Spleen enlargement following recombinant human granulocyte colony-stimulating factor administration for peripheral blood stem cell mobilization

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Background and Objectives. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) is widely used to mobilize peripheral blood stem cells (PBSC) for autologous or allogeneic transplants. Such treatment may cause spleen enlargement; exceptionally, spontaneous spleen rupture has been reported. We investigated changes in spleen size during stem cell mobilization.

Design and Methods. We evaluated spleen size, comparing palpation with ultrasound (US)-evaluated longitudinal diameter and volume, in 13 healthy donors and 22 patients with a hematological malignancy who were undergoing PBSC mobilization with rhG-CSF-including regimens.

Results. Intraobserver and interobserver variability of US-calculated spleen volume was very low; the correlation between the volume calculated by US and that measured by 3-dimensional computed tomography was excellent. During mobilization, spleen enlargement was detected by palpation in 17% of subjects, by US-measured longitudinal diameter in 60%, and by US-calculated volume in 91%. The median increase in spleen volume was 300 mL (range, 54-820; $p<0.001$) in healthy donors and 135 mL (range, 0-413; $p=0.004$) in the group of patients; the enlargement correlated with white blood cell count elevation ($p=0.016$) but not with circulating CD34$^+$ cells. One month after the last administration of rhG-CSF, the median decrease was 160 mL (range, 35-800) in healthy donors and 58 mL (range, 0-310) in patients.

Interpretation and Conclusions. When evaluated by sensitive methods, rhG-CSF caused spleen enlargement in almost all individuals treated. US-calculated volume proved to be an excellent method, much better than longitudinal diameter, for detecting non-palpable splenomegaly induced by rhG-CSF.

Key words: spleen enlargement, rhG-CSF, peripheral blood stem cell collection, ultrasound scan.

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Peripheral blood stem cells (PBSC) are increasingly being used as an alternative to bone marrow for autologous or allogeneic transplants.[1] Recombinant human granulocyte colony-stimulating factor (rhG-CSF) alone or in combination with other drugs is highly effective in mobilizing stem cells, and available data regarding its short- and long-term toxicity have shown no serious adverse effects.[2,3] However, about one-third of neutropenic patients chronically treated with rhG-CSF develop palpable splenomegaly,[4] and there have been reports of spontaneous spleen rupture in rhG-CSF- or cyclophosphamide plus rhG-CSF-mobilized individuals,[5-7] or even in patients treated with rhG-CSF or rhGM-CSF after chemotherapy for acute leukemia or lymphoma.[8,9] Few data are available on changes in spleen size as a result of a brief course of rhG-CSF.[10,11] We tested the accuracy of ultrasound (US)-calculated spleen volume compared with palpation and US-measured longitudinal diameter in detecting changes in spleen size in two groups of subjects whose PBSC were mobilized by rhG-CSF-including regimens (healthy donors for allogeneic transplant, and patients scheduled for autologous transplant). We compared spleen volume changes in the two groups of subjects, and correlated the changes with the mobilizing regimen used and with circulating leukocyte and CD34$^+$ cell counts. In a subgroup of patients, we assessed interobserver variability of US measurements and examined the correlation between US-calculated and computed tomography (CT)-measured spleen volume. Finally, in 10 healthy volunteers we assessed reference ranges for US volume and intraobserver variability of US measurements.

Design and Methods

We prospectively studied 35 consecutive subjects (healthy donors or patients affected by a hematologic malignancy) who underwent mobilization to collect PBSC for allogeneic or autologous transplant. After written informed consent, the healthy donors received a mobilization regimen of *s.c.* rhG-CSF (Lenograstim, Italfarmaco, Rome, Italy) 263 μg twice a day, while patients received i.v. cyclophosphamide 7 g/m^2 plus s.c. rhG-CSF 263 μg once a day starting the day after the administration of cyclophosphamide (with the exception of patients with acute myeloid leukemia, who were mobilized with rhG-CSF only, 263 μg once a day, at recovery after consolidation chemotherapy). Flow cytometric counts of CD34$^+$ cells were monitored by a flow cytometer (FAC-

Scan, Becton Dickinson, San Jose, CA, USA) and expressed as cells/μL.[12] Circulating leukocytes, neutrophils and $CD34^+$ cells were evaluated in all subjects on the day of the last rhG-CSF administration. PBSCs were collected by a double lumen venous catheter or venipuncture of both arms, performing large-volume apheresis with a continuous-flow cell separator (Spectra, COBE, Lakewood, CO, USA).

