Published in final edited form as:

Transfusion. 2009 March ; 49(3): 513–518. doi:10.1111/j.1537-2995.2008.01983.x.

Ten-year follow-up of unrelated volunteer granulocyte donors who have received multiple cycles of granulocyte–colony-stimulating factor and dexamethasone

Karen Quillen, Phyllis Byrne, Yu Ying Yau, and Susan F. Leitman

Department of Transfusion Medicine, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Maryland.

Abstract

BACKGROUND—The combination of granulocyte–colony-stimulating factor (G-CSF) and dexamethasone is an effective granulocyte mobilization regimen. The short-term side effects of G-CSF are well studied, but the potential long-term effects of repeated G-CSF stimulation in unrelated volunteer granulocyte donors have not been reported.

STUDY DESIGN AND METHODS—Donors who had received G-CSF three or more times for granulocytapheresis between 1994 and 2002 were identified and attempts were made to contact them if they were no longer active donors. They were matched with control platelet (PLT) donors for sex, age, and approximate number of cytopheresis donations. A health history was obtained and complete blood counts (CBCs) and C-reactive protein (CRP) determined where feasible.

RESULTS—Ninety-two granulocyte donors were identified, and 83 of them were contacted. They contributed to 1120 granulocyte concentrates, or a mean of 13.5 granulocytapheresis procedures per donor (and a mean of 87.5 plateletpheresis procedures per donor). There was no difference in CBCs between the granulocyte donors and the control PLT donors. There was no difference in CRP between the two groups, and no difference in pre- and post-G-CSF CRP in a subset of 22 granulocyte donors. Predefined health events included malignancies, coronary artery disease, and thrombosis. At a median 10-year follow-up, there were seven such events in the granulocyte donors and five in the PLT donors.

CONCLUSION—Although the number of granulocyte donors studied is small and continued surveillance of healthy individuals after G-CSF is prudent, our data suggest that G-CSF/dexamethasone stimulation appears to be safe.

Before the mid-1990s, granulocyte transfusion therapy was limited by the inadequate cell dose collected. A single subcutaneous administration of recombinant human granulocyte–colony-stimulating factor (G-CSF) in normal donors followed by leukapheresis 12 to 16 hours later harvested three times the number of functionally normal neutrophils compared with corticosteroid pretreatment;¹ the addition of corticosteroids resulted in even higher donor neutrophil counts.² In most studies, the granulocyte donors were family members of the patient; in a few centers, unrelated volunteer apheresis donors were recruited to undergo G-CSF and dexamethasone mobilization to donate granulocytes for patients.³ Some blood centers are reluctant to administer G-CSF to volunteers because of concerns regarding possible long-term toxicity.

Address correspondence to: Karen Quillen, 88 East Newton Street, H-3600, Boston, MA 02118; kq@bu.edu.

The views expressed in this paper are those of the authors and are not to be construed as the official position of the United States Department of Health and Human Services.

The authors have no conflict to disclose.

The short-term side effects of G-CSF such as bone pain, headache, and myalgia are well studied in standard mobilization regimens for peripheral blood stem cell (PBSC) collection. A single dose of G-CSF plus dexamethasone produces a similar side effect profile compared to G-CSF alone for granulocyte donors.⁴

At least two studies have reported on 2- to 4-year follow-up of related PBSC and granulocyte donors who received G-CSF.^{5,6} The potential long-term effects of repeated G-CSF stimulation in unrelated volunteer granulocyte donors have not been reported and form the basis for this study.

MATERIALS AND METHODS

Volunteer apheresis donors have been recruited to undergo G-CSF and dexamethasone stimulation for granulocytophoresis at our institution since 1994, after appropriate informed consent. The standard regimen after 1996 was a combination of G-CSF and dexamethasone. The dose of G-CSF was 5 µg per kg until July 2005, when it was changed to a uniform dose of 480 µg, given 12 to 18 hours before leukapheresis; the dose of dexamethasone is 8 mg taken orally 12 hours before the procedure. The frequency of granulocyte donations was generally once per month; increased frequency and decreased intervals between mobilizations were considered if the donor was an HLA match for an alloimmunized recipient. Ninety-two granulocyte donors who had received G-CSF three or more times between 1994 and 2002 were eligible for study; 2002 was chosen to make sure the minimum duration of follow-up for the donors would be 5 years. Granulocyte donors were matched with platelet (PLT) donors (who donated during the same period of time) for sex, age (within 5 years), and approximate number of cytophoresis donations.

