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.

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.

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.

Haematologica 2003; 88:794-800
http://www.haematologica.org/2003_07/794.htm

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Peripheral blood stem cells (PBSC) are increasingly being used as an alternative to bone marrow for autologous or allogeneic transplants. 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. However, about one-third of neutropenic patients chronically treated with rhG-CSF develop palpable splenomegaly, and there have been reports of spontaneous spleen rupture in rhG-CSF- or cyclophosphamide plus rhG-CSF-mobilized individuals, or even in patients treated with rhG-CSF or rhGM-CSF after chemotherapy for acute leukemia or lymphoma. Few data are available on changes in spleen size as a result of a brief course of rhG-CSF. 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, Italfarma, Rome, Italy) 263 µg twice a day, while patients received i.v. cyclophosphamide 7 g/m² 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-
Spleen sizing after PBSC mobilization

Scan, Becton Dickinson, San Jose, CA, USA) and expressed as cells/μL. Circulating leucocytes, 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 and 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 curvilinar 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 = $\pi \times \text{area}^2/3 \times \pi \times \text{longitudinal diameter}$) the volume (in milliliters), as already reported. 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). 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 multirrow 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. 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 $\chi^2$ 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 m² (range, 1.6-2.1) for healthy donors, and 51.5 years (range, 18-63) and 1.8 m² (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.

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*Cyclophosphamide 7 g/m²; °Vials per day x number of days; ^a donor with β-thalassemia trait; *patients with spleen involved by lymphoma.
Spleen sizing after 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 \( 50 \times 10^9/L \) and spleen enlargement from 170 to 470 mL; patient #14 had multiple myeloma with leukocyte peak of \( 30 \times 10^9/L \) and spleen enlargement from 240 to 520 mL; patient #17 had multiple myeloma with a leukocyte peak of \( 13 \times 10^9/L \) without spleen enlargement; patient #26 had non-Hodgkin’s lymphoma, with a leukocyte peak of \( 9.0 \times 10^9/L \) 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

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**Figure 1.** Statistical correlations. (A) Correlation between US-calculated volume and 3-dimensional CT-measured volume in 3 subjects 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.
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 \((p = 0.016; r = -0.4)\) (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 \((p = 0.48, r = 0.12)\).

**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
those reported by Stroncek and arguing against stem cell homing, thus fitting with the hypothesis of myeloid cell 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. 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. 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. 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.12-23

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

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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.

Funding
Supported by the Associazione Italiana contro le Leucemie (A.I.L.), Sezione Salerno, Italy.

Disclosures
Conflict of interest: none.
Redundant publications: no substantial overlapping with previous papers.

Manuscript processing
This manuscript was peer-reviewed by two external referees and by Professor Paolo Anderlini, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Professor Anderlini and the Editors. Manuscript received March 27, 2003; accepted May 13, 2003.

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.