All spleen US scans were performed by the same operator, who used an EUB 525 Hitachi (Tokyo, Japan) instrument with a 2.5/3.5-MHz broadband curvilinear probe. Three scans were obtained for each subject: 1) the day before starting rhG-CSF, 2) the day of PBSC harvest, soon before collection, in mobilized donors (or the last day of rhG-CSF administration in the case of unsuccessful mobilization), 3) one month after rhG-CSF withdrawal. The spleen was scanned in the longitudinal and transverse planes by an intercostal and/or subcostal approach in subjects in the fasting state, in the supine or right-sided position, until complete organ visualization had been achieved. Longitudinal diameter, perimeter and area, defined as the maximum measurements with splenic borders and angles clearly defined, were measured, and the software of the US machine automatically calculated (area-length method: volume= $8 \times \text{area}^2/3 \times \pi \times$ longitudinal diameter) the volume (in milliliters), as already reported.[13] For each subject, the mean value of 3 measurements repeated on the same occasion was calculated and recorded for the final analysis.

In 10 healthy volunteers (matched for sex, age, and body-surface area with the cohort of subjects analyzed) we established reference values for US-calculated spleen volume and repeated the measurements 3 times at 1-week intervals to evaluate intraobserver reproducibility. In 3 unselected patients the US scan was repeated on 3 occasions (pre-, during-, and post-rhG-CSF course) by another operator unaware of the previous results and using the same US machine (interobserver reproducibility).[14] After additional informed consent, spleen CT scanning was performed in these 3 patients soon after the US examinations. Spleen axial images were obtained by a multirow helical instrument (Mx 8000; Marconi Medical Systems, Cleveland, OH, USA) to produce a 3-dimensional model (including length, width, thickness and cross-sectional area) used to calculate spleen volume automatically.[15] Technical parameters included a 6.5-mm slice width with identical reconstruction index, pitch 1, 200 mA, 120 kilovolt potential, and a rotation time of 0.75 seconds.

Statistical evaluations, including χ^2 testing, analysis of variance with Bonferroni's correction and Pearson's correlation, were performed with SPSS for Windows software (version 9.0, SPSS, Chicago, IL, USA).

Results

Characteristics of healthy donors and patients

As shown in Table 1, we analyzed 13 healthy donors and 22 patients affected by multiple myeloma (n=11), aggressive non Hodgkin's-lymphoma (n=4), acute myeloid leukemia (n=4) or Hodgkin's lymphoma (n=3) who had received chemotherapy courses 1 to 3 months before mobilization. The median age was 38 years (range, 28-55) and median body-surface area 1.8 m^2 (range, 1.6-2.1) for healthy donors, and 51.5 years (range, 18-63) and 1.8 m^2 (range, 1.5-1.98) for patients. No subject had palpable splenomegaly at entry to the study. During the study, screenings for infectious diseases possibly associated with splenomegaly (hepatitis A, B, and C viruses, human immunodeficiency virus 1/2, Epstein Barr virus, herpes simplex virus, varicella zoster virus, cytomegalovirus, toxoplasma sp.) and for the underlying hematologic malignancy were performed. No current viral or toxoplasma infection was detected, and in all patients the underlying hematologic disease was stable.

Spleen size assessment by different methods

In 10 healthy volunteers used for reference values, US-measured spleen longitudinal diameter ranged from 8 to 11.5 cm (median, 10) and US-calculated volume from 70 to 300 mL (median, 240). Intraobserver and interobserver reproducibility of spleen volume evaluation by US scan was excellent, with a Pearson value of 0.93 and 0.91, respectively. Spleen volume evaluation by US and CT scanning were well correlated, with a Pearson value of 0.94 ($p<0.001$) (Figure 1A).