Active donors (defined as a donation of whole blood and/or apheresis component within the past 2 years) were approached during a regular donation and asked to complete a short customized questionnaire and undergo blood sampling for a complete blood count (CBC) and highly sensitive C-reactive protein (hsCRP) just before the apheresis procedure. Donors who were no longer active were contacted by mail and by phone, to assess their current health status using the same questionnaire. The questionnaire specifically addressed the presence of coronary artery disease (CAD; angina, myocardial infarction, or coronary revascularization) or a history of stroke, deep venous thrombosis, hematologic disease, or cancer. Questions regarding cataract diagnosis and extraction were not addressed, because this is the subject of a separate study. Inactive donors were invited to return for blood sampling or submit the results of a recent CBC they had obtained through their own physician. All donors who could be contacted are included in this study, whether or not blood samples were obtained. A search was made in the social security death index for donors whom we were unable to locate.

The primary health outcome was a composite of CAD, stroke, deep venous thrombosis, and cancer. The incidence of this composite outcome was determined for granulocyte donors and control PLT donors.

CBCs within the past 2 years and hsCRP levels were compared between granulocyte donors and PLT donors who underwent blood sampling. Unstimulated CBCs, generally from a recent plateletpheresis donation, were used for all donors. For granulocyte donors, their baseline (unstimulated) CBCs before the first granulocyte donation were compared to those from the last cytophoresis donation. For PLT donors, the CBC at the first PLT donation or in 1997 (whichever was later) was used for comparison with the most recent CBC available.

A subset of granulocyte donors who underwent granulocytapheresis during the study period had an additional blood sample obtained for hsCRP before receiving G-CSF; in these donors, pre- and post-G-CSF CRP levels were compared.

Statistical analysis

Standard data analysis was performed with a spreadsheet application (Microsoft Excel, Seattle, WA). Data are provided as mean $\pm$ standard deviation (SD) unless otherwise noted. Comparison between the two groups was performed with two-tailed, nonpaired t tests, except for variables over time for the same donor (such as pre- and post-G-CSF hsCRP), which were compared using a paired t test.

RESULTS

We were able to contact 83 of 92 (90%) granulocyte donors. This group of 83 donors contributed to 1120 granulocyte concentrates, a mean of 13.5 granulocytaphereses per person. These donors were matched with 83 control PLT donors, who had never undergone G-CSF-stimulated granulocytapheresis. Donor demographics are shown in Table 1. The median follow-up period was 10.5 years.

In the group of granulocyte donors, there were seven health events: two cases of lymphoma, two cases of solid tumor (one lung cancer, one melanoma), one deep venous thrombosis, and two cases of CAD. In the group of control PLT donors, there were five health events: three cases of solid tumor (one colon cancer, one prostate cancer, one breast cancer), and two cases of CAD. There was no occurrence of stroke in either group.

Recent CBC results were available on 73 granulocyte donors and 76 PLT donors; these are shown in Table 2. There was no statistical difference between the two groups on any variable, including absolute neutrophil count (ANC) and absolute lymphocyte count (ALC). However, comparison of individual granulocyte donors' first and last baseline CBC shows a small but significant ($p < 0.001$) drop in ALC (from 1870 to 1600/ μ L) and ANC (from 3710 to 3280/ μ L); these donors had undergone a mean of 75 lifetime cytapheresis procedures. Comparison of the control PLT donors' first and last CBCs does not show any significant change in ALC and ANC, despite these donors having undergone an average of 105 lifetime cytapheresis procedures.

