Hematopoietic Growth Factors*  
Defining the Appropriate Clinical Role in Multimodality Cancer Therapy

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Laboratory investigations have begun to elucidate the regulatory molecules that control the processes of blood cell growth and differentiation. Recombinant human colony-stimulating factors are examples of biotechnology-produced molecules that have epitomized the translation of such basic scientific investigation into therapeutic advances. Small cell lung cancer, a malignancy that is overall highly sensitive to aggressive myelosuppressive chemotherapy at initial presentation, has been used as a clinical model in which the activity of human colony-stimulating factors has been tested. In this article, the clinical applications of hematopoietic growth factors are reviewed in brief. The appropriate clinical use of these agents may allow novel therapeutic strategies to be developed in a research setting. Similarly, these agents have the potential to improve supportive care and improve certain clinical outcomes in the non-research clinical care of patients. Issues of cost of treatment are raised by these agents, but the true clinical value of hematopoietic growth factors needs to be studied more rigorously, with emphasis on quality of life and redistribution of care costs outside of hospitals before definitive statements can be made.

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Myelosuppression is a significant problem in the administration of currently available chemotherapy for patients with small cell lung cancer (SCLC). The risk of severe myelotoxicity is greater when high doses of commonly used agents are given or debilitated patients are treated, eg, patients who have received extensive prior radiation therapy or elderly patients with extensive comorbid disease.

As myelotoxicity is increased, so is the potential for infectious complications. In 1966, Bodey et al1 first described this relationship in patients, with leukemia, linking the risk of infection to both the extent of neutropenia and the duration of severe myelotoxicity. This finding was then extended to patients with solid tumors, but with little objective data to corroborate the logical leap. The intensity of both the chemotherapy given to and the myelosuppression experienced by patients with leukemia is, after all, far greater than it is in patients with solid tumors. Almost 100% of patients with leukemia who are neutropenic for 4 weeks have severe infections. However, myelosuppressive chemotherapy of any intensity can result in severe morbidity and even death; thus, the clinical ramifications of myelosuppression cannot be trivialized.

In the mid-1980s, recombinant human blood growth factors, or hematopoietic cytokines, became available for laboratory and clinical investigations.2-4 The use of hematopoietic cytokines offers a novel supportive care technology to facilitate the safe delivery of chemotherapy. The first generation of these agents underwent tremendously rapid clinical development, commercial implementation, and acceptance by practicing physicians. In general, recombinant hematopoietic cytokines have been easy to use and generate few toxic reactions compared with other recombinant human molecules like the highly toxic interleukin-2. Randomized trials have shown certain clinical outcomes to be improved by the use of hematopoietic cytokines like granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF).

This article will focus on the clinical application of these fascinating molecules that provide an excellent model for laboratory to clinical translation. Randomized trials, their conclusions, and how they relate to the conventional non-research practice of oncology will also be discussed.

Background

Laboratory studies of hematopoietic cytokines have yielded several important findings, and these have allowed us to make rational decisions about the expected clinical benefits of these agents. It has been known for a long time, from the work of Metcalf5 in Australia, Sachs6 in Israel, and other experimental hematologists, that if a population of bone marrow cells is placed in a culture dish for 2 weeks under the right conditions, ie, in a medium with a feeder layer of cells underneath to supply certain proteins or a medium that is appropriately conditioned, a small subset of those cells will generate colonies. These

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mature colonies represent different hematologic lineages: granulocyte colonies, RBC colonies, and platelet precursor colonies. Because the precise nature of these so-called colony-forming assays remains unknown for 2 weeks, it is impossible to conduct a "real-time" assessment of the qualitative nature and function of the cells plated. Despite these limitations, such assays do provide an important "read-out" system with which to assess the cellular machinery of blood production, and this ultimately has allowed the discovery of different proteins that regulate the growth and differentiation of blood cells. Laboratory investigations of colony-stimulating factors would have been impossible without such colony-forming assays, and these in vitro systems have facilitated both the laboratory investigation of hematopoiesis and subsequent clinical applications.

In early studies, this field was easy to understand because there were only four known colony-stimulating factors, operationally defined on the basis of their laboratory activities. G-CSF, for example, induces growth of granulocyte colonies, whereas GM-CSF produces both granulocyte and macrophage colonies. Yet it was later learned that GM-CSF also causes eosinophil proliferation, as well as some minor effects on RBC lineages and primitive platelet precursor cells. So the nomenclature is somewhat misleading.

Today there is an ever-expanding list of biotechnology products available in the clinic. Investigators have identified molecules from interleukin-1 to interleukin-15, as well as many other proteins without "interleukin" or "colony-stimulating factor" designations that have shown important blood growth-factor activities. The challenge to oncologists is how best to employ this increasing number of biotechnology products in the clinical setting.

