Impact of Hematopoietic Growth Factors on the Management of Small-Cell Lung Cancer*

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Hematopoietic growth factors regulate the production and differentiation of immature progenitor cells and activate mature effector cells. With recombinant DNA technology, these human proteins have been biosynthesized, and their clinical applications hold promise for beneficial therapeutic effects. The hematopoietic growth factors are generally classified in 2 groups, the colony-stimulating factors (CSFs) and the interleukins. In oncology, it has been shown that the administration of CSFs will attenuate chemotherapy-induced myelosuppression and permit administration of the planned chemotherapy doses, especially in chemosensitive tumors like small-cell lung cancer. Widespread clinical administration of the CSFs at this time without regard to the predicted risk of a given therapeutic regimen would seem to be inappropriate both therapeutically and economically. Continuing investigations should focus on important clinical end points. Until then, our ability to use the CSFs optimally, rationally, and in a cost-effective manner will remain limited. (Chest 1993; 103:427S-32S)

*The recent availability of hematopoietic growth factors in clinical practice has generated both intense interest and justifiable confusion regarding the appropriate use of this novel class of agents. While certain insights may be drawn and reasonable suggestions made based on the somewhat limited data that now exist, this field of clinical research is changing very rapidly. Thus, continuing investigations using appropriate clinical end points and critical assessments of results are necessary to define the proper clinical role of these agents.

In oncology, the use of hematopoietic growth factors as adjuncts to chemotherapy against small-cell lung cancer (SCLC) has ignited interest because of the known chemosensitivity of these tumors. The stimulation of blood cell production induced by these growth factors is seen as a way to permit safe administration of increased dose intensities of chemotherapeutic agents by attenuating the myelosuppressive effects of these treatments. It is hoped this will then increase both response rates and, most importantly, survival in a clinically meaningful way. This article will suggest the potential clinical scope of the hematopoietic growth factors, focus specifically on their use in studies of patients with SCLC, and attempt to place these studies in a clinical perspective, suggesting critical criteria for the clinician attempting to review the expanding literature in this area.

Hematopoietic Growth Factors

The mature cells seen in peripheral blood arise from a hierarchical array of immature cells that are generated from the poorly understood hematopoietic stem cell. Hematopoietic growth factors regulate the production and differentiation of progenitor cells and activate functions in mature effector cells. Through recombinant DNA techniques, these growth factors—and their various effects—can now be manipulated clinically. Several general reviews of hematopoietic growth factors have been published as background in this field.1,2

The colony-stimulating factors (CSFs) were generally first identified on the basis of their ability to simulate progenitor cell growth in culture systems, whereas the interleukins' ability to serve as molecular mediators of communication between immune system cells—most prominently lymphocyte subsets and monocytes—first brought these agents to light. The nomenclature of the hematopoietic growth factors has thus far proved as varied (and confusing) as their potential uses. First identified as the natural products of activated lymphocytes, probably in response to infection, they were named "lymphokines," but as it became clear that a variety of stimulated cells could produce hematopoietic growth factors, the more inclusive term "cytokine" was adopted for these humoral mediators of hematopoiesis. To date, 3 hematopoietic growth factors have been approved by the US Food and Drug Administration and are widely available commercially (erythropoietin, granulocyte-macrophage CSF [GM-CSF], and granulocyte CSF [G-CSF]), and at least 6 others are being investigated in clinical research trials (including interleukin-3, interleukin-6, macrophage-CSF, stem cell factor, interleukin-4, and a synthetic combination of GM-CSF and interleukin-3 known as PIXY 321). Newer interleukins (eg, interleukin-11) are being identified by their primary action of stimulating hematopoiesis, and important hematopoietic activity has been identified in other molecules that do not belong to the CSF or interleukin nomenclature (eg, the c-kit ligand, also known as stem cell factor).