CRP levels were available on 56 PLT donors and 47 granulocyte donors (unstimulated baseline sample). The CRP was 0.25 ± 0.30 mg per dL for the PLT donors and 0.25 ± 0.23 mg per dL for the granulocyte donors (reference range, 0.8 mg/dL; $p = \text{NS}$). For the 22 donors who underwent pre- and post-G-CSF blood sampling, the pre-G-CSF CRP was 0.27 ± 0.22 mg per dL, and the post-G-CSF CRP was 0.35 ± 0.30 mg per dL ($p = \text{NS}$).

DISCUSSION

This study represents the first report of long-term health outcomes in a cohort of unrelated volunteer granulocyte donors followed for a median of 10 years from the first receipt of G-CSF. Bux and colleagues⁷ reported on 2-year follow-up of 183 granulocyte donors; this group included family and unrelated donors. It was a relatively young group (mean age, 37 years) and, similar to our cohort, contained more than twice as many males as females. The mean dose of G-CSF was $5.1 \mu\text{g}$ per kg (range, $3.6\text{--}10 \mu\text{g/kg}$) given 8 to 16 hours before apheresis without concurrent steroids; consecutive daily or alternate-day collections were performed up to four times per donor. There were no adverse events noted at 2-year follow-up.

The safety of G-CSF administration to healthy individuals has been recently reviewed.^{8,9} The common acute short-term adverse effects of G-CSF administration to normal individuals are well described by our group and others. A rare complication of G-CSF for PBSC mobilization is splenic rupture. The spleen increases in size by 10 percent after 5 days of G-CSF for PBSC collection, returning to baseline 10 days after the administration of G-CSF.¹⁰ Four cases of splenic rupture have been reported in healthy adult PBSC donors, most commonly after 5 days of daily G-CSF administration.^{8,9} Splenic rupture has not been reported in G-CSF-stimulated granulocyte donors, likely reflecting a lower dose of G-CSF, lack of consecutive daily dosing, and the absence of a fluid load which is common after PBSC collection.

There is evidence that G-CSF activates the coagulation system. At least two groups^{11,12} have reported a transient but significant effect of G-CSF on plasma markers of hypercoagulability (prothrombin fragment 1+2, thrombin-antithrombin complex, D-dimer) as well as endothelial activation (thrombomodulin and von Willebrand factor antigens) in 30 healthy PBSC donors receiving G-CSF at 10 to 15 µg per kg per day for 4 to 7 days. These changes normalized within 1 month of G-CSF administration, and no clinical thrombotic events were noted. One granulocyte donor in our series developed a lower extremity deep venous thrombosis 1 month after receiving one dose of 480 µg of G-CSF; he had no other obvious predisposing factors for deep venous thrombosis such as trauma, immobility, obesity, or familial hypercoagulable states. He has remained thrombosis-free 15 months after the discontinuation of oral anticoagulants and has resumed plateletpheresis donation.

Although the effects of G-CSF on PLT function are not consistent among studies,^{13,14} patients with known CAD are at higher risk of vascular events during G-CSF mobilization, as shown during trials of autologous blood stem cell collection for tissue regeneration. Two of 16 patients with treatment-refractory CAD who underwent G-CSF mobilization at 10 µg per kg per day for 5 days experienced myocardial infarction, one on Day 5 of G-CSF and the other (fatal) at 17 days.¹⁵ The German Donor Registry reported one myocardial infarction and three strokes between 3 months and 2.5 years after G-CSF-primed PBSC collections in 3286 healthy allogeneic donors.¹⁶ Another report⁵ of 3- to 6-year follow-up of 101 related donors who received G-CSF for PBSC or granulocyte collections noted one stroke at 15 months in a 27-year-old female with a prior history of Moyamoya disease; she had received 10 µg per kg per day for 4 days for granulocyte collections.

