Follow-up of healthy donors receiving granulocyte colony-stimulating factor for peripheral blood progenitor cell mobilization and collection. Results of the Spanish Donor Registry

Javier de la Rubia, Felipe de Arriba, Cristina Arbona, María J. Pascual, Concha Zamora, Andrés Insunza, Dorleta Martínez, Carmen Paniagua, Miguel A. Díaz, and Miguel A. Sanz

Hematology Service, University Hospital La Fe Valencia, Spain

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Correspondence:
Javier de la Rubia
Hematology Service, University Hospital La Fe, Avda. Campanar, 21
46009 Valencia, Spain.
E-mail: delarubia_jav@gva.es

ABSTRACT

Background

Information about the long-term follow-up and safety of granulocyte colony-stimulating factor administration to healthy donors is limited. The aims of this study were to analyze the side effects of granulocyte colony-stimulating factor administration in donors included in a Spanish Registry of hematopoietic stem cell donors and to determine the long-term outcome of these donors.

Design and Methods

The Spanish National Donor Registry was developed to record the short- and long-term results of granulocyte colony-stimulating factor administration to mobilize peripheral blood progenitor cells in normal donors. To date, 1436 donors (771 males, 665 females) with a median age of 37 years (range, 1 to 74 years) have been registered. Granulocyte colony-stimulating factor was the only cytokine administered. A baseline investigation was performed in every donor before granulocyte colony-stimulating factor administration and follow-up investigations (controls) were planned at 4 weeks and annually thereafter for up to 5 years after the mobilization.

Results

At least one of the scheduled controls was performed in 736 donors, while 320 donors have been followed for 2 years or more. The peripheral white blood cell count decreased significantly from 6.8×10^9/L at baseline to 5.9×10^9/L at 4 weeks after leukapheresis ($p<0.0001$) and remained at values lower than those observed premobilization until 2 years after mobilization. In contrast, hemoglobin concentration and platelet count returned to normal values within 1 year after mobilization. Bone pain (90%) and headache (33%) were the most frequently reported granulocyte colony-stimulating factor-related side effects. Five patients (0.68%) were diagnosed as having solid tumors (lung cancer in two patients and thyroid carcinoma, choroid melanoma, and colon carcinoma in one patient each) between 10 and 64 months after administration of granulocyte colony-stimulating factor. No hematologic malignancies have been reported.

Conclusions

The clinical side effects of granulocyte colony-stimulating factor administration in healthy donors are generally mild. Changes in blood counts were minimal and mainly affected white blood cell counts, which returned to normal values within 2 years after granulocyte-colony stimulating factor administration. No patient developed a hematologic malignancy. A larger number of donors and longer follow-up are needed to determine the safety of granulocyte colony-stimulating factor administration definitively.

Key words: Healthy donors, granulocyte colony-stimulating factor, follow-up, side effects.

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Introduction

Peripheral blood is currently the main source of hematopoietic stem cells for patients requiring an allogeneic transplantation.[1–3] Granulocyte colony-stimulating factor (G-CSF) is the cytokine administered most frequently to healthy donors as part of the regimen to mobilize progenitor cells into the peripheral blood for collection and has been administered to thousands of related and unrelated donors worldwide.[4] Although the short-term toxicity of G-CSF in this population has been analyzed exhaustively,[5-11] data on the long-term impact of G-CSF in normal donors are scarce, and only a few series, involving small numbers of donors, have addressed this point.[12–15] It is important to understand the side effects of G-CSF administration in this population more comprehensively in order to provide consistent information for the long-term follow-up of G-CSF-primed donors of peripheral blood progenitor cells.

The development of nation-based donor registries can help in recruiting a sufficient number of donors with adequate follow-up to study the long-term effects of G-CSF in donors. In the United Kingdom, the British Research on Adverse Drug Events and Reports (RADAR) [16] project, a National Cancer Institute-funded research program, identifies and disseminates clinical information on adverse drug reactions, with a particular emphasis on drugs used in hematology and oncology and as part of studies on serious adverse events. Likewise, in 1998 Spain developed a multicenter national donor registry involving 23 centers with the primary aims, among other objectives, of improving the efficiency of cell mobilization and harvesting techniques, as well as exploring the short- and long-term biological and clinical effects of G-CSF in normal donors. The objectives of this study were, first, to analyze the side effects observed during G-CSF administration in donors included in the registry, and, second, to present the long-term results of follow-up of a large number of donors.