Spleen size changes following rhG-CSF administration

In the 35 subjects analyzed during mobilization, splenomegaly was detected by palpation in 6, by US assessment of longitudinal diameter in 9, and by US assessment of volume in 27 (Figure 2). Compared to pre-rhG-CSF status, the spleen was found to be enlarged by palpation in 6, by US assessment of longitudinal diameter in 21 and by US assessment of volume in 32. Volume assessment had significantly higher sensitivity in detecting spleen enlargement than did the measurement of longitudinal diameter and palpation (91% of subjects versus 60% and 17%, respectively; $p=0.001$). Pre-rhG-CSF, spleen volume ranged from 81 to 380 mL (median, 254) in healthy donors and from 50 to 567 mL (median, 232) in patients. On the last day of rhG-CSF administration, spleen volume was enlarged in 13/13 healthy donors (median, 470 mL; range, 135-1200 mL) and in 19/22 patients (medi-

Table 1. Characteristics of patients and healthy donors.

Nr.	Sex	Age	Dx	Previous CHT	Mobilization CTX*	Mobilization G CSF°	WBC peak $\times 10^9$/L	CD34+ cell peak/μL	Spleen volume (mL) before	Spleen volume (mL) during	Spleen volume (mL) after
1	F	33	Hdon		–	2×5	85.5	118	270	600	312
2	F	45	Hdon		–	2×6	56.5	70	287	370	300
3	M	38	Hdon		–	2×6	54.0	43	280	650	350
4	F	29	Hdon		–	2×5	53.4	66	254	406	246
5	F	28	Hdon		–	2×6	53.3	175	232	583	319
6	M	32	Hdon		–	2×7	51.6	66	380	1200	400
7	M	30	Hdon		–	2×8	50.0	10	170	470	390
8	F	35	Hdon		–	2×6	45.0	90	150	450	350
9	F	39	Hdon		–	2×6	44.8	90	250	350	280
10	F	41	Hdon		–	2×4	40.1	80	336^	450	400
11	F	55	Hdon		–	2×6	36.0	118	81	135	100
12	M	39	Hdon		–	2×6	30.6	98	200	660	400
13	M	38	Hdon		–	2×7	30.8	40	376	671	370
14	F	44	MM	Thal+D	+	1×12	30.0	10	240	520	280
15	F	63	MM	VAD	+	1×13	16.5	155	215	467	210
16	F	44	MM	Thal+D	+	1×10	14.3	52	220	360	310
17	F	54	MM	VAD	+	1×17	13.0	5	80	80	80
18	F	57	MM	VAD	+	1×13	10.0	211	50	130	100
19	F	53	MM	VAD	+	1×13	10.0	46	407	820	600
20	F	57	MM	VAD	+	1×13	9.8	78	180	560	250
21	F	46	MM	Thal+D	+	1×7	5.9	80	210	270	250
22	F	32	MM	VAD	+	1×12	2.4	153	350	350	350
23	F	53	MM	VAD	+	1×12	2.1	101	73	170	160
24	M	59	MM	Thal+D	+	1×12	1.8	30	225	458	300
25	M	47	NHL	CHOP	+	1×11	10.8	148	320	360	310
26	F	52	NHL	CHOP	+	1×13	9.0	10	418#	680	510
27	M	49	NHL	CHOP	+	1×13	7.5	37	66	114	70
28	M	55	NHL	CHOP	+	1×12	5.0	34	567#	770	600
29	F	35	AML	AML-12	–	1×6	16.8	35	370	510	360
30	M	51	AML	AML-12	–	1×6	16.4	51	104	176	110
31	F	55	AML	AML-12	–	1×5	16.0	97	240	370	360
32	M	40	AML	AML-12	–	1×13	3.0	4	260	260	260
33	F	24	HL	VEBEP	+	1×12	24.0	70	200	328	300
34	F	32	HL	VEBEP	+	1×8	20.0	30	280	490	320
35	M	18	HL	VEBEP	+	1×12	16.1	29	330	600	400

