Colony-Stimulating Factors and Neutropenia: Intersection of Data and Clinical Relevance

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Until recently, neutropenia was regarded as an unalterable consequence of many cancer chemotherapies. Oncologists have long realized that the depth and duration of neutropenia are the primary risk factors for the development of infections that could seriously undermine cancer treatment (*1*). The morbidity and mortality associated with these infectious complications have been dramatically reduced during the past two decades with the use of early empirical broad-spectrum antibiotic therapy (*2*). It has also become increasingly clear, however, that neutropenic patients can generally be divided into "low-risk" versus "high-risk" categories on the basis of the duration of their neutropenia. Low-risk patients have durations of neutropenia less than 7 days, and they appear to do well with a variety of therapeutic approaches. In contrast, high-risk patients remain neutropenic for more than 7-10 days, and they are subject to secondary infections, frequently requiring the addition of one or more antimicrobial agents to their initial regimen, including empirical antifungal therapy (*3*).

Differentiating between the high-risk and low-risk subsets of patients in a prospective fashion, or at a time soon after hospital admission for fever and neutropenia, is becoming a critical factor in deciding what interventions might be used in the management of neutropenic cancer patients. This stratification allows for new approaches, targeted specifically to patients in a given category. For those patients in the low-risk group, there have already been promising trials of outpatient intravenous or oral antibiotic therapy for neutropenic fever and of early hospital discharge for those patients who fit criteria for good prognosis (i.e., afebrile promptly, negative bacterial cultures, and increasing neutrophil counts) (*4-7*). Clinically relevant end points to evaluate these new approaches should include some measure of the impact they have on patients' lives and, in this era, a comparison of their overall costs with those of conventional therapy.

In recent years, there has also been a revolutionary change in our view of neutropenia, engendered by the discovery and cloning of the myeloid growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF). When administered to a patient, these agents can dramatically increase the number and, perhaps, the function of granulocytes (*8*). Thus, these hematopoietic growth factors or CSFs have provided us with the potential to increase endogenous neutrophil numbers to levels that may abrogate the severity and the duration of neutropenia resulting from intensive chemotherapy regimens, potentially converting high-risk patients into low-risk patients.

Several potential roles have emerged for the use of the myeloid growth factors with respect to ameliorating infectious complications in cancer patients. First, they may be used prophylactically, starting immediately following chemotherapy and extending through the period of neutropenia in an effort to abrogate the duration, if not the depth, of therapy-related neutropenia. A substantial amount of data exists to show that the prophylactic use of either G-CSF or GM-CSF can, in many circumstances, significantly abbreviate the ensuing period of neutropenia, and several trials have also demonstrated reductions in the incidence of fever and/or of documented infections (*9-11*). A variation of this approach is to administer growth factors to the patient after a course of cytotoxic therapy, to collect large quantities of peripheral blood stem cells (PBSC) via leukopheresis during the rebound from neutropenia, and then to reinfuse those cells during a subsequent intensive course of chemotherapy. Markedly shortened durations of neutropenia have been seen in early studies (*12-14*) in which patients received autologous transplants of PBSC compared with those obtained in patients receiving equally intensive therapies without these transplants. Another application of G-CSF or GM-CSF is to use them as adjuncts to antimicrobial therapy in the setting of an established infection to "boost" neutrophil and/or macrophage numbers and function. It is hoped that this treatment will tip the balance in favor of the patient during this critical period, although there is little practical experience with this proposal at present. Finally, the growth factors might be beneficial if administered when the patient presents with fever and neutropenia. In this regard, growth factors might play a role that is adjunctive to empirical antibiotic therapy in limiting infection-related morbidity and mortality.

Mayordomo, Rivera, and coworkers (*15*) have addressed the third possibility in an article published in this issue of the Journal. They compared a population of solid-tumor patients with fever and chemotherapy-induced neutropenia who were treated with standard doses of chemotherapy and administered either G-CSF or GM-CSF versus a placebo as an addition to the routine provision of empirical antibiotic therapy. Statistically significant reductions in both the duration of neutropenia and hospital stay were demonstrated with the use of G-CSF or GM-CSF given at the time of febrile neutropenia, as compared with placebo, lead-

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ing the authors to cautiously conclude that this is a strategy worthy of further investigation. Nonetheless, while statistical significance was achieved for these end points, it is important to question whether the results are truly meaningful from a clinical perspective. For example, that the median duration of grade IV neutropenia (absolute neutrophil count [ANC]$<500/\mathrm{mm}^3$) was decreased from 3 days to 2 days by the adjunctive use of either G-CSF or GM-CSF is a difference that few practicing physicians would regard as clinically important. Furthermore, the duration of fever was unaltered by the adjunctive use of growth factors; the fever lasted only 1 day for G-CSF recipients and 2 days for those patients in the GM-CSF and placebo groups. Thus, if a very brief period of neutropenia in this patient population is only marginally shortened by the growth factors, and fever duration is not affected, what really is the practical benefit of this intervention?

Duration of hospitalization itself may be a relevant end point, although it is also important to recognize that it is, to a large extent, an artificial one primarily controlled by medical caregivers. For example, the requirement for all patients to remain in the hospital for at least 5 days for treatment of febrile neutropenia [per Mayordomo, Rivera, and coworkers (*15*)] is one that is not universally accepted. In many institutions, patients are permitted to leave the hospital when their ANC is above $500/\mathrm{mm}^3$ and they are afebrile. One could envision further alterations of such a policy to accommodate patients who fall into a low-risk category, allowing for early discharge on oral antibiotics or even without any antibiotic coverage in some cases. It seems likely that such alternatives could obviate the 2-day advantage in hospitalization duration that was observed in the group of patients who received growth factors and that these policies would also be more cost-effective.

Ultimately, it seems that the approach of Mayordomo, Rivera, and coworkers (*15*) is burdened by the fact that their study population, as a whole, consisted of patients who were already at relatively low risk for infection-related complications or prolonged hospitalization. The authors are correct, therefore, in pointing out that we need more accurate means for identifying patients who are at greatest risk for prolonged or complicated courses of neutropenia and to target these patients for adjunctive growth factor use. Indeed, they have provided a first step in this endeavor, by narrowing the application of these costly agents to only that subset of patients with neutropenia and fever, as opposed to the entire population of patients who receive cancer chemotherapy—a practice which has been recently criticized by the American Society of Clinical Oncology Ad Hoc Colony-Stimulating Factor Guideline Expert Panel (*16*). Current recommendations are to use G-CSF prophylaxis only for patients whose base-line incidence of febrile neutropenia is anticipated to be at least 40%, as there is no evidence of practical clinical or cost benefit for those with a lower base-line frequency of fever. This proposal demonstrates the importance of risk stratification as a guide to therapy.

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