Design and Methods

Data collection

Information about peripheral blood progenitor cell mobilization and harvesting was collected prospectively and monitored by means of a standardized data sheet.[10] Detailed, written informed consent was obtained from each donor before the start of the procedure. Informed consent was obtained from guardians of minors.

Donor registration

Donors were included in the registry when they were administered G-CSF for peripheral blood progenitor cell mobilization. At the time of the initial assessment (baseline), general information concerning the donor, including age, sex, and grade of HLA matching, was collected. Complete blood counts and biochemistry surveys were performed. Blood chemistry data included the concentrations of glucose, urea nitrogen, creatinine, uric acid, total bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase. Donors were also questioned about side effects observed during G-CSF administration. Adverse events were recorded and graded according to the duration of symptoms, and whether the donors required medication for pain or symptom relief.

Long-term follow-up protocol design

As mentioned above, one of the main objectives of the registry is to collect information about the long-term side effects of G-CSF administration with special emphasis on the development of severe complications such as neoplastic diseases. To achieve this goal, donors underwent several follow-up controls after donation. The first one (control #1) was performed within 4 to 6 weeks after mobilization. At that time, the complete physical examination and hematologic and chemistry profiles performed at baseline were repeated. The remaining five controls (control #2 to control #6) were planned to be done annually for 5 consecutive years. To evaluate possible changes in hematologic parameters, the same variables measured at baseline were measured at every follow-up control. Likewise, a complete physical examination was performed at the center responsible for harvesting the peripheral blood progenitor cells, or was done by a general practitioner for donors who had to travel a long distance to the mobilization service. Controls consisting of only mail or telephone calls were not accepted as follow-ups.

Donors' characteristics

From January 1998 to December 2006, 1436 healthy donors who underwent 1538 mobilization procedures in 23 Spanish centers were registered and assessed for short-term side effects. There were 771 men and 665 women whose median age was 37 years (range, 1 to 74 years). The main characteristics of the donors are shown in Table 1. Only those donors who had at least one of the scheduled controls have been included in the follow-up part of the study.

Statistical analysis

Statistical analysis was performed using BMDP statistical software. The baseline and follow-up complete blood counts were compared using the non-parametric Wilcoxon's signed ranked test. The variables compared were the white blood cell and platelet counts, as well as the hemoglobin concentration.

Results

Short-term side effects

Information about side effects observed during G-CSF administration was available for 1278 of the 1538 mobilization procedures (82%), of which 870 (68%) presented with some G-CSF-related toxicity. Bone pain was observed most frequently (784 donors, 90%), followed by headache (290 donors, 33%), fever (56 cases,

Table 1. Donors' characteristics.

	With follow-up	*Without follow-up N. (%)*	*Overall series*
Donors	736	700	1436
Mobilization procedures			1538
Age (years), range	37 (1-74)	37 (1-74)	37 (1-74)
Sex			
Male	394 (53)	377 (54)	771 (54)
Female	342 (47)	323 (46)	665 (46)
G-CSF form[a]			
Filgrastim	590 (80)	607 (76)	1197 (78)
Lenograstim	141 (19)	150 (19)	291 (19)
Unknown	5 (1)	45 (5)	50 (3)
Dose of G-CSF (μg/kg per day), range	11 (5-22)	10 (4-23)	10 (4-23)
Type of donor[b]			
Identical sibling	599 (87)	637 (89)	1236 (88)
Non-identical related	35 (5)	52 (7)	87 (6)
Unrelated	37 (5)	15 (2)	52 (4)
Monozygote twin	19 (3)	13 (2)	32 (2)
Venous access[a]			
Peripheral	686 (86)	627 (84)	1313 (85)
Central	86 (11)	70 (9)	156 (10)
Unknown	23 (3)	46 (7)	69 (5)
Leukapheresis, n; range	1 (1-4)	1(1-5)	1 (1-5)

[a]According to the number of mobilization procedures; [b]available for 1407 cases.

Table 2. Common symptoms during G-CSF administration reported by peripheral blood progenitor cell donors included in the Spanish Donor Registry.

