Granulocyte Colony-Stimulating Factor Administration and Peripheral Blood Progenitor Cells Collection in Normal Donors: Analysis of Leukapheresis-Related Side Effects

To the Editor:

Grigg et al,[1] in their recent report in *Blood* (aimed at defining the optimal dose of granulocyte colony-stimulating factor (G-CSF) for peripheral blood progenitor cells (PBPC) mobilization in normal volunteers), also addressed several questions concerning the G-CSF toxicity. However, side effects associated with leukapheresis for PBPC collection were not analyzed. Whereas G-CSF toxicity in healthy donors has been studied,[2,3] morbidity related to the PBPC collection procedure itself has not been extensively investigated. We would like to summarize the short-term effects of G-CSF administration and PBPC collection in 20 healthy donors.[4]

All donors (5 women, 15 men, median age 35 years, range, 18 to 61) received G-CSF (Filgrastim) 10 μg/kg/d for 5 to 7 consecutive days subcutaneously. Apheresis sessions were started on day 5 of G-CSF administration (12 to 18 hours after the fourth dose of G-CSF) and were performed for 1 day (n = 5), 2 days (n = 10), 3 days (n = 4), and 4 days (n = 1). Ten to twelve liters of blood were processed daily at flow rates of 50 to 60 mL/min (Fenwall CS3000 plus cell separator; Baxter, Deerfield, IL) using antecubital veins in all cases. Donors tolerated G-CSF administration well. In agreement with the data reported by Grigg et al,[1] filgrastim induced a median increase of 17-fold (range, 6 to 78) in $CD34^+$ cells after 5 days of G-CSF treatment, with peak counts being observed after 4 and 5 doses (on day 5, n = 12; on day 6, n = 8) and a decrease on day 7. T ($CD3^+$, $CD4^+$, $CD8^+$), B ($CD19^+$), and natural killer (NK) ($CD3^-$ $CD56^+$) cells increased significantly on day 5 compared with baseline counts (Fig 1A). CD4/CD8 ratio was not modified by G-CSF administration.

Whereas no significant change in the hemoglobin level was observed, PBPC collections resulted in a significant decrease in the platelet count in all donors (median, 106 $\times$ 10^9/L; range 178 to 45 $\times$ 10^9/L) (P = .0001) (Fig 1B), being below 100 $\times$ 10^9/L in 9 of 18 cases and below 50 $\times$ 10^9/L in 1 case. No bleeding episodes occurred, and in all donors platelet counts were over 100 $\times$ 10^9/L 7 days after the procedure. Normal hemoglobin level and platelet counts (similar to the baseline ones) were observed on day 30 after the apheresis procedure. PBPC collection also resulted in a significant decrease of lymphocyte counts. Thus, 7 days after leukapheresis, lymphocytes decreased from a median baseline count of 1.59 $\times$ 10^9/L (range, 1.22 to 3.17 $\times$ 10^9/L) to a median of 1.13 $\times$ 10^9/L (range, 0.83 to 1.89 $\times$ 10^9/L) (P = .001). That decrease involved all the lymphocyte subpopulations analyzed ($CD19^+$, $CD3^+$, $CD4^+$, and $CD8^+$) with the exception of NK ($CD3^-$ $CD56^+$) cells. At 30 and 90 days after PBPC collection, lymphocytopenia still persisted (P = .028 and P = .008, respectively), although a tendency to achieve pretreatment values was observed (Fig 1A). Of note, these results are in line with those recently communicated by Körbling et al.[5] A statistical trend correlating the number of leukapheresis with the subsequent decrease of both the platelet (P = .09) and the lymphocyte counts (P = .08) was observed. Finally, with this strategy (G-CSF 10 μg/kg/d for 5 days; 10 to 12 L per apheresis session) in most of the donors (80%) a target dose of $\geq 2 \times 10^6$/kg $CD34^+$ cells was collected with the first leukapheresis. These results are similar to those reported by Grigg et al,[1] where with a single leukapheresis, enough number of progenitor cells for PBPC allogeneic transplantation (allo-PBPCT) was obtained in all cases with G-CSF doses of 10 μg/kg/d.

