Increased Consumption of Antithrombin III in Patients Receiving Granulocyte-Macrophage Colony-Stimulating Factor After Bone Marrow Transplantation

To the Editor:

Granulocyte-macrophage colony-stimulating factor (GM-CSF) can activate macrophages to secrete tumor necrosis factor α (TNFα) and interferon γ (IFNγ). Recombinant TNFα and IFNγ are inducers of macrophage procoagulant activity in vitro.1 We analyzed the activation of coagulation and the plasma levels of antithrombin III (AT III) in patients that received either GM-CSF or G-CSF after high-dose chemotherapy.

From 1988 to 1993, 30 patients with solid tumors (Ewing’s sarcoma, n = 17; neuroblastoma, n = 8; rhabdomyosarcoma, n = 5; allogeneic bone marrow transplantation [BMT], n = 5; autologous stem cell grafts, n = 25) were treated according to the Hyper-ME² protocol. Each of the 15 patients received GM-CSF and G-CSF, respectively, from day 0 until a stable engraftment was achieved. Because there is no sufficient number of patients that received Hyper-ME ± C protocol.² Each of the 15 patients received GM-CSF and G-CSF, respectively, from day 0 until a stable engraftment was achieved. Because there is no sufficient number of patients that received Hyper-ME ± C and no hematopoetic growth factor, we assessed 21 patients with acute lymphoblastic leukemia (ALL) as the best available control group. These control patients underwent allogeneic BMT after 12 Gy total body irradiation plus 60 mg/kg etoposide³ as conditioning therapy. All patients were in complete or very good partial remission.

AT III was assessed using the chromogenic substrate S-2238 (Chromogenix, Malmö, Sweden); the results were expressed as percent of pooled normal human plasma (NHP). Plasma prothrombin fragment F1 + 2 and thrombin-AT III complexes (TAT) were measured using commercially available enzymelinked immunosorbent assay systems (Behringwerke AG, Marburg, Germany). All parameters were measured at 3- to 4-day intervals through day +49 after BMT.

Substitution of AT III (Atenativ, Kabi, Uppsala, Sweden) was performed when an AT III level below 90% of NHP was detected.

The daily dose was calculated as: AT III concentrate (IU) = (100 − detected AT III level) × kg body weight. When this substitution was insufficient to increase the AT III level to greater than 90% NHP, the dose of AT III substitution was doubled.

In the GM-CSF patients, minimum mean AT III levels (80% of NHP) were found from day +4 through day +18 (P < .05, unpaired t-test when compared with the other patient groups), followed by slow normalization until day +49 (Fig 1). In contrast, the mean AT
III levels in the G-CSF patients, and in the patients without growth factor were greater than 90% NHP at any time point through day +49 (Fig 1). In the GM-CSF patients, the mean daily AT III substitution was 22 to 37 IU/kg body weight from day +7 through +25, whereas the G-CSF patients and the patients without growth factor received maximum 7 IU/kg at day +11 (Fig 2).

TAT levels, before the first substitution with AT III, were significantly higher in the GM-CSF group (15.3 ± 5.6 μg/L; mean ± SD) than in the G-CSF group (4.5 ± 1.8 μg/L; P = .025, unpaired t-test). F1 + 2 levels were normal in both groups. The mean (maximum) length of hematopoetic growth factor infusion was 25 (40) days for G-CSF, and 28 (47) days for GM-CSF (Fig 2).

This analysis shows increased consumption of AT III in patients that received GM-CSF compared with those that received G-CSF. The AT III levels and the doses of AT III substitution were similar in patients that received G-CSF and in patients that received neither growth factor, with respect to the limitation, that patients without growth factors had another underlying disease and conditioning therapy. Activation of the coagulation system is proved by the increased TAT levels.

Indirect evidence for activation of humoral coagulation under GM-CSF was shown by Stephens et al,4 who described an increased rate of clots in central venous catheters in patients that received GM-CSF for stem cell apheresis. These clots developed despite prophylaxis with the platelet inhibitor acetyl salicylic acid (ASA). However, ASA does not inactivate humoral clotting factors.

GM-CSF does not directly induce macrophage procoagulant activity in vitro.5 The in vivo activation of coagulation in the context of GM-CSF shown here and by Stephens et al may be explained by indirect mechanisms, such as generation of TNFa and IFNy, that are able to induce a procoagulant state. GM-CSF may in part contribute to the hemostatic dysregulations observed after BMT.

REFERENCES

Fig 1. Demonstration of relatively low levels of AT III activity (vertical axis) in patients under GM-CSF (△) compared to G-CSF (□) and patients without growth factor (○). Mean ± SD is given in 3- to 4-day intervals from day 7 before to day 49 after BMT (horizontal axis).

Fig 2. Demonstration of higher doses of daily AT III substitution (vertical axis) in patients under GM-CSF (■) compared to G-CSF (pointed bars) and to patients without growth factor (□), shown as mean ± SD in 3- to 4-day intervals. The symbols in the upper part show the duration of G-CSF (pointed symbol) and GM-CSF (dark symbol) infusion, that started at day 0 (left side of the rectangles). The right end of the rectangle shows the mean, the right peak the maximum day of growth factor infusion.
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