is performed as for unrelated donation, a population at lower (cardiovascular) risk will be selected. We also found that related donors who do not meet acceptance criteria for unrelated donors have a higher incidence of cardiovascular events, indicating smaller safety margins. Therefore, these criteria—including age—should in our opinion also be taken into consideration in the assessment of related donors. If a family member presents factors that would lead to deferral for unrelated donation because of potential higher risk of the procedure, it should not be assumed these risks may be accepted even if the donor is willing to proceed for the sake of a family member.

Overall our results show acceptable risks of the use of G-CSF in these related donors concerning most important side effects. The long-term occurrence of CVD and of malignancy for both eligible and deferrable donors falls within the range reported for the population. However, the small size of the study means that the CIs are wide. There is insufficient information to conclude that there are no relevant long-term increases of cardiovascular or malignant disease. Late medical events will not be systematically captured unless active follow-up extends beyond the first year, not only for unrelated but also for related donors. We therefore strongly support efforts by the international transplantation community to ensure long-term follow-up for unrelated donors and related donors as well.[22,23]

In conclusion, this study gives no indication of long-term increased risks of CVD or of malignancies in related donors who have undergone G-CSF mobilization and PBSC apheresis, but cannot exclude this either because of the small size of the cohort.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Related donor selection procedures at Leiden University Medical Center, 1996-2006.