Given the various effects of hematopoietic growth factors shown in Table 1,3,4,5 the commonly accepted term "colony stimulating factor" seems limiting if not misleading, although adequate for their current oncologic role of inducing blood production. Briefly, the most well-studied cytokines (GM-CSF and G-CSF) are lineage-restricted growth factors that not only induce the production of specific blood cells but actually increase the cell-killing capability of those cells. This has been demonstrated in both neutrophils (for both G-CSF and GM-CSF) and monocytes (for GM-CSF). The potential clinical applications of these activities are far-ranging. For example, young bone marrow cells can be induced to move into the bloodstream by the growth factors where they can be removed from a patient by leukapheresis and retransfused at a later date to serve as extra support to the "blood production machinery" that may be damaged by aggressive chemotherapy. Additionally, vascular endothelial
Table 1—Biologic Activities of Hematopoietic Growth Factors

*Stimulate proliferation of blood precursor cells
  - Accelerated transit time through cell cycle* (eg, GM-CSF and G-CSF decrease duration of S phase)
  - Shorten G0 of quiescent progenitor pool
*Induce differentiation
  - Factor-directed lineage-specific maturation with lineage-specific factors (eg, G-CSF, Epo)
*Activate mature cell function
  - ADCC, complement-mediated phagocytosis, TNF-dependent cell-mediated cytotoxicity
*Redistribute (mobilize) cells
  - Acute, transient neutropenia (G-CSF and GM-CSF)*
  - Rapid neutrophilia within 24 h following GM-CSF or G-CSF likely represents redistribution of mature neutrophils, not solely an acute increase in proliferation/differentiation
  - Mobilize hematopoietic progenitor cells (and stem cells?) from bone marrow into peripheral blood on administration of CSFs alone (10-fold increase with G-CSF or GM-CSF) or after chemotherapy (50- to 100-fold increase with either after aggressive chemotherapy)*
*Nonhematologic effects
  - G-CSF and GM-CSF receptors present on nonhematologic cells
  - Vascular endothelial cells
  - Placenta and trophoblastic cells
  - SCLC cell lines
  - G-CSF and GM-CSF stimulate proliferation and migration in vascular endothelial cells in vitro and in vivo*
  - Minor stimulation of proliferation by GM-CSF and G-CSF in 2 human colon carcinoma cell lines (HTB-38 and CCL 187)* and 2 SCLC cell lines (H69 and H128)* and by GM-CSF in 2 osteosarcoma cell lines (MG-63 and HOS), the MCF-7 breast carcinoma cell line, and marrow stromal fibroblast cells.* The physiologic or clinical significance of the observations is unclear.

*Epo = erythropoietin; ADCC = antibody-dependent cell-mediated cytotoxicity; TNF = tumor necrosis factor.

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![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21670/ on 04/06/2017)

**Figure 1.** Hematologic response to recombinant human G-CSF (Filgrastim) administered before and following courses 2 and 4 of chemotherapy (CT) in a patient with SCLC. CT consisted of doxorubicin 50 mg/m² and ifosfamide 5 g/m², both on day 1, as well as etoposide 120 mg/m² on days 1, 2, and 3. The patient received G-CSF 1 µg/kg/day by continuous intravenous infusion during the times indicated by the bars. The shaded areas represent the total area of absolute neutropenia (neutrophils <1 × 10⁹/L). BT = blood transfusions; closed circles = leukocytes; open circles = neutrophils. Reprinted from Bronchud et al,* with permission.

**Impact of Hematopoietic Growth Factors in SCLC (George D. Demetri)**

cells have receptors for GM-CSF and G-CSF—and possibly other growth factors—and the CSFs can induce the migration and proliferation of these cells.

A theoretically disturbing finding is the identification of receptors for certain hematopoietic growth factors on the surface of a subset of cancer cells, including selected cell lines derived from SCLC, breast cancer, and sarcomas. However, the physiologic relevance of these findings, although not studied directly, seems questionable. Of the thousands of patients who have received these factors worldwide thus far, there has been no gross clinical evidence that hematopoietic growth factors actually stimulate tumor cell growth in vivo.

**CLINICAL TRIALS OF CSFs IN SCLC**

In the first administration of CSFs to humans, GM-CSF was administered to leukopenic acquired immune deficiency syndrome (AIDS) patients. This study did demonstrate that a recombinant CSF could induce a leukocytosis, and that the white blood cell proliferation was transient, abating in response to cessation of GM-CSF. Also, this study showed that patients tolerated the treatment well, with none of the severe side effects that had been observed with other biological drugs such as high doses of interferons or interleukin-2.