In our study, we chose CRP as a coronary risk factor.¹⁷ In the 22 granulocyte donors who underwent CRP testing before and after one dose of G-CSF, there was no significant change. This is in contrast to the report by Hill and colleagues¹⁵ in patients with known CAD, where CRP increased significantly from 0.45 ± 0.13 to 0.86 ± 0.13 mg per dL after 5 days of G-CSF at 10 µg per kg per day; the difference could be attributable to the lower dose and duration of G-CSF used to mobilize granulocytes. The occurrence of coronary events was not different in the granulocyte donor group compared to the PLT control group (two events in each group, all four donors had identifiable coronary risk factors). This is reassuring given that our granulocyte donors are older than those in other reported series.^{5,7,18}

We obtained recent CBCs (unstimulated) in all active granulocyte and PLT donors and a small number of inactive donors who either returned for blood sampling or forwarded results of a recent CBC from their own medical records. The mean interval between the first G-CSF dose and the most recent CBC was 9 years for the granulocyte donors. All hematologic variables were within the reference range for both groups of apheresis donors, and there was no significant difference between the groups. Specifically, both groups had normal lymphocyte counts and normal neutrophil counts. A recent study⁶ obtained serial CBCs on 94 healthy sibling PBSC donors who received G-CSF (lenograstim) at 10 µg per kg per day

for 5 to 7 days or 12 µg per kg per day for 6 days; the mean G-CSF dose was 4.1 ± 0.9 mg. Thirty donors were followed for at least 4 years (maximum of 7 years). Relative lymphopenia (a mean 13% decrease, compared to pre-G-CSF baseline) was observed in 10 of 83 donors at 1 year and 2 of 30 donors at 4 years, with recovery to baseline thereafter. Relative neutropenia was observed in 23 of 83 donors at 1 year and 4 of 30 donors at 4 years (a mean decrease of 25% in the latter 4 donors, compared to their own pre-G-CSF baseline). In our study, we compared ALCs and ANCs between the PLT donors and the granulocyte donors and found no difference. However, individual granulocyte donors' most recent baseline CBCs did show an 11 percent decrease in ANC and a 14 percent decrease in ALC, compared to their initial baseline counts before the first granulocyte donation, although both ANC and ALC remain within the reference range. In contrast, PLT donors' ANC and ALC did not change in the interval 10 years between CBC assessments. The clinical significance of these findings is uncertain.

We observed four cases of solid tumors, two in each donor group. The PLT donor who had colon cancer died from the disease within 2 years of diagnosis; incidentally, he was referred for workup after *Streptococcus agalactiae* was noted on bacterial screening of the PLT product.¹⁹ The experience of the National Marrow Donor Program (NMDP) reported recently²⁰ included 4015 PBSC donors who had been followed for at least 1 year, and 897 donors followed for 4 or more years (up to 9 years), for a cumulative total of 9785 years of follow-up. In this G-CSF-stimulated donor cohort, 20 cases of cancer were noted, with no organ predilection, consistent with the age-adjusted incidence of cancer in adults in the United States.

The risk of hematologic malignancy, specifically acute myeloid leukemia (AML) and myelodysplastic syndrome, is increased in patients with breast cancer treated with G-CSF.^{21,22} Citing a personal communication from Gratwohl in 2004 on the experience of the European Bone Marrow Transplant registry, Pulsipher and coworkers¹⁶ reported 5 hematologic malignancies out of 16,431 (0.030%) G-CSF-primed PBSC donors, compared to 9 of 28,134 (0.032%) in marrow donors. Bennett and colleagues²³ reported 2 cases of AML in 200 related PBSC donors: in 1 case, AML developed in the donor 4 years after the PBSC donation and 2 other family members also had AML (including the PBSC recipient); the second case involved a donor who developed AML 5 years after undergoing two courses of PBSC mobilization 2 weeks apart (each course consisted of 10 µg/kg/day G-CSF for 5 days) for a sibling with AML. Siblings of patients with AML are at higher risk of AML compared to the general population.²⁴ Lymphocyte aneuploidy persisting up to 9 months has been described in 18 PBSC donors.²⁵ In other studies, DNA microarray analysis in 13 normal PBSC donors before and after G-CSF administration showed transient gene expression modifications in the mononuclear cells.^{26,27} The generalizability and clinical significance of these findings are not clear. In our cohort of granulocyte donors, there were 2 cases of lymphoma: 1 was a 39-year old female who had donated 6 G-CSF-primed granulocyte concentrates in a 1-year period; she was diagnosed with non-Hodgkin's lymphoma less than 1 year after the last dose of G-CSF and is in complete remission more than 5 years after therapy. The second case was a 54-year-old female who had donated 4 G-CSF-primed granulocyte concentrates within an 18-month period; she was diagnosed with chronic lymphocytic leukemia within 6 months after the last dose of G-CSF and continues to have stable disease over the ensuing 9 years. There is no evidence to date supporting an association between G-CSF and lymphoma; specifically, the NMDP experience cited above of 9785 donor-years' follow-up did not note any case of leukemia or lymphoma.

