Hematopoietic Growth Factors

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Introduction

Although there have been significant and potentially curative advances in the treatment of many common human malignancies in the past 20 years, conventional combination chemotherapy regimens continue to have dose-limiting toxicities that place practical limitations on dose-intensity. In particular, most common chemotherapy regimens produce dose-limiting hematopoietic toxicity, a factor that until recently has constrained the ability to safely design more dose-intense treatment regimens. Inevitable periods of neutropenia and thrombocytopenia place patients at risk for potentially serious and occasionally life-threatening infectious and hemostatic complications, particularly in the setting of high-dose cancer therapy.

Pharmacologic agents that accelerate hematopoietic recovery obviously have the potential to improve selected therapeutic and supportive care aspects of cancer medicine. This article will review the important clinical and scientific aspects of hematopoietic growth factors, with an emphasis on their present-day use in the care of cancer patients.

Hematopoietic Growth Factors

Hematopoietic growth factors are a family of cytokines that interact with specific receptors on hematopoietic cells. These molecules regulate the functional activation of the specific cells with which they interact and are required for the survival, proliferation, and differentiation of hematopoietic progenitors. The development of recombinant DNA technology has made it possible to synthesize and purify pharmacologic doses of a variety of hematopoietic growth factors. A number of growth factors have been studied in clinical trials since the mid-1980s, including granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), erythropoietin (EPO), interleukin-3 (IL-3), and, more recently, the molecule putatively thought to represent thrombopoietin.

THE HEMATOPOIETIC SYSTEM

The hematopoietic system is a hierarchical structure, with multipotent stem cells eventually becoming nonreplicative mature hematopoietic cells that circulate in the peripheral blood. The earliest hematopoietic cells are called stem cells, because of their presumed lifelong ability to replicate and produce progeny that develop and differentiate along all three
Hematopoietic lineages. Early hematopoietic progenitors probably contain multiple cytokine receptors, selectively losing the ability to respond to all but a few selected growth factors as they become mature committed hematopoietic cells.

The human stem cell has not truly been morphologically and immunologically characterized, although certain cell-surface receptors (such as the receptor for CD34) have been used as markers of cells that currently represent our understanding of the “least committed” hematopoietic progenitors. Except for these earliest stem cells, all major hematopoietic progenitors have now been identified in culture and are known to be dependent on specific hematopoietic growth factors for differentiation along specific lineages. The major endogenous sources of hematopoietic growth factors include fibroblasts, endothelial cells, lymphocytes, monocytes, and macrophages.3-5

Some growth factors (e.g., GM-CSF) appear to have a rather broad array of action on very early hematopoietic progenitors, leading to multilineage increases in hematopoietic cell production/differentiation, while others (e.g., G-CSF) seem to act mainly on more terminally differentiated cell types, producing fairly incisive changes in specific committed populations, such as neutrophils.

Granulocyte colony-stimulating factor (GM-CSF) is produced in vivo by T lymphocytes,13 monocytes,14 fibroblasts,15 and endothelial cells.16 The molecule affects a series of somewhat less-committed progenitors, including progenitors for the granulocyte, macrophage, eosinophil, and megakaryocyte lineages. The predominant effect of GM-CSF is seen on the granulocyte/macrocyte lineages, leading to increases in the production of mature neutrophils and macrophages.17 GM-CSF sustains the viability of and potentiates the function of mature neutrophils,18 and it appears to have the ability to increase microbial killing through increased phagocytosis and superoxide production.19,20

The broad array of cellular interactions (including the ability to induce the production of other cellular cytokines) for differentiation along specific lineages. The major endogenous sources of hematopoietic growth factors include fibroblasts, endothelial cells, lymphocytes, monocytes, and macrophages.3-5

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has made it difficult to separate out the primary activity of GM-CSF from secondary effects caused by the induction of other cytokines. This broad scope of activity likely explains the more diffuse and systemic nature of its side effect/toxicity profile, which includes fever, chills, malaise, hypersensitivity reactions, musculoskeletal effects, and several clinical manifestations of a capillary leak syndrome, including generalized edema with weight gain and pleural and pericardial effusions.