**G-CSF Support**

Bronchud and colleagues* were among the first to employ a myeloid growth factor in a phase I/II pilot study of chemotherapy (ifosfamide with mesna, doxorubicin, and etoposide) against advanced SCLC in 12 patients. The initial continuous intravenous infusion of G-CSF (before chemotherapy was begun) was accompanied by an increased white blood cell count in all patients, which subsided on discontinuation of the infusion. During this initial phase, patients were entered in sequential groups at escalating G-CSF dose levels (from 1 to 40 µg/kg/day). Doses were not escalated in...
individual patients, and patients received the same G-CSF dose during the chemotherapy portion that they had received in the first part of the study. Patients were assigned sequentially to receive G-CSF with odd or even chemotherapy cycles. In this patient (Fig 1), who received adjunctive G-CSF during the second and fourth chemotherapy cycles, the chemotherapy-induced leukocyte nadirs were quite brief in duration and attenuated in depth, with levels barely falling below $1 \times 10^9/L$, the most conservative “danger level.” Moreover, recovery was relatively rapid. Adjunctive G-CSF was not given with the first and third chemotherapy cycles, during which the patient experienced more severe, prolonged nadirs, one of which was complicated by fever with neutropenia requiring hospitalization and intravenous antibiotics. This study design may be criticized: patients served as their own controls, and the impact of cumulative myelotoxicity may confound the data from later cycles. Nonetheless, the fourth chemotherapy dose, again given with G-CSF support, produced a nadir that mimicked the second-dose nadir in both degree and duration, suggesting a beneficial activity in this clinical setting.

These data suggested the potential of CSFs in limiting the duration of the leukocyte nadir in patients receiving chemotherapy, but major questions remained about the use of these data and about the CSFs themselves. Although many of these questions pertain to optimal doses and the dosing period, a paramount question remains: will the use of adjunctive therapy with a hematopoietic growth factor confer clinically significant advantages to patients given standard-dose combination chemotherapy? And, as important, will CSFs by themselves allow oncologists to maintain acceptable toxicities for patients during administration of heightened doses of chemotherapy? The major question in lung cancer also remains: does more chemotherapy dose correlate with improved clinical outcomes? Further, if such benefits are proven, can they be obtained at costs acceptable to the economy as a whole?

A large phase III randomized, double-blind, multicenter, placebo-controlled trial was undertaken by Crawford et al.\textsuperscript{10} to answer the question of whether adjunctive G-CSF conferred clinically significant advantages to patients treated with combination chemotherapy. More than 200 patients with SCLC were randomized to receive a fairly aggressive regimen containing cyclophosphamide, doxorubicin, and etoposide with either placebo or G-CSF (given at a dose of 230 $\mu g/m^2$ subcutaneously on days 4 through 17) as the adjunctive supportive care measure. Interestingly, patients who developed neutropenic fever—defined as a temperature $\geq 38.2^\circ C$ with absolute neutrophil counts $<0.5 \times 10^9/L$—were crossed over to receive open-label G-CSF, which reflected the dominant bias that denying hematopoietic growth factors to patients experiencing neutropenic fever would be unethical. Thus, even though the 2 arms of the study were well balanced in terms of patients’ performance status, marrow involvement, and disease stage, interpretation of the results from all cycles of chemotherapy is difficult. This is further complicated by the very high incidence of fever with neutropenia that occurred during the first cycle (57% of the placebo group and 28% of the G-CSF group). Many suggestions have been proffered to account for this high rate of fever and neutropenia: the fact that patients were told to take their temperatures every day (not routine in daily practice), the relatively conservative figure of 38.2°C (rather than 38.5°C, which many oncologists use), the aggressiveness of the chemotherapy doses used, etc. This high rate of fever with neutropenia meant that a significant

\begin{figure}
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\caption{Effect of recombinant human G-CSF (Filgrastim) compared with placebo as adjunctive support of chemotherapy for small-cell lung cancer. Median absolute neutrophil count (ANC) during cycle 1 plotted on a linear scale (A) and a log scale (B). The arrow shows the start of placebo or G-CSF administration. Hatched area denotes the degree and duration of severe neutropenia (counts $<0.5 \times 10^9/L$). Reprinted from Crawford et al.\textsuperscript{14} with permission.}
\end{figure}
fraction of patients was crossed over to receive open-label G-CSF after cycle 1, and this trend continued over 6 cycles of therapy, so that by the end of the study, only a small minority of the entered patients was receiving placebo.