Our study has several limitations. First, the numbers in each donor group were small compared to transplant registry data, thereby limiting the power to detect subtle increases in risk for certain conditions such as autoimmune disorders⁹ or changes in bone metabolism.⁸

Second, there were more active donors in the PLT group, which could be construed as a difference in the magnitude of effort involved in locating inactive granulocyte donors compared to inactive PLT donors. Every effort was made to avoid such an ascertainment bias in that equal numbers of mailings and telephone calls were made to inactive donors, regardless of category. However, active donors by definition meet allogeneic blood donation criteria which would exclude any individual with malignancy. It is possible that the inability to contact 9 of 92 granulocyte donors led to inadvertent underreporting of nonfatal adverse events; we did not locate any inactive donors in the death registry. Finally, there are other long-term aspects of granulocytapheresis donation we did not explore, such as the effects of G-CSF and/or dexamethasone on bone metabolism and cataract development; these are the subjects of separate studies.

Our data suggest that repeated administration of G-CSF and dexamethasone to healthy unrelated granulocytapheresis donors is not associated with long-term adverse vascular, hematologic, or malignancy outcomes, but continued surveillance is necessary.

Acknowledgments

The authors acknowledge the staff and the donors of the Platelet Center, without whose dedication this effort would not have been possible.

ABBREVIATIONS

ALC(s)	absolute lymphocyte count(s)
AML	acute myeloid leukemia
ANC(s)	absolute neutrophil count(s)
CAD	coronary artery disease
CBC(s)	complete blood count(s)
CRP	C-reactive protein
hsCRP	highly sensitive C-reactive protein

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TABLE 1Donor demographics^{*}

Demographic	Granulocyte donors (n = 83)	PLT donors (n = 83)
Sex, male/female	54/29	54/29
Median age, years (range)	56.5 (30–77)	58.5 (29–76)
Percentage of inactive donors	31	20
Number of lifetime cytappheresis procedures (granulocytes and PLTs)	101 ± 65	111 ± 61
Number of lifetime granulocytophesis donations	13.5 ± 8.6	N/A
Number of granulocyte donations per year while active	2.5 ± 1.2	N/A

^{*} Values are given as mean ± SD unless otherwise stated.

TABLE 2

CBCs *

Characteristic	Granulocyte donors (n = 73)	PLT donors (n = 76)	Reference range
Hemoglobin (g/dL)	14.1 (1.1)	14.1 (1.0)	
PLT count ($10^3/\mu\text{L}$)	241 (64)	241 (42)	154–345
WBC count ($10^3/\mu\text{L}$)	5.76 (1.59)	6.15 (1.45)	3.3–9.6
ANC ($10^3/\mu\text{L}$)	3.42 (1.21)	3.73 (1.04)	1.58–5.28
ALC ($10^3/\mu\text{L}$)	1.59 (0.57)	1.70 (0.53)	0.71–1.87
Absolute monocyte count ($10^3/\mu\text{L}$)	0.53 (0.17)	0.52 (0.16)	0.21–0.66
Absolute eosinophil count ($10^3/\mu\text{L}$)	0.17 (0.14)	0.15 (0.08)	0.02–0.23
Absolute basophil count ($10^3/\mu\text{L}$)	0.04 (0.04)	0.04 (0.04)	0.00–0.07

* All values are reported as mean (SD). All comparisons between the two groups are not significant.