Both G-CSF and GM-CSF are now routinely administered as subcutaneous injections, although in early clinical trials they were often administered as intermittent or continuous intravenous infusions.

ERYTHROPOIETIN

In the early 1900s, it was postulated that erythropoiesis was regulated by humoral agents that responded to changes in tissue oxygenation. In 1953 Erslev demonstrated that an increase in erythropoiesis could be brought about in normal rabbits by the infusion of large volumes of serum obtained from rabbits that had been rendered anemic from blood loss. The product, named erythropoietin, was eventually isolated, purified, cloned, and expressed in mammalian cells. Once pharmacologic amounts of EPO became available, clinical trials quickly followed demonstrating its efficacy in treating the anemia of chronic renal failure.

EPO is produced by the liver in utero, but after birth the major source of production is the kidney. EPO is present in physiologic quantities in normal individuals, and its production is increased in response to decreased oxygen tension as perceived by the kidney. It interacts with specific receptors on erythroid burst-forming units and erythroid colony-forming units and is effective when administered in pharmacologic doses either intravenously or subcutaneously.

MEGA KARYOCYTE GROWTH AND DEVELOPMENT FACTOR/THROMBOPOIETIN

Although several known hematopoietic growth factors have demonstrable effects on megakaryocyte and platelet production, the growth factor directly responsible for megakaryopoiesis/thrombopoiesis had until recently remained elusive. The discovery of the cytokine receptor c-Mpl and its relationship to megakaryopoiesis has led to the discovery of two cytokines that appear to be ligands for c-Mpl. These cytokines are thought to be lineage specific, affecting principally committed progenitors of megakaryocytes and platelets.

A murine ligand for c-Mpl has been identified and cloned, and its expression appears to be restricted to primitive stem cells, megakaryocytes, and platelets. Intraperitoneally injected mice demonstrate an increase in megakaryocytes in both bone marrow and spleen, with a fourfold increase in circulating platelets after seven days. This c-Mpl ligand demonstrates only minimal effects on erythrocyte and granulocyte lineages, although an apparent synergistic effect on erythropoietin has been described. The c-Mpl ligand seems to induce proliferative changes in megakaryocyte precursors as well as differentiation of mature megakaryocytes and may actually expand an earlier pool of committed megakaryocyte progenitors.

The cDNA for the human Mpl ligand has been identified, cloned, and expressed in mammalian cells and appears to encode a functional protein. Both the full-length and truncated forms of recombinant human Mpl ligand stimulate human megakaryopoiesis in vitro. Platelets produced in vitro by a ligand of the c-Mpl receptor appear to be morphologically and structurally identical to plasma-derived human platelets.

Functional c-Mpl receptors have been demonstrated on acute myelogenous leukemia cells, and recombinant hu-
man thrombopoietin appears to stimulate
the proliferation of such cell lines in
vitro.37 Currently available evidence from
de Sauvage et al35 suggests that their lig-
and is both a proliferative and maturation
factor. Continued studies both in vitro
and in vivo will hopefully define further
the clinical benefit expected from the
eventual use of this growth factor.

Clinical Use of Hematopoietic
Growth Factors

The ability to augment hematopoietic cell
cycling using hematopoietic growth fac-
tors has led to two interrelated areas of
clinical investigation: namely, application
of hematopoietic growth factors to facili-
tate more dose-intense treatments (in an
attempt to improve upon primary therapeu-
tic outcomes) and application of
hematopoietic growth factors for support-
ive care management (in an attempt to de-
crease treatment-related complications).
Mounting evidence, both direct and indi-
rect, supports the concept of maintaining
adequate dose-intensity in both standard-
dose and high-dose chemotherapy set-
tings.38-45 Because therapeutic progress in
this area has the potential to improve the
outcome in many malignancies, clinical
trials involving augmented dose-intensity
with hematopoietic growth factors are
likely to continue to be an active area of
research for years to come.