Symptoms	*N. of donors (%)*
Myalgia	784 (90)
Headache	290 (33)
Fever	56 (6)
Asthenia	54 (6)
Nausea, vomiting	44 (5)
Sweating	19 (2.2)
Insomnia	16 (1.3)

6%), fatigue (6%), and nausea (5%). Bone pain was treated easily with common analgesics such as acetaminophen or ibuprofen, and the symptoms generally resolved within 1 week after discontinuation of G-CSF administration. Other less common effects attributed to G-CSF were sweating and insomnia, which were observed in 19 (2.2%) and 16 (1.3%) donors, respectively. Two donors with previous hyperuricemia had gout crises during the mobilization procedure. One donor developed thrombocytopenia 1 month after mobilization. A bone marrow study excluded myelodysplastic syndrome and the donor was diagnosed as having immune thrombocytopenia.

Although there were no mobilization-related deaths, some rare but serious side effects of G-CSF were reported. One donor had a splenic rupture 12 hours after the last leukapheresis, which required splenectomy. This case has been reported elsewhere.[16] Another donor developed pneumothorax after central venous line placement. This was the only central line-related complication and resolved without sequelae. Table 2 describes the most frequent adverse events after peripheral blood progenitor cell mobilization.

Long-term follow-up

At least one of the scheduled controls was performed in 736 of the 1436 donors (51%) included in the registry, and 320 were followed for 2 years or more. These donors are included in the follow-up part of the study (Table 3). The white blood cell count was significantly lower at 4 weeks after leukapheresis than at baseline (5.9×10^9/L *vs.* 6.8×10^9/L; $p<0.0001$). At control #1, the hemoglobin concentration was lower than before mobilization (13.8 g/dL *vs.* 14.3 g/dL; $p<0.0001$). In contrast, the platelet count was higher 4 weeks after mobilization than at baseline (247×10^9/L *vs.* 240×10^9/L; $p=0.002$) (Table 3). In 23 (3.5%) of the 650 donors undergoing control #1, the white blood cell count was below normal values ($<3.5\times10^9$/L), while at that time only three (0.5%) donors had a platelet count lower than the basal value ($<130\times10^9$/L). Both hemoglobin concentration and platelet count returned to baseline values within 1 year after mobilization and remained at this level for the rest of the follow-up, with only one donor presenting thrombocytopenia during the first 2 years of follow-up (Table 3). In contrast, the median white blood cell count 1 year after mobilization remained lower than the baseline value (7.1×10^9/L *vs.* 6.6×10^9/L; $p=0.025$) although only three donors had a white cell count < 3.5×10^9/L. The median white blood cell count returned to pre-mobilization values 1 year later, and remained stable during the remaining follow-up controls. Table 3 shows the results of the complete blood counts performed at baseline and during the different controls. Finally, no significant abnormalities in serum chemistry values attributable to G-CSF administration were observed during follow-up controls (*data not shown*).

Neoplastic diseases

During the follow-up, five of the 736 (0.68%) evaluable donors developed a neoplastic disease between 10 and 64 months after G-CSF administration. Both donors diagnosed with lung cancer had a history of tobacco smoking, and the patient with carcinoma of the colon had had Hodgkin's lymphoma, which was managed with chemotherapy and radiotherapy, 16 years prior to the peripheral blood progenitor cell donation. So far, no hematologic malignancies have been reported to the registry. The characteristics of donors diagnosed with tumors after G-CSF administration are shown in Table 4.

Discussion

Since the introduction of G-CSF as a way of mobilizing progenitor cells into peripheral blood in healthy donors, one of the main concerns has been the long-term safety of the administration of this cytokine. Our

Table 3. Complete blood counts in the donors at baseline and during follow-up.

	Basal (n = 736)	Control #1 (n = 650)	Control #2 (n = 320)	Control #3 (n = 209)	Control #4 (n = 144)	Control #5 (n = 95)	Control #6 (n = 73)
Age	37 (1-74)	37 (1-74)	36 (2-68)	37 (4-68)	36 (1-68)	35 (2-68)	32 (1-68)
Sex (M/F)	393/341	337/313	157/163	104/105	74/70	47/48	38/35
G-CSF dose	11 (5-22)	11 (5-22)	11 (5-20)	11 (5-20)	11 (5-20)	11 (5-16)	11 (5-20)
N. of collections	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)	1 (1-4)
Complete blood count							
WBC ($x10^9$/L)	7.1 (1.7-15.06)	5.9* (2.2-43)	6.6*** (2.7-15.5)	6.7 (1.5-11.9)	6.9 (3.6-15.3)	7.0 (3.7-15.8)	6.75 (3.4-13.1)
Hemoglobin (g/dL)	14.3 (9.1-18.9)	13.8* (9.4-17.6)	14.2 (11.1-18)	14.4 (11.4-17.1)	14.3 (11.4-18.7)	14 (11-17.2)	14 (8.2-17.5)
Platelets ($x10^9$/L)	240 (72-544)	247** (76-631)	239 (95-570)	241 (82-387)	250 (130-447)	250 (147-498)	248 (163-413)

*Values are expressed as median (range); *p<0.0001; **p=0.002; *** p=0.025; WBC, white blood cells.*

Table 4. Malignancies diagnosed after the administration of G-CSF.