*Hdon: healthy donor; MM: multiple myeloma; NHL: non-Hodgkin's lymphoma; AML: acute myeloid leukemia; HL: Hodgkin's lymphoma; Thal+D: thalidomide and dexamethasone; VEBEP: an ABVD-like regimen including vinblastine, etoposide, bleomycin, epirubicin and prednisone; AML-12: induction and consolidation according to the EORTC-GIMEM Protocol. *Cyclophosphamide 7 g/m^2; °Vials per day x number of days; ^a donor with β-thalassemia trait; #patients with spleen involved by lymphoma.*

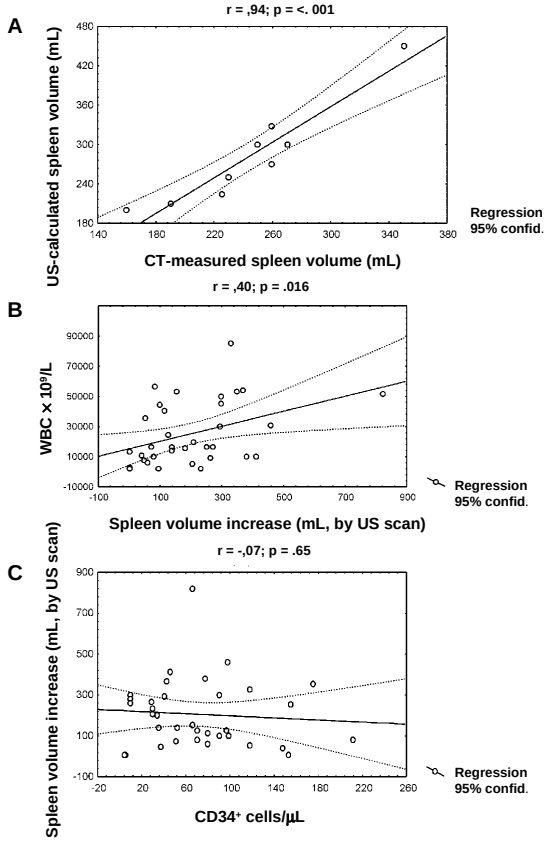

Figure 1. Statistical correlations. (A) Correlation between US-calculated volume and 3-dimensional CT-measured volume in 3 patients before, during, and after rhG-CSF administration. (B) Correlation between white blood cell count elevation and spleen volume increase in the whole cohort of subjects analyzed (n=35) on the last day of rhG-CSF administration. (C) Absence of correlation between spleen volume increase and circulating CD34⁺ cells in the whole cohort of subjects analyzed (n=35) on the last day of rhG-CSF administration.

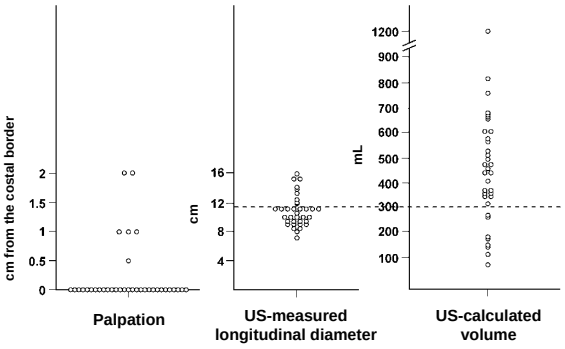

Figure 2. Spleen size soon after the last dose of rhG-CSF administration as detected by different methods. The dotted line is the upper limit of normal values.