Dose-Intensity

Maintaining/Increasing Dose-Intensity
in Standard-Dose Chemotherapy

Although retrospective39,46 and prospec-
tive38,41 studies have suggested improve-
ment in response rates and treatment
outcomes when dose-intensity is main-
tained, few randomized studies have ad-
dressed the potential benefit of increasing
the dose-intensity of standard-dose che-
motherapeutic regimens using hemato-
poietic growth factors alone (i.e., without
the use of peripheral blood or marrow
rescue products).

The rationale for dose-intensifica-
tion can be explored through the Goldie-
Coldman hypothesis.47 This mathemati-
cal model proposes that tumor resistance
to anticancer therapy is proportional to
both the total number of malignant cells
present (reflecting tumor burden) and the
spontaneous mutation rate (reflecting in-
herent genetic instability) of each of
those cells. If the Goldie-Coldman hy-
pothesis holds true, then dose-intensifica-
tion might be beneficial whether achieved
through increasing total dose delivered
(directly overcoming existing cellular re-
sistance mechanisms) or by shortening
the treatment interval (because both the
period of regrowth and the time for de-
velopment of resistant malignant cellular
clones would be correspondingly short-
ened). This could be advantageous
whether the malignant cell burden is mi-
croscopic (as in the setting of adjuvant
chemotherapy) or overt (as in a newly di-
agnosed malignant lymphoma).

Two randomized trials in small-cell
lung cancer offer limited evidence in sup-
port of this concept. In one trial patients
with small-cell lung cancer (n=65) were
randomized to receive chemotherapy
with or without G-CSF support.48 Be-
cause dose reductions were not allowed
in the study, both groups of patients re-
ceived essentially full doses of chemo-
therapeutic agents. However, there was
no prescribed treatment interval, and be-
cause of more expedient myeloid recov-
er, patients randomized to receive G-
CSF were able to receive their therapy
over a shorter duration, increasing their
dose-intensity. There was a suggestion of
increased two-year survival in the group
randomized to G-CSF (32 percent for pa-
tients randomized to G-CSF versus 15
percent in the control group), although
the result was not statistically significant
because of the small number of patients
in the study (the 95-percent confidence
intervals for the survival durations of the
two groups overlap).

Another prospective, randomized study of small-cell lung cancer reported improved progression-free and overall survival in patients who received combination chemotherapy/radiotherapy over a shortened period compared with controls, although in this study, the total treatment time was shortened by virtue of giving early versus late radiotherapy, not by altering the chemotherapy dose interval.49

Evidence for the importance of dose-intensity in adjuvant chemotherapy for breast cancer was first suggested by the 1981 retrospective analysis of Bonadonna and Valagussa.46 The authors found a correlation between doses actually received by patients and outcome, with patients who had received 85 percent or more of their planned total doses having improved relapse-free survival compared with patients receiving less.

Current mature prospective evidence for the effect of varying dose-intensity has been largely limited to studies that have not used growth factors in their design. The CALGB 8541 trial was a randomized, prospective study of three different dose levels of adjuvant cyclophosphamide, doxorubicin, and fluorouracil for patients with unilateral stage II breast cancer.41 The regimens were designed such that the most dose-intense arm of the trial still rested within fairly conventional dose levels for all agents, and as such, hematopoietic growth factors were not used. The dose-intensity of the high-dose arm was 50 percent greater than the moderate-dose arm and 100 percent greater than the low-dose arm. The results at a median of 3.4 years revealed a significant increase in both disease-free and overall survival when comparing the low-dose arm with both the moderate- and high-dose arms, although no statistically significant difference was seen between the moderate- and high-dose arms. Nevertheless, this is one of the few prospective studies of dose-intensity that demonstrates a relationship between dose delivered and outcome. It suggests at least the existence of a threshold dose below which treatment results are likely to be inferior. It does not exclude the possibility that further escalation in dose-intensity (e.g., beyond levels achieved in the 1981 retrospective analysis of Bonadonna and Valagussa.46) might produce a superior outcome.

