EDITORIAL

The Development of Granulocyte Colony-Stimulating Factor in its Various Clinical Applications

By Janice Gabrilove

The production of neutrophil granulocytes is a complex and dynamic process during which a small number of self-renewing stem cells give rise to lineage-specific progenitors that proliferate and mature in the bone marrow, subsequently entering the blood as mature polymorphonuclear leukocytes. One hematopoietic glycoprotein that appears to specifically control the survival, cycle activation, proliferation, and terminal maturation of this myeloid lineage is granulocyte-colony-stimulating factor (G-CSF).

Preclinical studies demonstrated early on the ability of G-CSF to augment the number of functionally normal neutrophil granulocytes in normal and tumor-bearing rodents and nonhuman primates. This neutrophil granulocytosis results from an augmentation in the number of divisions and a reduction (from 96 to 24 hours) in the time required for maturing neutrophil granulocyte precursors to develop into terminally differentiated cells released into the circulation. This particular biologic effect is unique to G-CSF. This property also foresees that the rate-limiting step in the ability of G-CSF to promote recovery from neutropenia is the availability of G-CSF-responsive progenitors.

Three initial studies in humans showed that an intravenous bolus, continuous intravenous infusion, subcutaneous injection, or continuous subcutaneous infusion of G-CSF administered in the absence of myelosuppression results in a dose-dependent increase in the circulating neutrophil granulocyte count and is associated with an expansion of the bone marrow myeloid compartment. The administration of G-CSF also results in a 10- to 100-fold increase in the number of circulating hematopoietic progenitors.

Neutropenia in cancer patients is a major cause of morbidity and mortality and results from malignant disease as well as its treatment. Phase I and II studies using a broad spectrum of commonly used chemotherapeutic regimens initially demonstrated the ability of G-CSF to accelerate recovery from chemotherapy-induced neutropenia. In all of these studies, G-CSF was administered 24 to 48 hours after the cessation of chemotherapy. Optimization of timing and duration of G-CSF treatment has also been investigated in patients receiving high-dose melphalan. This study demonstrated accelerated recovery from neutropenia even when G-CSF treatment was begun 8 days after chemotherapy. The ability to delay the use of G-CSF, but not granulocyte-macrophage-CSF (GM-CSF), and commence treatment closer to the time of expected nadir and still maintain an enhanced recovery from neutropenia most likely results from the ability of G-CSF to rapidly mobilize neutrophil granulocytes from the bone marrow mitotic compartment. In addition, these data reaffirm the hypothesis that for G-CSF-mediated recovery from neutropenia, the rate-limiting step is the availability of G-CSF-responsive progenitors.

Based on these phase I and II trials, a randomized double-blind placebo-controlled phase III trial of G-CSF was designed to definitively evaluate the incidence of infection as manifested by fever with neutropenia (absolute neutrophil count, <1,000 cells/mL; and temperature >38.2°C) in patients treated with one of the standard chemotherapeutic regimens for small cell carcinoma of the lung. This regimen used cyclophosphamide (100 mg/m², day 1), doxorubicin 50 mg/m², and etoposide (120 mg/m², day 1 through 3). A total of 211 patients was randomly assigned to receive placebo (n = 110) or G-CSF (n = 101), of which 199 were evaluable for efficacy. At least one episode of fever with neutropenia occurred in 77% of placebo, as compared with 40% of the G-CSF–treated group. Over all cycles of chemotherapy, the median duration of severe neutropenia (<500 cells/µL) was 6 days with placebo, as compared with 1 day with G-CSF. During cycles of blinded treatment, the days of intravenous antibiotic use, hospitalization, and the incidence of confirmed infections were reduced by 50% when G-CSF was administered as compared with placebo. This pivotal phase III trial, as well as early studies, led to the approval of the use of G-CSF to reduce the incidence of infection as manifested by febrile neutropenia in adult and pediatric patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy.

A recent European phase III trial has confirmed the findings of the Crawford et al. This trial, which was a double-blind placebo-controlled noncrossover design conducted by Trillet-Lenoir et al, demonstrated the therapeutic benefit of G-CSF administration in patients receiving comparable chemotherapy for small cell lung cancer over six cycles. The results of this study showed that over all six cycles, 53% of the 64 placebo-treated patients, but only 26% of the 65 G-CSF–treated patients had an episode of neutropenic fever. This, in turn, resulted in a statistically significant reduction in the use of parenteral antibiotics and culture-confirmed infections. Over all six cycles, 61% of the placebo-treated patients required at least one reduction in their dose of chemotherapy, compared with 29% of the G-CSF–treated patients. As a result of differences in both dose delays and dose reductions, the G-CSF–treated patients received a greater dose intensity than did the placebo-treated patients.