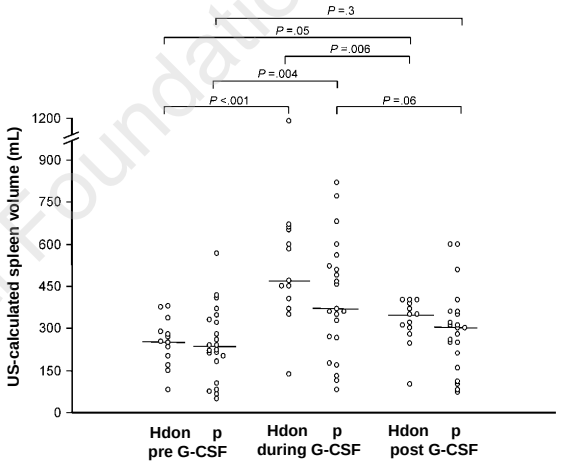

Figure 3. Spleen volume modifications following rhG-CSF administration. Spleen volume was evaluated by US before, during, and after rhG-CSF administration in 13 healthy donors (Hdon) and 22 patients (*p*) undergoing PBSC mobilization.

an, 365 mL; range, 80-820 mL); values were significantly higher than before rhG-CSF in both groups (healthy donors, $p<0.001$; patients, $p=0.004$). The difference in percent increase in spleen volume between healthy donors (median 122%; range, 29-230) and patients (median 66.5%; range, 0-211) was statistically significant ($p=0.02$) (Figure 3).

PBSC mobilization and collection

Overall, 30 subjects mobilized and underwent a single PBSC apheresis after a median rhG-CSF treatment of 6 consecutive days in healthy donors and of 12 days in patients. One healthy donor and 4 patients were poor mobilizers. The healthy donor (#7 in Table 1) had a circulating leukocyte peak of 50×10^9/L and spleen enlargement from 170 to 470 mL; patient #14 had multiple myeloma with leukocyte peak of 30×10^9/L and spleen enlargement from 240 to 520 mL; patient #17 had multiple myeloma with a leukocyte peak of 13×10^9/L without spleen enlargement; patient #26 had non-Hodgkin's lymphoma, with a leukocyte peak of 9.0×10^9/L and spleen volume increased from 418 to 680 mL; and patient #32 had acute myeloid leukemia, with neither circulating leukocyte elevation nor spleen enlargement. A single patient (#22) with multiple myeloma was a good mobilizer, showing neither leukocyte elevation nor spleen enlargement. Overall, spleen volume enlargement

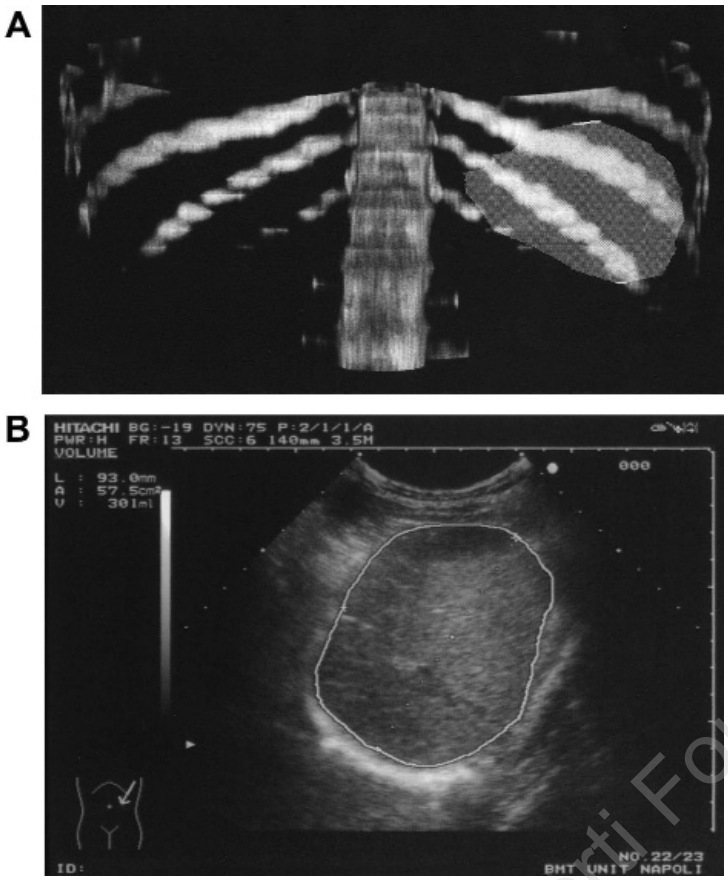

Figure 4. Spleen images obtained by three-dimensional CT scanning (A) and by US scanning (B). In this representative patient (#33) spleen volume was 300 mL by CT scan and 300 mL by US scan.

was detected in 32/35 rhG-CSF-treated subjects (91%), and in 29/30 mobilizers (97%).