One of the major advantages of allo-PBPCT over bone marrow transplantation is that for the donor the risks associated with general anesthesia and the discomfort caused by multiple bone punctures are avoided. Nevertheless, hematopoietic growth factor administration and PBPC collections by apheresis may be not totally innocuous. In two allo-PBPCT series[6,7] most of the donors required a central venous line to achieve adequate venous flow. To cannulate large veins is not without risks. However, in recent series such as the reported by Grigg et al[1] in 30 volunteers donors, and in that from Tabilio et al[8] and in our own study including 39 and 20 consecutive subjects, respectively, a central venous line was not necessary. In the present study, leukapheresis invariably resulted in a significant loss of platelets, probably because the mononuclear cell fraction of peripheral blood has a similar density to that of platelets. Modifications such as the use of a small volume collection chamber for apheresis as well as the reduction of the number of apheresis sessions could minimize this problem. PBPC collection also caused a modest, although significant, decrease of lymphocyte counts that tended to recuperate within 3 months after the procedure. Whether or not postapheresis lymphocytopenia may have some kind of clinical relevance, however, should be further investigated.

In conclusion, G-CSF administration on healthy donors is well tolerated and is associated with a significant increase in $CD34^+$ cells, T, B, and NK cells in donors' blood. In addition, PBPC

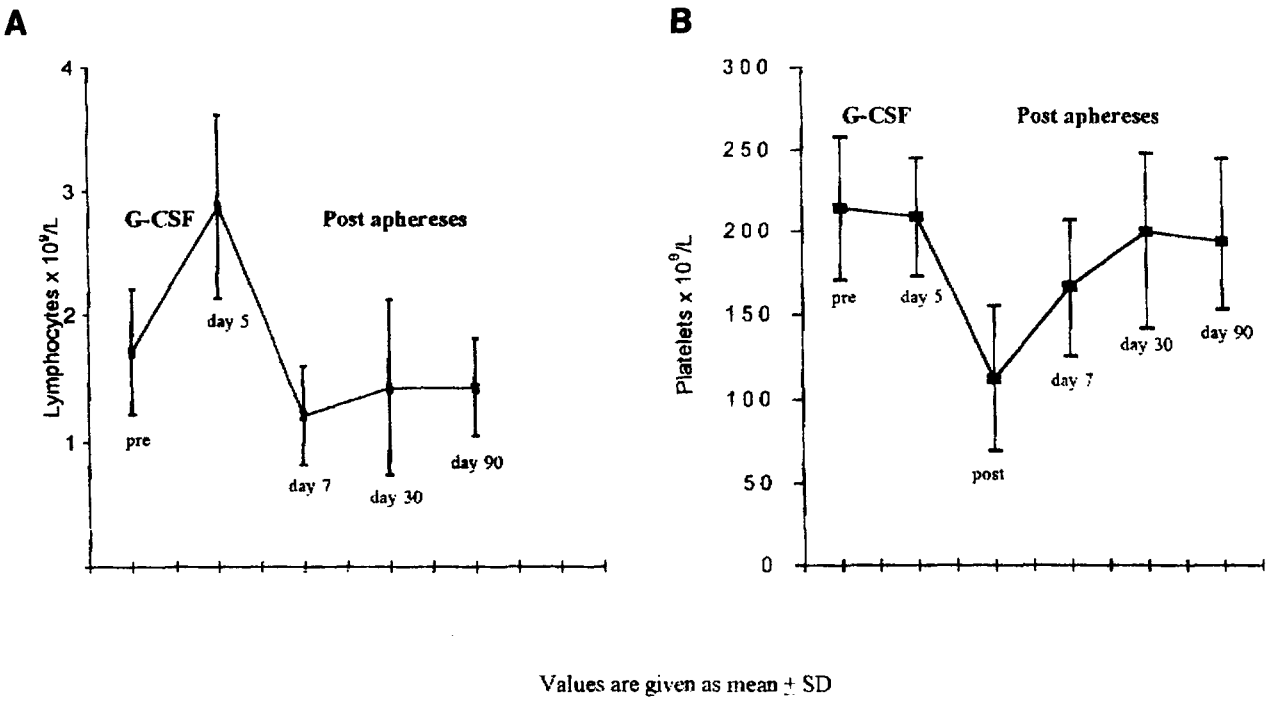

Fig 1. Effect of leukapheresis on peripheral blood lymphocyte (A) and platelet (B) counts.

collection by apheresis rarely requires a central vein access and results in a rapidly reversible thrombocytopenia and lymphocytopenia, which tends to resolve within the 3 months after the procedure.

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