Preservation of intended dose intensity has now also been shown in the randomized trial of patients with non-Hodgkin's lymphoma receiving VAPEC-B chemotherapy associated with dose-limiting neutropenia conducted by...
Pettengell et al.\textsuperscript{11} and published in this issue of \textit{Blood}. Forty-one patients were randomized to receive VAPEC-B with G-CSF and 39 patients to VAPEC-B alone. Febrile neutropenia occurred in 22\% of the G-CSF–treated group as compared with 44\% of the non–G-CSF–treated group. These differences were observed despite prophylactic ketoconazole and cotrimoxazole being administered to both groups throughout the study. Doses of chemotherapy were reduced in 10\% of the group treated with G-CSF and 33\% of the group treated with G-CSF. The dose intensity was significantly increased in the G-CSF group, who received greater than 95\% of their intended chemotherapy, compared with 83\% for the control patients. This trial, like that of Trillet-Lenoir et al.\textsuperscript{10} shows that chemotherapy dose intensity can be preserved with G-CSF treatment, as originally suggested by Gabrilove et al in their phase I trial of G-CSF in patients with genitourinary carcinoma receiving M-VAC chemotherapy.\textsuperscript{8} These studies, in turn, have supported the rationale for pursuing dose escalation trials with G-CSF in an attempt to improve the efficacy of chemotherapeutic regimens and survival of patients afflicted with a variety of cancers. In addition, the study by Pettengell et al\textsuperscript{11} demonstrates the feasibility of G-CSF to promote recovery for neutropenia even in regimens administered on a weekly basis.

In this regard, several trials have now been completed exploring the ability of G-CSF with and without the addition of G-CSF–primed peripheral blood progenitors to support the successful implementation of dose-intensified regimens. The first of these trials, conducted by Bronchud et al.,\textsuperscript{12} demonstrated the ability of G-CSF treatment to permit dose-intensified doxorubicin (100 mg/m\textsuperscript{2} every 2 weeks) to be administered for three cycles in patients with ovarian and breast carcinoma refractory to standard-dose chemotherapy. Treatment resulted in an improved response rate of 80\%.

Sarosy et al.\textsuperscript{13} undertook a study to determine if Taxol could be dose-intensified with the use of G-CSF, and whether such a dose-intensified regimen would result in an improved response rate in patients with recurrent ovarian cancer. In this study, when Taxol was administered with G-CSF, myelosuppression and mucositis were no longer dose-limiting features of Taxol therapy; instead, neurotoxicity defined a maximum tolerated dose of 250 mg/m\textsuperscript{2}. These investigators then conducted a phase II study of Taxol at this dose level, with G-CSF support. This study showed that a dose intensification of Taxol could be safely increased from 45 mg/m\textsuperscript{2}/wk to 83 mg/m\textsuperscript{2}/wk with G-CSF support, and that such a dose intensification was associated with an enhanced rate of disease response (from 35\% to >50\%). The feasibility of administering this dose of Taxol has also recently been reported by Seidman et al.\textsuperscript{14} in patients with metastatic breast carcinoma.

Additional dose escalation trials have either been completed or are ongoing in patients with non-small cell lung cancer,\textsuperscript{15} in patients with non-Hodgkin's lymphoma.\textsuperscript{16} advanced cancer receiving high-dose cisplatin and etoposide, and in patients with advanced breast cancer receiving either mitoxantrone\textsuperscript{17} or cytophosphamide/mitoxantrone/5-fluorouracil (CNF) chemotherapy.\textsuperscript{18} These studies will be of considerable importance in regards to the ability of a hematopoietic growth factor such as G-CSF to improve not only responses in patient with cancer, but to augment survival.

Although G-CSF has been shown to be of clinical benefit in the treatment of chemotherapy-induced myelosuppression in the setting of standard or dose-intensified regimens, the use of G-CSF after myeloablative chemotherapy for acute myelogenous leukemia is more controversial. Ohno et al.\textsuperscript{19} conducted a prospective randomized trial of G-CSF in patients with either de novo acute myelogenous leukemia, leukemic transformation from myelodysplastic syndrome (MDS), acute lymphocytic leukemia, or blastic phase of chronic myelogenous leukemia after mitoxantrone, etoposide, and bentenolycytosine arabinoside therapy. In addition, patients were documented to have a hypoplastic bone marrow before commencing G-CSF treatment. Using this schedule, the administration of G-CSF significantly accelerated the recovery of neutrophils, reduced the incidence of documented infection, and did not preferentially promote the regrowth of leukemic cells.