NSABP B-22 was another prospective, randomized study designed to look at the effect of differences in both total dose and dose-intensity of cyclophosphamide in the adjuvant setting for patients with axillary-node-positive breast cancer.50 The chemotherapy regimen consisted of cyclophosphamide and doxorubicin. The dose of doxorubicin was held constant (60 mg/m² per course) in all three treatment groups. The “standard” group received cyclophosphamide at a dose-intensity of 200 mg/m²/week (600 mg/m² every three weeks for four cycles). The dose-intensity of cyclophosphamide was doubled to 400 mg/m²/week in the second group (1,200 mg/m² every three weeks for two cycles only) and doubled as well as increased in total dose (1,200 mg/m² every three weeks for four cycles) in the third treatment group. Despite a large number of randomized patients (over 700 per group), the results of this study revealed no significant difference in

The main biologic effect of G-CSF is to cause an increase in proliferation and differentiation of neutrophils from committed progenitor cells.
disease-free or overall survival at three years for any of the three treatment groups. An arguable criticism of this study is that the preferable drug to dose escalate is doxorubicin, because it is the drug with the higher single-agent response rates in breast cancer.

Studies looking at the benefit of dose-intensifying chemotherapy regimens along with the use of hematopoietic growth factors (NSABP B-25, SWOG 9313, NCIC/EORTC MA-10) are currently under way or recently completed, but have not been reported.

In summary, although there is limited evidence to suggest that for some tumors “more is better” (within relatively conventional dosing schedules), there are insufficient data to truly characterize any existing dose-response curve for these tumors. Because definite improvements in outcome have not been demonstrated by maximizing delivery of standard-dose chemotherapy using growth factors, their use in standard-dose chemotherapy regimens should be restricted to (1) reducing the incidence of neutropenic complications in chemotherapy regimens with a significant risk (e.g., greater than 40 percent) of neutropenic fever, as discussed later, and perhaps (2) treating patients with tumors curable with primary chemotherapy (such as germ cell malignancies and lymphomas) in whom appropriate dose-intensity cannot be maintained due to prolonged myelosuppression. However, it should be stressed that good evidence for benefit in the second instance is still lacking. In other clinical situations (e.g., adjuvant chemotherapy for breast cancer), dose reductions or delays remain reasonable options for patients who experience prolonged myelosuppression. Additional appropriately designed prospective studies will hopefully define the extent of any survival advantage conferred from using growth factors in these settings.

High-Dose Therapy/Hematopoietic Cell Transplantation

The ability to treat various malignancies with potentially myeloablative doses of chemotherapy/irradiation has been made possible by the collection and reinfusion of various sources of hematopoietic progenitor cells.51-56 Use of a rescue product provides a means by which lethal marrow injury can be reversed. When nonmyeloablative regimens are used, the use of a rescue product dramatically shortens the duration of myelosuppression, reducing the risks associated with prolonged neutropenia/thrombocytopenia.

