To the Editor:

Granulocyte-macrophage colony-stimulating factor (GM-CSF) has been useful in accelerating neutrophil recovery in bone marrow transplant patients with regimen-related neutropenia and graft failure. However, the demonstration of diminished neutrophil migration into sterile skin windows during GM-CSF administration has raised several concerns. First, the potential for increased susceptibility to infection resulting from the inability of neutrophils to localize to areas of infection during treatment with GM-CSF is worrisome. Second, in neutropenic patients with severe infections who may benefit from granulocyte transfusions, the nonspecific localization of these cells may abrogate their ability to control infection and may have potentially adverse side effects. There is little clinical experience with the coadministration of GM-CSF and granulocyte transfusions. We report the effective localization of granulocytes to the site of invasive fungal infection in a patient receiving GM-CSF and pentoxifylline (PTX), a xanthine derivative that may preserve neutrophil migration during GM-CSF administration.

A 25-year-old man with Hodgkin’s disease in early first relapse underwent an autologous marrow transplant after conditioning with VP-16, carmustine, and cyclophosphamide. As part of an ongoing study, he received PTX (400 mg orally five times daily) preconditioning through day 100 posttransplant. On day 3 posttransplant, the patient developed an invasive skin infection with Candida albicans involving the scrotum and right inguinal region. Despite therapy with amphotericin B (0.6 mg/kg/d, Fungizone; Squibb, Princeton, NJ), his cutaneous infection progressed and he was started on single donor allogeneic granulocyte transfusions along with recombinant human GM-CSF (rhGM-CSF) (250 µg/m²/d intravenously over 2 hours for 21 days, Immunex, Seattle, WA). Indium labelled granulocytes (white blood cells [WBCs]) were infused via right atrial catheter before the third dose of GM-CSF. The patient was imaged under a gamma camera at 2, 16, 24, and 38 hours after infusion of the radiolabelled WBCs. Imaging demonstrated localization of the radiolabel in the right inguinal and scrotal region (Fig. 1). There was no evidence of nonspecific localization in lung or other organs (Fig. 1). The patient experienced marked relief in pain and erythema within several days of initiating this therapy accompanied by complete resolution of fever and invasive cutaneous fungal infection.

Peters et al postulated in their original report that a concentration gradient of intravascular GM-CSF may have been responsible for the diminished migration of neutrophils to peripheral inflammatory sites. Consistent with these findings was the observation that radiolabeled WBCs administered during GM-CSF infusion resulted in transient pulmonary sequestration, supporting the theory that GM-CSF may interfere with in vivo neutrophil migration. The in vitro effects of GM-CSF on neutrophil functions, including migration/adhesion, are complex but include upregulation of CD11b/18 adhesion molecules, inhibition of neutrophil migration, and activation of neutrophil functions including induction of tumor necrosis factor-α (TNF-α) production. The rhGM-CSF-induced decrease in neutrophil chemotaxis, and increase in CD11b expression is, at least in part, mediated by TNF-α. We have previously reported the ability of PTX to decrease TNF-α in patients undergoing bone marrow transplantation. In addition, Salyer et al demonstrated that in vitro administration of PTX prevents and reverses the ability of TNF-α to inhibit neutrophil migration while decreasing CD11b expression. In animal models of localized cutaneous infections and sepsis, treatment with PTX improved both the ability to sterilize abscesses and survival respectively. Additionally, Takahashi et al have demonstrated that PTX inhibits GM-CSF induction of TNF-α in early myeloid cells without affecting proliferation, making the combination of these two agents in clinical practice attractive. In this report we found that GM-CSF administration did not interfere with localization of granulocytes to the site of infection in a patient receiving PTX. The ability of PTX to prevent GM-CSF/TNF-α-induced inhibition of neutrophil migration/adhesion may have contributed to the effec-
tive localization of transfused granulocyte and deserves further investigation.

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REFERENCES


Localization of transfused neutrophils to site of infection during treatment with recombinant human granulocyte-macrophage colony-stimulating factor and pentoxifylline [letter]

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