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. We analyzed the activation of coagulation and the plasma levels of antithrombin III (ATIII) in patients that received either GM-CSF or G-CSF after high-dose chemoradiotherapy.

From 1988 to 1993, 30 patients with solid tumors (Ewing's sarcoma, n = 17; neuroblastoma, n = 8; rhabdomyosarcoma, n = 5; allogeneous 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 and no hematopoetic growth factor, we assessed 21 patients with acute lymphoblastic leukemia (ALL) as the best available control group. These control patients underwent allogeneous BMT after 12 Gy total body irradiation plus 60 mg/kg etoposide as conditioning therapy. All patients were in complete or very good partial remission.

AT III was assessed using the chromogenic substrate S-2238 (Chromogenix, Molndal, 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 enzyme-linked 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, with respect to the limitation, that patients without growth factor 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., 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. 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 TNFα and IFNγ, that are able to induce a procoagulant state. GM-CSF may in part contribute to the hemostatic dysregulations observed after BMT.

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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