The most instructive data are thus from cycle 1, when the double-blind design was wholly intact. Chemotherapy was given on days 1 through 3, with either placebo or adjunctive G-CSF administered on day 4. Figure 2A shows the rather impressive leukocytosis documented on day 5 in patients who had received hematopoietic growth factor support. This effect appears too rapidly to be accounted for solely by the stimulation of new marrow cells, and it is likely due to a G-CSF-induced redistribution of young neutrophils to the periphery. Figure 2A emphasizes the fact that such representations (with white blood cell counts plotted on a linear scale), while dramatic, may not be optimal for interpreting a patient’s condition during the critical period of absolute neutropenia. The clinically relevant action of growth factor support occurs after the initial leukocytosis: the leukocyte nadir still occurs, but its duration is shortened significantly by the growth factor support. It is important to remember that the pre nadir leukocytosis and the post nadir leukocyte count are likely to be far less important to the patient’s clinical well-being than are the degree and duration of the leukocytopenia. Figure 2B shows the same data plotted on a log scale, which graphically emphasizes the critical nadir period. Although the G-CSF support shortened the nadir period by about 50% (from 6 to 3 days), even the patients treated with G-CSF experienced severe neutropenia (defined as an absolute neutrophil count ≤0.5×10⁹/L).

Generally, patients given hematopoietic growth factor support experience the leukocyte nadir approximately one day earlier. This probably results from the growth factor-induced mobilization of the postmitotic marrow pool into the periphery, so that the effects of chemotherapy on the circulating white blood cell counts are seen earlier. Although leukopenia develops earlier, G-CSF support also significantly shortens its duration, consequently reducing the time that patients are at risk for infection and neutropenic fever. In this study, patients who received G-CSF had about a 50% reduction in the incidence of neutropenic fever. As noted before, the incidence of neutropenic fever was substantial in the control group, on the order of 65% at the different centers. Moreover, neutropenic patients who had received G-CSF required fewer days of hospitalization.

In Europe, Green and colleagues40 from several different countries conducted a similarly designed trial using the same drugs and doses in patients with SCLC, but no crossover to open-label G-CSF was permitted. The definition of “fever with neutropenia” in this trial also used a temperature of 38.2°C, but the absolute neutrophil count of <1.0×10⁹/L was higher. An interim analysis showed that 24 of 51 placebo-treated patients (48%) and 13 of 50 G-CSF-treated patients (26%) had developed febrile neutropenia. The incidence of infection and neutropenic fever was somewhat lower in the control arm in this trial than it had been in the American study.41 Nevertheless, the patients who received G-CSF still had a nearly 50% lower incidence of neutropenic fever.

The critical factors to oncologists (and our patients) are, of course, response rates and survival. In this respect, results from the American42 and British43 trials were superimposable for both arms whether or not G-CSF was given. The similarity of response and survival in both trials is especially interesting when the drawback of the American trial—the virtual ubiquity of G-CSF administration in the control arm by the time the trial ended—is considered. The similarity of these data lends some indirect support to the lack of any tumor stimulation by the G-CSF. Although direct evidence that specifically addresses this issue is lacking, the results of these studies are nonetheless reassuring in light of the numbers of patients now being treated outside of the investigational setting with these agents. Also reassuring is the remarkable absence of serious adverse effects associated with G-CSF, the major problem reported being a mild bone pain. The toxicities of other biological agents, such as high doses of interleukin-2, had caused some concern in this regard, but no serious adverse events have been noted in studies of G-CSF.

GM-CSF Support

A study that, to date, has only been reported in abstract form, by Hamm and colleagues44 again used the combination of cyclophosphamide, doxorubicin, and etoposide to treat patients with SCLC, who were randomized to receive either placebo or 1 of 2 doses of GM-CSF (10 or 20 μg/kg/day subcutaneously for 10 days). Preliminary analysis of these data shows that the placebo group had 6 days of severe neutropenia, with neutrophil counts <0.5×10⁹/L. The effect of GM-CSF on the neutrophil nadir was apparently dose-related, with the lower dose (GM-CSF 10 μg/kg/day) dramatically reducing the duration the nadir compared with placebo, and the higher GM-CSF dose associated with an even shorter nadir. When these data are reviewed in terms of the actual incidence of fever and neutropenia, however, the results are far less impressive. Patients who received placebo in this trial had a low 17% incidence of neutropenic fever, while the patients who received the lower GM-CSF dose had a statistically nonsignificant 12% incidence. Patients randomized to the higher GM-CSF dose actually had a higher incidence, possibly because the growth factor itself may have induced fever at this higher dose level. Moreover, even this slight, nonsignificant difference in the incidence of neutropenic fever between placebo- and GM-CSF-treated patients disappeared during the second course, when the chemotherapy doses were reduced. In all, 62% of the placebo group, 28% of the low-dose, and 44% of the high-dose GM-CSF groups required dose reductions. It remains to be shown that such differences in delivered dose intensity significantly change clinical outcomes in patients with SCLC.