The clinical rationale for the use of hematopoietic growth factors with anticancer chemotherapy is quite straightforward. Myelosuppression has limited traditionally our ability to give high doses of most available chemotherapy in practice. Hematopoietic growth factors allow the delivery of more dose-intensive cytotoxic therapy, which in turn may improve the clinical outcome of patients with breast cancer and other dose-responsive diseases, including SCLC. Thus, with such improved supportive care, we may be able to obtain the maximal therapeutic effect from currently available agents while waiting for the development of true "magic bullets" with true antitumor specificity.

**EARLY STUDIES**

Early studies of G-CSF and GM-CSF in humans showed that these recombinant molecules increase circulating WBC counts in a time- and dose-dependent manner and are well tolerated. The questions arising out of these trials were, "is this increase in WBC count clinically meaningful," and "how can these agents best be applied in the clinical oncologic setting." Several strategies were proposed. One aimed to reduce the myelosuppression, specifically infectious complications, of conventional-dose chemotherapy with hematopoietic cytokines. This, in turn, would allow administration of conventional doses to be maintained without dose reductions, thereby potentially improving therapeutic outcome. Other strategies focused on whether these cytokines would aid the recovery of patients following bone marrow transplantation. It was hoped that these approaches, by reducing chemotherapy-related toxic reactions and speeding the recovery process, would also result in reduced hospital stays, reduced hospital-based costs, and improved patient quality of life.

Both G-CSF and GM-CSF have been tested widely in clinical trials, most often as "primary prophylaxis" (ie, before any infectious events have occurred) in chemotherapy-naive patients who are about to receive myelosuppressive therapy. Randomized studies have demonstrated that primary prophylaxis with G-CSF before conventional-dose chemotherapy is associated with significantly fewer episodes of fever and neutropenia and fewer hospitalizations. GM-CSF has not been as rigorously tested in a randomized setting with conventional-dose chemotherapy. In a trial of very-high-dose chemotherapy with autologous bone marrow transplantation for hematologic malignancies, however, GM-CSF significantly decreased the need for antibiotics and shortened the length of hospital stays. On the basis of these studies, both G-CSF and GM-CSF were approved for commercial distribution and routine clinical use by the US Food and Drug Administration in 1991.

**DIFFERENCES BETWEEN G-CSF AND GM-CSF**

Because of the similarity in their names, G-CSF and GM-CSF have not been well differentiated in the literature. Indeed, some investigators have published reports in which it appears these two products were interchangeably administered. It is important to know that G-CSF and GM-CSF, despite their similar names, have a strikingly different biology at a very basic level: different signal transduction pathways, a somewhat different spectrum of target cells, and certainly different kinetics of activity. Unfortunately, to our knowledge, no randomized clinical trial has compared directly these molecules.

In terms of clinical activities, both G-CSF and GM-CSF induce leukocytosis, but their toxicity profiles differ somewhat; the incidence of fever associ-
ated with cytokine administration is near 0% for G-CSF, for example, whereas for GM-CSF it is 20 to 30%.4,13

**SCLC Treatment Strategies Using Colony-Stimulating Factors**

The clinical relevance of *in vitro* stimulation of leukocyte production by G-CSF and GM-CSF has been evaluated in several studies. Colony-stimulating factors have been used in two situations to treat chemotherapy-associated toxic reactions: (1) as “primary prophylaxis” or in previously untreated patients during the first cycle of chemotherapy, and (2) as “secondary prophylaxis” or in patients who have experienced significant chemotherapy-associated toxic reactions during prior cycles of chemotherapy administered without colony-stimulating factors. In this section, results obtained in both treatment settings are discussed.

**Primary Prophylaxis**

In a rigorous, prospective, double-blind, multicenter study by Crawford et al,9 chemotherapy-naive patients with SCLC were randomized to receive cyclophosphamide, doxorubicin, and etoposide on days 1 to 3, either with or without G-CSF administered subcutaneously after chemotherapy. The results were striking. The group receiving G-CSF reached their nadir about a day earlier but recovered much more quickly than the group not receiving G-CSF. The nadir period was 3 days for G-CSF-treated patients vs 6 days for the placebo-treated patients. These results were corroborated in a similar multicenter trial performed in Europe.10

The study9 also found that G-CSF impacts positively on clinical outcomes. The placebo group experienced approximately twice the incidence of infectious complications with fever and neutropenia (57%) as compared with 28% in the G-CSF group during the first chemotherapy cycle. In conjunction with this decreased incidence of fever, hospitalization and antibiotic requirements for the placebo group were also greater than for the group treated with G-CSF, a finding that would have dramatic implications for decreasing the costs of hospital care.