Circulating cells and spleen size changes

On the day of the last rhG-CSF dose, leukocyte and neutrophil counts were significantly higher in healthy donors than in patients, although the number of circulating $CD34^+$ cells was similar (Table 2). Spleen volume increase correlated with the increase in white blood cell count (p= 0.016; r=.4) (Figure 1B); by contrast, no correlation existed between spleen volume increase and the rise in circulating $CD34^+$ cell count (Figure 1C). Indeed, white blood cell and $CD34^+$ cell increases were not correlated (p=0.48, r=.12).

Spleen enlargement reversal

One month after the last dose of rhG-CSF, spleen volume had regressed to between 100 and 400 mL (median, 350) in healthy donors and to 70 and 600 mL (median, 300) in patients; there was a borderline statistical difference (p=0.05) between the first and the third US examination in the group of healthy donors.

Spleen size change-related symptoms or complications

Even upon specific questioning, no subject reported any discomfort or pain in the splenic area during or after mobilization; US images always showed splenic parenchyma to be homogeneous, with no nodules or hematoma.

Discussion

There are anecdotal reports of spleen enlargement after rhG-CSF administration for PBSC collection. This was systematically investigated in a

Table 2. Peripheral blood values in the two groups of subjects soon after the last dose of rhG-CSF.

	Healthy donors median (range)		*Patients median (range)*		*P*
Leukocytes $\times 10^9$/L	50.0	(30.6-85.5)	10.4	(1.8-30.0)	<.001
Neutrophils $\times 10^9$/L	40.2	(24.0-68.0)	8	(1.4-19.2)	<.001
CD34+ cells /μL	80	(10-175)	48.5	(4-211)	NS

series of 91 healthy donors by Platzbecker *et al.*, using one-dimensional measurements:[10] after s.c. rhG-CSF 7.5 μg/kg/day for 5 days, US measurement of longitudinal and diagonal diameters showed that spleen size increased by a factor of 1.1, with no correlation with white blood cell elevation. An attempt to calculate spleen volume changes indirectly was also made, resulting in a supposed median volume increase of about 30%. In our series, the number of individuals with spleen enlargement after rhG-CSF administration rose from 17% and 60% as detected by palpation and US-measured longitudinal diameter, respectively, to >90% when the volume was taken into account. Multidimensional US spleen volume estimation showed a median size increase of 122% in the group of healthy donors. Low intraobserver and interobserver variability of measurements, and the excellent correlation with 3-dimensional CT-measured volume proved the high reliability of US-calculated volume for sizing the spleen (Figure 4).

The mechanisms by which splenic tissue enlarges during rhG-CSF administration are still unclear. They may include: i) intrasplenic accumulation of circulating granulocytes and myeloid precursors; ii) extramedullary myelopoiesis; and iii) intrasplenic trapping and/or proliferation of stem cells. In a few instances of splenectomy during mobilization with rhG-CSF, histological analyses documented intrasplenic infiltration by mature and immature myeloid cells;[5-7] animal studies suggested a massive migration of myeloid precursors from the marrow to the spleen via the blood, which was reversed one month after the end of rhG-CSF administration.[16-19] Myeloid accumulation could be due to modification of the adhesion molecule pattern induced by rhG-CSF on the cell surface of myeloid cells as well as of their receptors on splenic stromal cells.[17,20] In our study, the extent of spleen enlargement during rhG-CSF correlated with the increase in white blood cell count but not with that of circulating $CD34^+$ cells, thus fitting with the hypothesis of myeloid cell accumulation and arguing against stem cell homing and proliferation. These findings are consistent with those reported by Stroncek *et al.*[11]