Donor #	*Age*	*Sex*	*G-CSF dose (μg/kg per day)*	*Event*	*Months after G-CSF*
229	23	Female	5	Choroid melanoma[a]	64
964[b]	45	Male	12	Colon cancer	61
1385	47	Female	12	Lung cancer	39
1722	25	Female	10	Thyroid carcinoma	12
1806	49	Male	15	Lung cancer	10

[a]*Left eye;* [b]*previous history of Hodgkin's disease.*

study is the largest prospective series reported so far involving long-term follow-up after administration of G-CSF in healthy donors. Started in 1998, the registry collates the clinical and laboratory findings in donors of peripheral blood progenitor cells subjected to G-CSF mobilization in several Spanish hospitals.

The main short-term clinical adverse effects were similar to those already described and reproduced, those reported previously by our registry; mild bone pain and headache were the toxicities observed most frequently.[5–11] In contrast to our previous experience, we also documented some rare but serious cases of G-CSF toxicity in normal donors, including one patient with spontaneous splenic rupture.[17] Several studies have evaluated the effects of short-term administration of G-CSF on the spleen in normal donors and patients with cancer or neutropenia.[18-20] These studies show a median increase of 11 mm in spleen length in G-CSF recipients.[19,20] At least four cases of splenic rupture have been associated with an increase in spleen size in healthy adult donors.[21] This highlights the need to include this complication when informing healthy donors about the potential risks of the process of peripheral blood progenitor cell mobilization.

Other uncommon side effects observed were insomnia, also reported in other series, although with a higher incidence,[4,9] and hyperuricemia, probably related to the large increase in white blood cell count associated with G-CSF administration. Some groups have reported flare-ups of autoimmune disorders after G-CSF administration,[21,22] although others have not.[23] We registered only one donor who developed immune thrombocytopenia shortly after mobilization, although the relationship with growth factor administration remains unproven. So far, the data on the short-term safety of G-CSF in healthy donors indicate that this cytokine is generally well tolerated. However, the appearance of several uncommon and potentially serious toxicities of G-CSF supports the recommendation that every donor receiving G-CSF should be informed thoroughly of its potential adverse effects.

Post-donation cytopenia, which is a well-known adverse effect in peripheral blood progenitor cell donors, is partly related to the apheresis procedure, which removes a large number of blood cells, although an additional G-CSF-related effect, especially on platelets, cannot be ruled out.[10,15,24-26] Contrary to reports by other groups,[25] we observed a prolonged decrease in white blood cell count, lasting up to 2 years after G-CSF administration, even though the count was within the normal range in the great majority of the donors. This difference probably reflects the higher number of donors in our series, which gave sufficient power to detect significant differences. The lower white blood cell count could be attributed to long-term lymphopenia and neutrophil reduction.[15,26] Unfortunately, lymphocyte and neutrophil counts are not recorded routinely in our registry, and additional studies are required to establish definitively the evolution of white blood cell populations during G-CSF administration. From the clinical point of view, no infections were registered during the follow-up.

Since 1999, we have observed five cases of solid tumors, a rate that is consistent with the age-adjusted Spanish incidence of cancer in adults during this period.[27,28] Originally, a 5-year follow-up was recommended for our registry. However, we note that in two of the five donors who developed a solid tumor, cancer was diagnosed after the initially scheduled 5-year follow-up (61 and 64 months), raising the questions of whether 5 years is long enough and whether these donors should undergo annual follow-ups for the rest of their lives.