Again, this study underscores the necessity of going beyond leukocyte counts when evaluating data on hematopoietic growth factors. Although the comparably poorer results with the GM-CSF in this trial44 vs the reported results for G-CSF from the Crawford trial45 are intriguing, no inherent inferiority for GM-CSF should be deduced based on a single study. Nonetheless, it should be pointed out that, although the drug regimens comprised the same agents—cyclophosphamide, doxorubicin, and etoposide—the GM-CSF study by Crawford et al45 employed higher planned doses of chemotherapy for both the etoposide dose
(120 mg/m²/day for 3 days vs 80 mg/m²/day for 3 days in the GM-CSF trial) and the doxorubicin dose (50 mg/m²/cycle vs 40 mg/m²/cycle in the GM-CSF study).

**Clinical Relevance of Hematopoietic Growth Factors**

Because growth factors will almost certainly add to the costs of cancer therapy, it is important to focus on some hard clinical end points when assessing their activity. Despite their tantalizing clinical promise, numerous questions remain about the optimal clinical use of these agents. Laudable as preventing or decreasing hospitalization for antibiotic administration is in those high-risk patients receiving aggressive cytotoxic chemotherapy, the indiscriminate use of the growth factors in all cancer patients receiving any sort of chemotherapy would be irrational as well as expensive.

The task is to determine the precise role of these agents in supportive care. Oncologists must determine which regimens should be supported with these agents and when treatment is optimally administered, as well as a way to prospectively identify which patients are most likely to benefit from growth factor support. There is good reason to believe that these agents can be cost-effective if used properly.

The optimal doses and schedules of the CSFs also need to be elucidated, including the best starting time for their administration postchemotherapy. In general, rapid intravenous bolus administration achieves suboptimal hematopoietic responses compared to more prolonged infusions.

Subcutaneous bolus administration appears to provide clinical results equal to or better than equimolar doses of hematopoietic growth factors administered by short intravenous infusions, at least for G-CSF or GM-CSF. A variety of other questions must be addressed concerning the growth factors to assure optimal therapy. What laboratory criteria suggest adequate hematologic recovery and cessation of growth factor support? Are there prognostic indicators of failure to respond to growth factors? Are there differences in toxicity among the hematopoietic growth factors when ideal doses and schedules are used? Will any future growth factor allow reproducible support of platelet counts? What are the effects of giving cytotoxic chemotherapy concomitantly with hematopoietic growth factor stimulation of hematopoiesis? (Until data are available, the last question should be addressed only in the setting of a research study.)

The existing literature on hematopoietic growth factors certainly demonstrates their ability to aid the delivery of planned chemotherapy doses on the scheduled days. What remains to be determined is the effect of this increased dose intensity on the response and survival of patients who receive the planned protocol doses. (Again, any attempt to escalate chemotherapy doses further must be done in the research setting.) Few studies, however, have assessed dose as an independent variable. The interpretation of existing data is, unfortunately, flawed by the problems of multiple variables, including different drugs between regimens, different dose intensities, and different patient populations (with older patients and those with poor prognostic factors getting a lower dose intensity). Nevertheless, several lines of evidence in a variety of malignancies suggest a link between dose intensity and clinical outcomes. It is now imperative to maximize the therapeutic index of current antineoplastic therapies, and hematopoietic growth factors will prove enormously useful in this regard.

**Conclusions**

Despite the great promise of the hematopoietic growth factors, their clinical activities and their ultimate role in routine cancer therapies are still being assessed. The literature on cytokines and CSFs in particular demonstrates their ability to attenuate the effects of chemotherapy-induced myelosuppression. When viewed critically, these data provide an important set of tools to use in designing further investigations that will help us use these agents rationally. The routine use of these agents with standard-dose chemotherapy may be reasonable in certain subsets of patients, but these categories remain poorly defined. Thus, the widespread indiscriminate clinical application of these agents at present would add more to the cost of therapy than to its results. For certain patients, however, CSF support may prove extraordinarily useful in providing cost-effective therapy with optimal clinical results. The clinical importance of dose intensity requires some further rigorous testing to substantiate. Clinical trials are needed to resolve questions regarding dose-response relationships, and such trials are particularly appropriate for chemotheraphy-responsive malignancies like SCLC and breast cancers.

**References**