Spleen enlargement was significantly greater in healthy donors than in patients. The difference observed between the two groups can be attributed essentially to the different schedule of rhG-CSF administration (double daily dose in healthy donors, although the cumulative dose was about the same in the two groups) and to residual myeloid suppression in the patients, who received rhG-CSF soon after high doses of cytotoxic drugs. Indeed, even peak white blood cell counts were significantly different in the two groups of individuals studied. Since the daily dose of rhG-CSF seems to be the major determinant for both white blood cell elevation and spleen enlargement, caution should be taken in scheduling high-dose rhG-CSF, especially in healthy donors.[21-23]

By one month after the end of rhG-CSF administration, spleen volume had decreased in both groups of subjects, suggesting that the enlargement is a temporary phenomenon.

It is noteworthy that no individual had any subjective symptoms of rapid spleen enlargement, not even the normal donor whose spleen size increased in a few days from 400 to 1200 mL; the absence of pain may be detrimental, since spontaneous splenic rupture could occasionally occur without any premonitory symptoms. US-calculated volume may help to identify donors with greater spleen enlargement, thus needing close monitoring.

In conclusion, in virtually all individuals submitted to stem cell mobilization a brief course of rhG-CSF induced significant spleen volume enlargement, which was directly correlated with an increase in circulating leukocyte count. There is a need to investigate whether different mobilizing regimens, including rhG-CSF in different pharmaceutical forms (e.g., pegfilgastrim) or other cytokines, have the same effect on spleen size.

References

1. Gratwohl A, Baldomero H, Horisberger B, Schmid C, Passeweg J, Urbano-Ispizua A. Current trends in hematopoietic stem cell transplant in Europe. The Accreditation Committee of the European Group for Blood and Marrow Transplantation (EBMT). Blood 2002;100:2374-9.
2. Anderlini P, Przepiorka D, Champlin R, Korbling M. Biologic and clinical effects of granulocyte colony-stimulating factor in normal individuals. Blood 1996;88:2819-25.
3. Cavallaro AM, Lilleby K, Majolino I, Storb R, Appelbau FR, Rowley SD, et al. Three to six year follow-up of normal donors who received recombinant human granulocyte colony-stimulating factor. Bone Marrow Transplant 2000; 25:85-9.
4. Dale DC, Bonilla MA, Davis MW, Nakanishi AM, Hammond WP, Kutzberg J, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. Blood 1993;81:2496-502.
5. Falzetti F, Aversa F, Minelli O, Tabilio A. Spontaneous rupture of spleen during peripheral blood stem-cell mobilisation in a healthy donor. Lancet 1999;353:555.
6. Becker PS, Wagle M, Matous S, Swanson RS, Pihan G, Lowry PA, et al. Spontaneous splenic rupture following administration of granulocyte colony-stimulating factor (G-CSF): occurrence in an allogeneic donor of peripheral blood stem cells. Biol Blood Marrow Transplant 1997;3:108.
7. Pitini V, Ciccolo A, Arrigo C, Aloi G, Micali C, La Torre F. Spontaneous rupture of spleen during peripheral blood stem cell mobilization in a patient with breast cancer. Haematologica 2000;85:559-60.
8. Zimmer BM, Berdel WE, Ludwig WD, Notter M, Reufi B, Thiel E. Fatal spleen rupture during induction chemotherapy with rh GM-CSF priming for acute monocytic leukemia. Clinical case report and in vitro studies. Leuk Res 1993;17:277-83.
9. Litam PP, Friedman HD, Loughran TP. Splenic extramedullary hematopoiesis in a patient receiving intermittently administered granulocyte colony-stimulating factor. Ann Intern Med 1993;118:954-5.
10. Platzbecker U, Prange-Krex G, Bornhauser M, Koch R, Soucek S, Aikele P, et al. Spleen enlargement in healthy donors during G-CSF mobilization of PBPCs. Transfusion 2001;41:184-9.

