short report
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TREATMENT OF A DELAYED GRAFT FAILURE AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION WITH IL-3 AND GM-CSF

Alessandro M. Vannucchi, Alberto Bosi, Daniele Laszlo, Stefano Guidi, Riccardo Saccardi, Pierluigi Rossi-Ferrini

Bone Marrow Transplant Unit, Division of Hematology, University of Florence, Ospedale di Careggi, Florence, Italy

ABSTRACT

We report on the partial effectiveness of sequential IL-3 and GM-CSF administration, following an ineffective 5-day trial with G-CSF, in a case of delayed graft failure after allogeneic bone marrow transplantation. Therapy with these growth factors was followed by a prompt (within 2 days) increase of neutrophil count, suggesting the possibility of a priming effect due to the previous G-CSF administration. The potential usefulness of this growth factor schedule administration in the treatment of graft failures after allogeneic bone marrow transplantation requires confirmation in controlled trials.

Key words: graft failure, IL-3, GM-CSF, bone marrow transplantation

Graft failure after allogeneic bone marrow transplantation (BMT) can be due to degree of HLA compatibility, disease recurrence, graft-versus-host disease (GVHD), damage to the microenvironment from previous treatment, cytomegalovirus (CMV) infection, concomitant therapy with myelotoxic drugs, or to a combination of these.[1] The survival of patients with marrow graft failure at 2 years is < 20%, compared to 40% of patients without graft failure.[2] Until recently, therapy for such patients was limited to supportive care only, and even a second graft infusion was effective in less than 20% of these cases. The availability of recombinant myeloid growth factors was supposed to have an impact on the treatment of this syndrome, and there are indeed encouraging reports in patients with graft failure following allogeneic or autologous BMT.[2-4] We report here on a patient who experienced a delayed graft failure after an allogeneic BMT, in whom therapy with IL-3 and GM-CSF successfully resulted in a prompt recovery of neutrophil count.

Case report

A 24-year-old man was diagnosed as having a B-cell non-Hodgkin lymphoma (intermediate grade) with bone marrow involvement in August 1992, and a complete remission was obtained after six cycles of Promace-Cytabom. As consolidation therapy, in April 1993 he was submitted to high-dose chemotherapy (BEAM) followed by peripheral blood stem cell rescue. However, in February 1994 hematological relapse occurred, and a second complete remission was obtained after six of twelve delivered cycles of MACOP-B. In June 1994, the patient underwent an allogeneic BMT from his HLA-identical brother after conditioning with a TBI-CY regimen; details of the conditioning regimen and GVHD prophylaxis have been reported.[5] The post-BMT course was uncomplicated except for grade II oral mucositis. There was no evidence of acute GVHD, and hematopoietic recovery occurred promptly (granulocytes $>0.5\times10^9$/L by day +14 and platelets $>30\times10^9$/L by day +17); the patient was discharged on day +30. On day +43, he was readmitted to the hospital with an erythematous

Correspondence: Dr. Alessandro M. Vannucchi, Bone Marrow Transplant Unit, Division of Hematology ,University of Florence, USL 10/D Ospedale di Careggi, 50134 Florence, Italy. Fax: international +39.55.4277794 or +39.55.412098.
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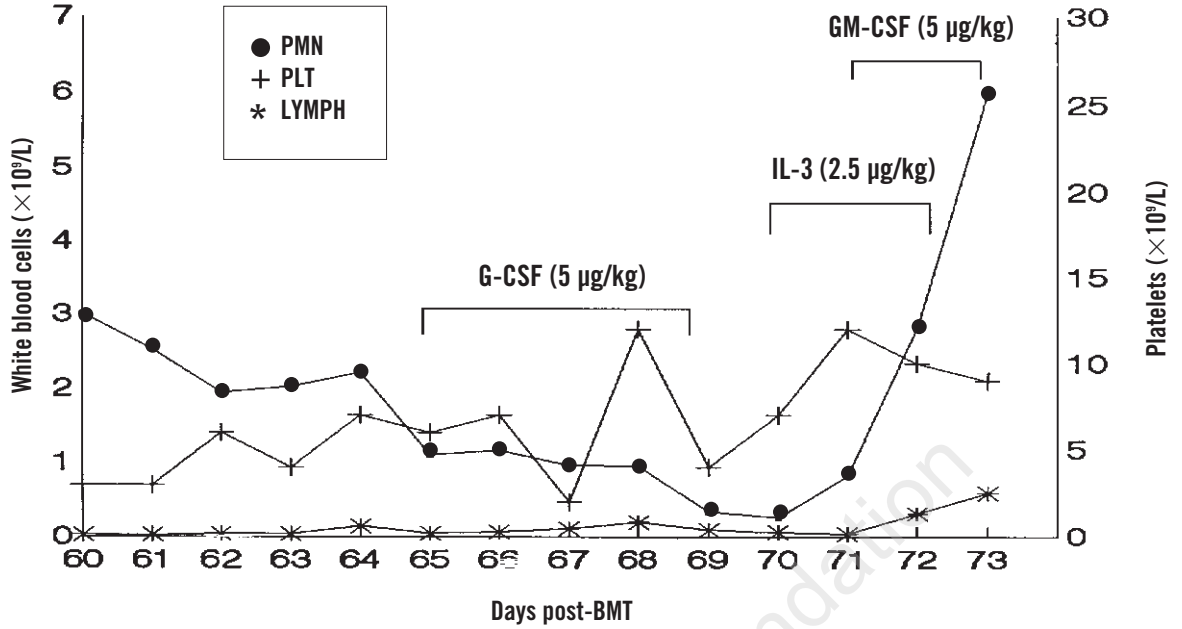