Another recent study evaluated two different doses of GM-CSF (10 μg/kg/d and 20 μg/kg/d) vs no GM-CSF in previously untreated patients with SCLC receiving the same three-drug regimen.14 Results showed median duration of severe neutropenia was 6 days for patients receiving no GM-CSF, 2 days for those receiving 10 μg/kg/d of GM-CSF, and only 1 day for those given GM-CSF, 20 μg/kg/d. However, the clinical benefits noted by Crawford et al9 using G-CSF did not materialize in this study of GM-CSF. Although GM-CSF decreased the duration of severe neutropenia (a laboratory-based surrogate indicator of outcomes), it had no significant impact on true adverse clinical events. In fact, patients receiving the higher GM-CSF dose (20 μg/kg/d) actually experienced somewhat higher rates of fever and neutropenia that were associated probably with high-dose GM-CSF use.

What can explain the differences in the impact of G-CSF vs GM-CSF on actual clinical outcomes in these studies? Both studies used the same chemotherapy combination in previously untreated patients with SCLC. The G-CSF study, however, used significantly higher doses of doxorubicin and etoposide compared with the GM-CSF study (50 mg/m² and 120 mg/m² vs 40 mg/m² and 80 mg/m², respectively). Clearly, the higher toxicity rates observed in the G-CSF study resulted from the higher drug doses used; this increased toxicity, in turn, was ameliorated more demonstrably by G-CSF. Thus, it is important to remember that dose intensity of chemotherapy (and the true rate of chemotherapy-associated clinical toxic reactions from myelosuppression) are integral to determining whether colony-stimulating factors will significantly mitigate chemotherapy-induced toxic reactions.

**Secondary Prophylaxis**

In the study by Crawford et al,9 placebo-treated patients who experienced infectious complications during the first cycle of chemotherapy were crossed over to receive G-CSF treatment following the second chemotherapy cycle (secondary prophylaxis). The beneficial results from G-CSF obtained in these patients were nearly identical to those achieved in the chemotherapy-naive group, with the same magnitude of accelerated recovery from nadir neutropenia. This supports the observation that previously treated patients (and not only previously untreated patients) are able to exhibit improved hematologic recovery with colony-stimulating factors.

**Cost Considerations**

A retrospective analysis from Indiana University15 estimated the average cost of SCLC treatment without G-CSF vs SCLC treatment utilizing G-CSF for primary or secondary prophylaxis. First, the authors determined the average cost of treating patients with SCLC with chemotherapy in the decade before G-CSF became available. Results showed the average patient with SCLC required about 155 days in hospital and an average total cost of treatment without G-CSF of $186,000. Because the population analyzed had received a variety of chemotherapeutic regimens, the figures arrived at may be somewhat skewed; however, such a population is also reflective of the wide range of agents used in the nonresearch
practice of oncology.

Using the same database, the authors then factored in figures based on results of randomized studies of G-CSF. When G-CSF is used as primary prophylaxis, overall needs for hospitalization are estimated to be reduced from 155 days to 51 days, and associated non-G-CSF treatment costs are reduced from $186,000 to $61,000. However, when the cost of G-CSF given to every patient in every cycle (the *sine qua non* of "primary prophylaxis") is factored in, the average cost of treatment soars to $1.2 million. When G-CSF is used as secondary prophylaxis, duration of hospitalization is reduced from 155 days to 134 days, the cost of G-CSF is reduced to $190.00, and the total cost of treatment is $351,000—still more than the cost of treatment without G-CSF, but not nearly as expensive as primary prophylaxis with G-CSF.

It is important to note that the regimens examined in this retrospective, and somewhat speculative, study were associated with relatively low rates of myelosuppression, and that the value of G-CSF increases dramatically as the myelosuppressive potency of chemotherapy increases. Nevertheless, in today's cost-conscious health-care environment, it has become necessary to assess the clinical value of a given therapy by weighing its monetary costs against its clinical activity. Because colony-stimulating factors are not true anticancer treatment agents, but rather are agents of improved supportive care, their role is going to have to be defined carefully so as to derive optimal therapeutic benefits at reasonable costs.

**Delaying Administration of Colony-Stimulating Factors**

Data on new applications for colony-stimulating factors are beginning to appear in the research literature. One such application involves using colony-stimulating factors for established fever and neutropenia, or, in other words, delaying administration until a patient experiences chemotherapy-induced myelosuppression. Although this "therapeutic use," rather than "prophylactic use," is not the approved indication for either G-CSF or GM-CSF in the United States at this time, it is a widely accepted manner of use both in the United States and abroad. It should be noted, however, that this strategy is based on little or no supporting data.

To my knowledge, only one published, prospective, randomized multicenter study has attempted to define the benefits of delayed administration of G-CSF as an adjunct to antibiotics for fever and neutropenia. In the study that was performed in Australia, patients were randomized to receive either standard treatment, including good nursing care and empiric parenteral antibiotics, or the same standard treatment plus G-CSF. Results showed that G-CSF significantly decreased the duration of severe neutropenia from 4.3 to 3.3 days.