11. Stroncek DF, Shawker T, Follman D, Leitman SF. Spleen size transiently increases in G-CSF-mobilized peripheral blood stem cell donors. Blood 2002;100:826a[abstract].
12. Sutherland DR, Anderson L, Keeney M, Nayar R, Chin-Yee I. The ISHAGE guidelines for CD34+ cell determination by flow cytometry. International Society of Hematotherapy and Graft Engineering. J Hematother 1996;5:213-26.
13. Picardi M, Martinelli V, Ciancia R, Soscia E, Morante R, Sodano A, et al. Measurement of spleen volume by ultrasound scanning in patients with thrombocytosis: a prospective study. Blood 2002;99:4228-30.
14. Chinn S. Repeatability and method comparison. Thorax 1991;46:454-6.
15. Prassopoulos P, Daskalogiannaki M, Raissaki M, Hatjidakis A, Gourtsoyiannis N. Determination of normal splenic volume on computed tomography in relation to age, gender and body habitus. Eur Radiol 1997;7:246-8.
16. de Haan G, Dontje B, Engel C, Loeffler M, Nijhof W. The kinetics of murine hematopoietic stem cells in vivo in response to prolonged increased mature blood cell production induced by granulocyte colony-stimulating factor. Blood 1995;86: 2986-92.
17. Fukushima N, Nishina H, Koishihara Y, Ohkawa H. Enhanced hematopoiesis in vivo and in vitro by splenic stromal cells derived from the mouse with recombinant granulocyte colony-stimulating factor. Blood 1992;80:1914-22.
18. Molineux G, Pojda Z, Dexter TM. A comparison of hematopoiesis in normal and splenectomized mice treated with granulocyte colony-stimulating factor. Blood 1990; 75:563-9.
19. Nakayama T, Kudo H, Suzuki S, Sassa S, Mano Y, Sakamoto S. Splenomegaly induced by recombinant human granulocyte-colony stimulating factor in rats. Life Sci 2001;69: 1521-9.
20. Turner ML, McIlwaine K, Anthony RS, Parker AC. Different expression of cell adhesion molecules by human hematopoietic progenitor cells from bone marrow and mobilized adult peripheral blood. Stem Cells 1995;13:311-6.
21. Murata M, Harada M, Kato S, Takahashi S, Ogawa H, Okamoto S. Peripheral blood stem cell mobilization and apheresis: analysis of adverse events in 94 normal donors. Bone Marrow Transplant 1999;24:1065-71.
22. Anderlini P, Korbling M, Dale D, Gratwohl A, Schmitz N, Stroncek D. Allogeneic blood stem cell transplantation: considerations for donors. Blood 1997; 90:903-8.
23. Mc Cullough J, Clay M, Herr G, Smith J, Stroncek D. Effect of granulocyte-colony-stimulating factor on potential normal granulocyte donors. Transfusion 1999;39:1136-40.

Pre-publication Report & Outcomes of Peer Review

Contributions

MP, GDR and BR were the main investigators who designed the study. MP performed the ultrasound examinations and wrote the paper. NS performed the collections of PBSC. ES performed the computed tomography examinations. CS, VM, and RC were responsible for the clinical care of analyzed subjects. All the authors gave their critical contribution to the manuscript. BR revised the paper and gave final approval for its submission. Primary responsibility for the paper: MP; primary responsibility for Tables 1, 2 and Figures 1-3; MP, BR; primary responsibility for Table 4: ES, MP.

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Disclosures

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Manuscript processing

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In the following paragraphs, Professor Anderlini summarizes the peer-review process and its outcomes.

What is already known on this topic

Recombinant granulocyte colony-stimulating factor (rhG-CSF) is now frequently administered to normal stem cell donors to mobilize and collect peripheral blood stem cells for allogeneic transplantation.

Splenic enlargement and, rarely, non-traumatic rupture have emerged as adverse events related to rhG-CSF administration to healthy donors, although data on this complication remain sketchy.

What this study adds

The study by Picardi *et al.* expands on what is presently known, providing valuable information for physicians caring for these donors..