Bone marrow was logically the initial source of progenitor cells used for autologous transplantation, but because not all patients were candidates for marrow harvesting (marrow involvement with tumor, prior pelvic irradiation, marrow hypocellularity), attempts were made to collect and reinfuse circulating peripheral blood progenitor cells as an alternative source of hematopoietic rescue. Initially these cells were collected without any attempt to increase their number (nonmobilized), but achieving an adequate number of cells for transplantation required numerous aphereses.51 Subsequently, chemotherapeutic agents,57 hematopoietic growth factors,58 or both59 have been used to augment the number of circulating progenitor cells for transplantation, such that an adequate number of cells can now often be collected with a single apheresis.52 Potential advantages of peripheral blood progenitor cells include

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There are now several established roles for the use of hematopoietic growth factors in high-dose therapy with progenitor cell support.
ease of collection, diminished contamination with tumor,60-63 accelerated hematologic recovery,64 perhaps some degree of immunomodulatory antitumor activity,65 and more rapid immunologic recovery compared with bone marrow.64

It has recently been suggested that hematopoietic recovery may depend more on the presence of graft priming prior to harvest (bone marrow or peripheral blood collected after growth factor administration) than on the actual progenitor cell source.66 As confidence with the long-term engraftment capability of peripheral blood continues to grow, its use is likely to continue to expand because current evidence would suggest that peripheral blood collections appear to be less contaminated by tumor cells than is bone marrow. This is of increasing importance as evidence implicating infused tumor cells as a source of disease relapse accumulates.67,68

There are now several established roles for the use of hematopoietic growth factors in high-dose therapy with progenitor cell support. Numerous studies support the use of G-CSF or GM-CSF to shorten the duration of profound neutropenia after high-dose therapy using autologous bone marrow as the source of progenitor cell support.69-73 Evidence of benefit from using growth factors after infusion of allogeneic bone marrow is more limited. However, the evidence does suggest that some enhancement in neutrophil recovery is achieved with no apparent increase in graft-versus-host disease or nonengraftment.74-77 Hematopoietic growth factors have also been used to “prime” marrow prior to autologous bone marrow harvest, with some evidence (at least historically) to suggest that hematopoietic recovery is hastened over the use of unprimed bone marrow.66

The need for administration of hematopoietic growth factors to patients after infusion of peripheral blood progenitor cells, although standard practice in many transplant centers, was until recent-
pared with patients receiving G-CSF starting at day zero (median, 10 days). However, the group receiving no G-CSF postinfusion experienced a significant prolongation in time to neutrophil recovery (median, 15 days) compared with the cohorts receiving G-CSF. Therefore, although current data suggest more rapid myeloid recovery in patients who receive hematopoietic growth factors after rescue product infusion, the required duration and starting point for infusion are less well defined.

Recently, one of the most active areas in autologous transplantation has been the use of hematopoietic growth factors for the purpose of ex vivo expansion. Hematopoietic recovery is influenced by the absolute number of granulocyte-macrophage colony-forming units infused and probably by the proportion of mature to immature cells that constitute the graft. The apparent improvement in engraftment time using mobilized peripheral blood progenitors (as opposed to bone marrow) is likely the result of the relative increase in more mature (postprogenitor) cells present in a mobilized graft. By producing greater numbers of postprogenitor cells, cytokine-supported ex vivo expansion could reduce even further the time to hematopoietic recovery, decrease the required number of harvested cells, and perhaps also purge grafts of tumor cells by providing a microenvironment conducive only to the growth of hematopoietic cells.

The feasibility of ex vivo amplification/expansion has been well demonstrated in both short- and long-term culture systems, including the amplification of peripheral blood collected from patients with extensive prior chemotherapy exposure. At present, experience with reinfusion of ex vivo expanded progenitor cells is limited, but has been performed after expansion of about one tenth of a single leukapheresis product. Reinfusion of the expanded product appears to produce rapid sustained engraftment profiles similar to that of standard nonexpanded progenitor cell collections.

Lastly, mobilized peripheral blood progenitor cells have recently been used in allogeneic transplantation. In studies reported to date, engraftment of neutrophils (day 10 to 12) and platelets (day 10 to 18) appears to be rapid, without an obvious increase in the incidence of acute severe graft-versus-host disease.

From the donor perspective, apheresis can be accomplished without the need for central catheters by using antecubital veins, and adequate numbers of progenitor cells for transplantation can be collected after five days of G-CSF followed by two to three leukaphereses.