Neutropenia is also an important problem in hematopoietic malignancies, pancytopenic states, acquired immunodeficiency syndrome (AIDS), and genetic disorders of granulocyte production. Pilot studies of G-CSF in patients with hairy cell leukemia\textsuperscript{20} and MDS\textsuperscript{21} have shown improvement in circulating neutrophil counts associated in some instances with a decrease in the incidence of or enhanced recovery from active infection. In addition, no evidence of treatment-induced proliferation of the malignant clone has been observed. G-CSF, administered alone or in combination with erythropoietin, has been shown to ameliorate zidovudine-induced myelotoxicity in patients with AIDS without stimulating p24 antigen expression.\textsuperscript{22} Finally, initial pilot studies of G-CSF in patients with primary neutropenic disorders\textsuperscript{23-29} demonstrated the ability of G-CSF to augment circulating neutrophil counts, reduce the incidence of infection and mucositis, and improve quality of life parameters. These preliminary findings have now been confirmed by a phase III randomized trial of G-CSF in patients with severe chronic neutropenia,\textsuperscript{27} suggesting that this hematopoietic growth factor can play an important role in the management and treatment of these disorders. Recently, G-CSF has also been shown to reduce infection and, therefore, to be of therapeutic benefit in the treatment of myelokathexis\textsuperscript{28} and to correct the neutropenia associated with glycogen storage disease type 1b.\textsuperscript{29}

CSFs have been used to promote hematologic recovery after ablative therapy and autologous bone marrow reinfusion.\textsuperscript{30-35} In this regard, yeast-derived glycosylated GM-CSF has been shown to augment recovery from neutropenia in patients undergoing autologous bone marrow transplantation for lymphoid malignancies and has been approved by the Food and Drug Administration for this indication. The report by Gorin et al.\textsuperscript{36} further supports these original observations and demonstrates the ability of nonglycosylated GM-CSF to accomplish a comparable hematologic effect. Of interest is the greater side effect profile of...
GM-CSF observed for this study. This may result from the differences in (1) GM-CSF preparations; (2) preparative ablative regimens used for bone marrow transplantation; and/or (3) patient characteristics. In addition, it was noteworthy that, despite the reduction in neutropenia and hospitalization, no difference in actual infection was noted. This underscores the need for novel strategies to further reduce the number of days of neutropenia, because the period of infectious risk after bone marrow transplantation appears to occur before 14 days after marrow reinfusion.

One way to better affect hematopoietic reconstitution would be to provide CSF-responsive progenitors in an easily obtainable form. This can be accomplished by using CSF-primed peripheral blood progenitors and/or using earlier acting factors in an attempt to mobilize committed progenitors from a more immature stem cell compartment. Already, these types of approaches have been pioneered by Petros et al., Gianni et al., and Sheridan et al. in the setting of autologous bone marrow transplantation, and by Shea et al. using GM-CSF in the setting of dose-intensified chemotherapy. In these studies, CSF-primed progenitors are administered after an ablative regimen along with the coadministrative of a CSF. Interestingly, not only is the period of neutropenia further reduced, but the period of thrombocytopenia is markedly decreased when this technique is used. The reason for this remains obscure and could reflect a difference in the quality of progenitors and/or in the infusion of activated accessory cells that might be a source of other cytokines responsible for platelet production.

By reducing treatment complications resulting from hematopoietic injury, the use of CSFs alone or in combination with other hematopoietic growth factors and/or progenitors will likely unmask other nonhematopoietic toxicities related to dose-intensified regimens, as suggested by Patten-gell et al. In their study, a suggested increase in vascular complications was noted in the G-CSF-treated group, most likely related to the increase in dose intensity achieved. It is clear that if dose-intensified regimens result in improved responses and cure rates for patients afflicted with different malignancies, novel strategies to overcome or reduce injury to other organ systems will become critical.

REFERENCES

G-CSF AND THE TREATMENT OF NEUTROPENIA


The development of granulocyte colony-stimulating factor in its various clinical applications [editorial]

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