Figure 1. Modifications of neutrophil (PMN), lymphocyte (LYMPH) and platelet (PLT) counts under treatment with G-CSF, followed by IL-3 and GM-CSF in a case of graft failure after allogeneic BMT.

rash on the palms of his hands, trunk and neck, and because of watery diarrhea (800 mL/day). His white blood cell count was 3.9×10^9/L with a normal differential count, Hb 7.9 g/dL, and platelet count 83×10^9/L. A diagnosis of acute GVHD (grade III) was made, and the patient was treated with i.v. high-dose methylprednisolone (20 mg/kg/day for 5 days on days +42 to +46, and tapered thereafter). Skin resolution was observed on day +47 but since diarrhea was still present on day +49, antilymphocyte globulin was started and diarrhea ceased on day +51. However, from day +56 the patient developed progressive pancytopenia; a search for CMV infection was repeatedly negative and a bone marrow biopsy on day +64 revealed a hypocellular marrow (cellularity < 10%). On day +65 blood counts were as follows: neutrophils 0.8×10^9/L, hemoglobin 9.9 g/dL (transfused), platelets 6×10^9/L. Therefore i.v. continuous infusion of 5 ug/kg/day recombinant human (rHu) G-CSF was started on day +65 up to day +69, without any evidence of improvement in neutrophil count. Then rHuIL-3, 2.5 ug/kg/day by continuous i.v. infusion, was started on day +70 up to day +72, followed by rHu GM-CSF, 5 ug/kg/day by continuous i.v. infusion, from day +71. A prompt increase of neutrophil count was observed from the second day of IL-3, and on day +73 neutrophil count reached 6.0×10^9/L (Figure 1). However, the course was complicated by fever (39°C), accompanied by progressive alterations in consciouness, hyperreflexia and tonic-clonic seizures. A CT scan of the brain showed several hyperdense areas suggestive of cerebral toxoplasmosis, and specific therapy was started. On day +73 a comatose state developed, followed by respiratory failure and death on day +74. A *postmortem* examination was refused by his parents.

Discussion

Graft failure after allogeneic BMT is a difficult condition to manage and although spontaneous recovery may take place, survival is greatly reduced with respect to engrafted patients. Previous experience with GM-CSF after autologous BMT has been encouraging,[2-4] and a significant improvement in survival demonstrat-

ed.[2] On the other hand, there are few available data on the effects of IL-3, either alone or in association with GM-CSF,[6,7] and only patients subjected to autologous transplantation were included in these series. Therefore the efficacy of IL-3 and GM-CSF in our patient is of potential interest, although only a recovery of granulocytes could be documented owing the early death of the patient; overall, it still remains to be ascertained whether IL-3 and GM-CSF can stimulate a trilineage hematological response in these patients. Indeed, some patients with graft failure after autologous BMT who responded to GM-CSF with a neutrophil increase remained red cell and platelet transfusion dependent.[3] In addition, in a recent report Crump *et al.*[6] observed little benefit from IL-3 therapy in graft failure after autologous BMT, although the addition of GM-CSF resulted in a magnified response, likely due to a *priming* action of IL-3. Moreover, Fay *et al.*[8] showed a synergistic effect of IL-3 and GM-CSF given sequentially after autologous BMT for lymphoma, with a reduction in the period of neutropenia and thrombocytopenia as compared to patients receiving IL-3, GM-CSF or G-CSF alone.

The pathogenesis of the delayed graft failure in our patient remains unknown; one possible factor might have been the therapy with antilymphocyte globulin that could have caused a depletion of cytokine-producing T cells. Therefore the exogenous administration of IL-3 and GM-CSF might have acted by restoring the proliferative potential of present, yet quiescent, hematopoietic progenitors.

It is of interest that, although previous therapy with G-CSF alone was apparently ineffective, it was followed by a prompt increase in neutrophil count as early as two days after beginning IL-3 administration; this time lapse was too short to be ascribed to a direct effect of IL-3 on hematopoietic progenitors. Given the demonstrated ability of G-CSF to stimulate quiescent pluripotent hematopoietic progenitor cells to enter the G1-phase of the cell cycle,[9] one is tempted to speculate that IL-3 (and GM-CSF) amplified the response driven by G-CSF on hematopoietic precursors.

Therefore we suggest that controlled trials should be started to address the question of the efficacy of IL-3 (and GM-CSF) following a *priming* effect of G-CSF in the treatment of graft failure after allogeneic BMT.

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