However, it appears that more T lymphocytes and natural killer cells are contained in allogeneic progenitor cell grafts, and early data on small numbers of patients suggest that the use of unmanipulated (non-T-cell depleted) grafts may be associated with a higher incidence of chronic graft-versus-host disease than when allogeneic bone marrow is used. A much larger body of comparative clinical data is clearly required, and the determination of the actual T-cell subsets responsible for graft-versus-host disease as well as further work on the effects of T-cell depletion (selective or nonselective) may enhance the attractiveness of mobi-
lized allogeneic peripheral blood as a rescue product.

Clinical Results of High-Dose Therapy/Hematopoietic Cell Transplantation

The generation of high-quality data comparing high-dose therapy with conventional therapy has been slow largely because many centers have focused on continuing phase II trials rather than on randomized, controlled trials. Accrual to randomized trials has been hampered in many instances by preexisting bias (on the part of both physicians and patients) in favor of high-dose therapy as the superior treatment. There are now a limited number of randomized trials that despite imperfections in design and small numbers offer the best current available evidence to support the use of high-dose therapy/stem cell transplantation in certain clinical settings.

Hodgkin’s Disease

The British National Lymphoma Investigation undertook a randomized trial comparing high-dose chemotherapy with bone marrow transplantation to conventional-dose chemotherapy for patients failing primary therapy for Hodgkin’s disease. The high-dose arm consisted of high-dose BCNU, etoposide, cytosine-arabinoside, and melphalan, and the conventional arm consisted of conventional doses of the same agents. Event-free survival (53 percent versus 10 percent at three years) and progression-free survival (about 62 percent versus 10 percent) were significantly increased in the high-dose arm.

Relapsed Intermediate- and High-Grade Non-Hodgkin’s Lymphoma

A recent randomized trial compared high-dose chemotherapy/bone marrow transplantation with continuation of conventional-dose salvage chemotherapy in patients with chemosensitive relapses of intermediate- or high-grade non-Hodgkin’s lymphoma. Patients were ineligible if at relapse they had involvement of the central nervous system or bone marrow. Eligible patients (n=215) received two cycles of induction chemotherapy with dexamethasone, Ara-C, cisplatin (DHAP) followed by an assessment of disease response. Patients with responding disease (n=109) were then randomized to continuation of conventional chemotherapy (n=54) or high-dose chemotherapy with bone marrow transplantation (n=55). The high-dose arm used a regimen of high-dose BCNU, etoposide, Ara-C, and cyclophosphamide (BEAC). Patients randomized to continuation of salvage therapy received four additional cycles of DHAP. At a median follow-up of 63 months, the results of this trial reveal significantly higher event-free survival (46 percent versus 12 percent) and overall survival (53 percent versus 32 percent) in the high-dose arm.

High-Risk Non-Hodgkin’s Lymphoma

The question of consolidative high-dose chemotherapy/transplantation for patients with high-risk non-Hodgkin’s lymphoma (i.e., as consolidation of first remission therapy) has unfortunately been less well answered. A randomized trial comparing continuation of chemotherapy with use of autologous bone marrow transplantation in slowly responding patients with intermediate- or high-grade non-Hodgkin’s lymphoma failed to find any benefit to transplantation, although the study had inadequate statistical power to demonstrate anything other than a very large difference in outcome between the two groups.

The recently reported LNH87-2 trial randomized 918 patients to either consolidative conventional-dose therapy or to consolidative high-dose therapy with high-dose cyclophosphamide, BCNU,
etoposide, and autologous bone marrow support. Although no overall benefit to transplantation could be demonstrated, the subset of patients identified by the International Prognostic Index with high-intermediate or high-risk disease (2 to 3 negative prognostic factors) who achieved a complete response to initial chemotherapy (n=542) and were subsequently randomized to consolidation with high-dose chemotherapy/bone marrow transplantation experienced increased disease-free and overall survival.