This shortened duration, however, did not translate into a decrease in the duration of hospitalization. I believe that this failing is consistent with a methodologic design problem in this study. The study was set up with extremely conservative rules that required patients to remain hospitalized until the neutropenia had resolved and the patients had remained afebrile for a full 4 days (afebrile was defined very strictly as <38.3°C). At the Dana-Farber Cancer Institute, we are no longer that stringent in the management of febrile neutropenic episodes; once a patient's neutrophil count has recovered sufficiently (eg, >500/µL) and there are no other debilitating symptoms, that patient is discharged from the hospital. Thus, it is difficult to determine from this study whether therapeutic use of G-CSF as an adjunct to antibiotic therapy does or does not decrease the duration of hospitalization.

**Scheduling Dosing of Colony-Stimulating Factors**

Administration of the optimal treatment for SCLC is very much a multidisciplinary collaboration. When scheduling dosing of hematopoietic cytokines, it is crucial to define the impact of the schedule on radiation therapy and the specific chemotherapy regimen one chooses to use. Importantly, one should not use colony-stimulating factors (which stimulate the growth and differentiation of young blood cells) concurrently with chemotherapy; good data in the literature suggest that by increasing the cycling of bone marrow progenitor cells, one may actually increase their sensitivity to chemotherapy and, paradoxically, worsen myelosuppression.

One study, for example, evaluated the concomitant administration of G-CSF and 5-fluorouracil/leucovorin chemotherapy, which ordinarily is not a very myelosuppressive regimen. The data from patients receiving concomitant G-CSF plus chemotherapy were compared with data from a separate patient cohort that received the more-traditional sequential dose schedule (ie, beginning the dosing of G-CSF 24 h after chemotherapy). None of five patients given sequential chemotherapy followed by G-CSF had neutropenia, whereas four of five patients (80%) given the concurrent schedule had severe neutropenia. Other studies have corroborated these findings.

Many investigators also believe that colony-stimulating factors should not be administered concurrently with large-field radiation therapy. In a multicenter study conducted by the Southwest Oncology group, etoposide/cisplatin chemotherapy was given to patients with SCLC, followed by either...
GM-CSF administered concurrently with large-volume radiation therapy to the chest or radiation therapy alone (control). The results of this study, which stand in stark contrast to most other studies of blood growth factors in chemotherapy, showed absolutely no benefit for the GM-CSF group compared with the control group. In fact, patients receiving GM-CSF experienced worse thrombocytopenia, which suggests that GM-CSF may have activated the cycling of progenitor cells, and as these cells trafficked through the irradiation port, they may have been killed by the radiation. This explanation, however, is speculative. Additionally, patients receiving GM-CSF exhibited no benefit with regard to infectious episodes. Thus, the concurrent administration of radiation therapy with blood growth factors remains highly investigational.

CONCLUSIONS

Appropriate use of hematopoietic growth factors in patients with SCLC receiving myelotoxic chemotherapy can decrease the incidence and duration of neutropenia as well as the rates and duration of hospitalization. With colony-stimulating factor support, one can deliver aggressive and standard schedules of chemotherapy more effectively. The impact of such adjunctive treatment on quality of life, however, has not been objectively studied. One study using recombinant human erythropoietin as an adjunct to chemotherapy showed, in a fairly rudimentary way, that quality of life may be improved by the addition of erythropoietin. Additional studies will be required to confirm and expand on this finding.

The American Society of Clinical Oncology, in its first effort at development of data-based practice guidelines, has drafted practice guidelines on how best to use hematopoietic growth factors. This effort was prompted largely in response to the often irrational policies in this area adopted by insurance carriers. Corporate strategies by the biotechnology concerns are certainly going to have an impact on colony-stimulating factor usage patterns, as are new clinical research initiatives.

Questions remain to be answered in future trials. The risks of myelosuppressive chemotherapy need to be weighed carefully against the potential for beneficial clinical outcomes in SCLC. We need to define rigorously at what point dose-intensive chemotherapy most effectively influences clinical outcome, as well as the costs involved in such treatment. We need to find ways to overcome the nonhematologic toxic reactions, including mucositis, cardiotoxicity, and dermatologic and gastrointestinal toxicities, associated with many chemotherapeutic agents. Tumor resistance and the regrowth of SCLC malignancies remain major problems to be addressed as well. The availability of colony-stimulating factors offers clinicians a powerful new set of tools to strengthen host defense mechanisms and blood production. It is now imperative to use these agents to develop new treatment strategies that can improve the chances for palliation and survival in patients with chemotheraphy-sensitive tumors such as SCLC.

REFERENCES