Regardless of these factors, the most important point

concering G-CSF administration to normal donors is whether this cytokine can induce or contribute to leukemogenesis in this population. The answer to this question is unknown at this point. The previously mentioned RADAR project identified two previously healthy individuals who received G-CSF and subsequently developed acute myeloid leukemia[16] and there are also reported other isolated cases of leukemia occurring in volunteer donors 4 to 5 years after exposure to G-CSF.[29] We have detected no case of hematologic malignancy in our registry, although the number of donors with prolonged follow-up is still low. The other cases might reflect an increased genetic risk in relatives of patients with leukemia. On the other hand, although laboratory investigations suggest that G-CSF administration might have leukemogenic potential in malignant cells, these findings are non-specific and the effects of short-term G-CSF stimulation on genomic stability and chromatin remodeling are unclear.[30-33] Likewise, the long-term consequences of these changes, if any, are unknown and the concerns remain largely speculative. Although the number of donors with prolonged follow-up is still insufficient, our findings as well as those from other large series,[14,22] in which there were no cases of leukemia or lymphoma associated with short-term G-CSF therapy, should reassure individuals who receive G-CSF for peripheral blood progenitor cell mobilization. If an association between G-CSF and an increased incidence of acute myeloid leukemia exists, it will not be easy to identify: more than 2000 donors will have to be followed for at least 10 years in order to detect a 10-fold increase in leukemia risk following G-CSF administration and detection of a smaller risk would require an even greater sample size.[34] Thus, it is strongly recommended that healthy donors are encouraged to partecipate in well-designed programs for follow-up monitoring.

Although our study is based on one of the largest donor cohorts so far reported, it has several limitations. Nearly 50% of the donors included in the registry have not been followed-up, and the number of donors followed for 2 years or more (319 cases) is still too low to draw decisive conclusions. This low follow-up rate could be due, partly, to poor donor adherence to the follow-up program and lack of motivation for psychological and personal reasons. Similarly, transplant physicians might perceive that mobilization and collection of peripheral blood progenitors cells is a low-risk, short-term technique, and that once the stem cells have been harvested, there is no need for further donor monitoring. Finally, although prospective, because ours is a voluntary registry, not every Spanish donor has been included and some events might not have been identified.

In summary, our results confirm that mild bone pain is the most frequently observed complication following G-CSF administration, although on very rare occasions, more serious complications can occur. Although we acknowledge the limitations of this study, our results, showing no increased cancer risk, help to resolve the question of the contribution of G-CSF administration to serious long-term side effects in healthy donors. However, until more definitive data are available, caution is still warranted, and larger cohorts of donors and more mature prospective data are needed before any doubts can be put to rest completely. Greater cooperation between major national and international registries would be of considerable help in conclusively determining whether normal donors have long-term risks from the administration of G-CSF.

Authorship and Disclosures

Provision of donors: JdlR, FdA, CA, MJP, CZ, AI, DM, CP, MAD; collection and assembly of data: JdlR, FdA, CA, MJP, CZ, AI, DM, CP, MAD; data analysis and interpretation, manuscript writing: JdlR, MAS; final approval of manuscript: JdlR, FdA, CA, MJP, CZ, AI, DM, CP, MAD, MAS. The authors reported no potential conflicts of interest.

Appendix

The following institutions and clinicians participated in this study: Madrid, H La Princesa (Dr. A Alegre); Valencia, H Clínico (Dr. C Arbona); Murcia, H Morales Messeguer (Dr. F de Arriba); Madrid, H La Paz (Dr. R Arrieta); Madrid, H Puerta de Hierro (Dr. L Barbolla); Barcelona, H Sant Pau (Dr. S Brunet); Salamanca, H Clínico (Dr. C del Cañizo); Madrid, H Niño Jesús (Dr. MA Díaz); Sevilla, H Virgen del Rocío (Dr. I Espigado); Palma de Mallorca, H Son Dureta (Dr. A Galmes); Santander, Banco de Sangre de Cantabria (Dr. A Insunza); San Sebastián, H Donostia (Dr. D Martínez); Barcelona, H Clinic (Dr. C Martínez); Madrid, Fundación Jiménez Díaz (Dr. C Paniagua); Málaga, H Carlos Haya (Dr. MJ Pascual); Barcelona, Institut Catalá d'Oncologia (Dr. J Petit); Badalona, H Germans Trias i Pujol (Dr. JM Ribera); Valencia, H La Fe (Dr. J de la Rubia); Madrid, H 12 de Octubre (Dr. J de la Serna); Madrid, H Gregorio Marañón (Dr. D Serrano); CTBT (Dr. M Torrabadella); Valencia, H La Fe (Dr. A Verdeguer); Madrid, H Ramón y Cajal (Dr. C Zamora).

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