Multiple Myeloma

Data from a prospective, randomized study have recently been presented comparing high-dose chemoradiotherapy/autologous transplantation with more conventional chemotherapy for patients with previously untreated Durie-Salmon stage II or III multiple myeloma. Patients were randomized at entry (100 patients each arm) to receive either conventional-dose chemotherapy or to receive two cycles of conventional-dose chemotherapy followed by high-dose melphalan/total body irradiation. Maintenance treatment with interferon alfa was used in both arms. The five-year probability of event-free survival (28 percent versus 10 percent) and overall survival (52 percent versus 12 percent) was increased in the group of patients randomized to the high-dose arm.

Metastatic Breast Cancer

The first randomized trial comparing high-dose chemotherapy/stem cell support with conventional therapy in metastatic breast cancer was recently reported. This trial randomized patients to receive either a maximum of eight cycles of a conventional-dose chemotherapy regimen with cyclophosphamide, mitoxantrone, vincristine or two cycles of a high-dose chemotherapy regimen of cyclophosphamide, mitoxantrone, etopo- side with hematopoietic rescue. Because the two regimens did not contain identical drugs at different doses, this study cannot be considered a pure study of dose-intensity. However, the median duration of response (80 weeks versus 34 weeks) and survival (90 weeks versus 45 weeks) were significantly longer for patients receiving high-dose therapy.

The study did not require induction therapy and the subsequent selection of only responding patients to determine eligibility for high-dose therapy; rather, patients were randomized at entry to one arm or the other. Some potential biases in favor of the high-dose arm include the fact that complete responders (of whom there were significantly more in the high-dose arm) received maintenance tamoxifen and patients randomized to the standard-dose chemotherapy arm do not appear to have received any type of “salvage therapy” at the time of disease progression. Nonetheless, this study suggests that brief, intense therapy as initial therapy for metastatic breast cancer may be superior to conventional-dose regimens.

As a caveat to the smaller studies just presented, it is important to remember that certain pitfalls may exist when one generalizes the results of single, small, randomized trials. One of the most powerful means of ensuring the external validity (generalizability) of a clinical trial is the ability to replicate the results in other trials with the same design and patient population. Unfortunately, it is likely that many of the above studies will not be replicated because of now even greater physician/patient bias toward high-dose therapy resulting from the positive results of these small randomized trials.

Hematopoietic Cell Cycling

It has long been known that cells that possess a larger growth fraction tend to be more susceptible to the effects of chemotherapeutic agents. This effect is most marked with agents that are cell-cy-
cell specific, such as antimetabolites. From a therapeutic standpoint, the ability to selectively augment cell cycling among tumor cells is one means by which chemosensitivity might be favorably altered.

Certain malignant cell lines, most notably human leukemias, have been demonstrated to contain cytokine receptors for hematopoietic growth factors. In vitro studies have revealed that growth factors such as G-CSF, GM-CSF, and IL-3 can stimulate the growth of malignant myeloid cell lines and render them more susceptible to the action of cytotoxic agents that are cell-cycle specific.

Clinical trials designed to measure the benefit of this strategy have been conducted in both relapsed and de novo acute myelogenous leukemia. Despite evidence suggesting that quiescent leukemic cells can be recruited into an actively cycling state, perhaps rendering them more susceptible to cytotoxic chemotherapy, studies to date have not demonstrated significant differences in complete remission rates or remission duration compared with historical or concurrent randomized controls. Although not a principal outcome measure, no early leukemic regrowth was described in any of the above studies. Because relatively small numbers of cells are recruited by exposure to hematopoietic growth factors, it seems unlikely that this strategy will produce substantial improvements in long-term outcomes, and the effect on relapse rates remains uncertain.

**Supportive Care/Complications**

**Anemia**

The etiology of anemia in cancer patients is often multifactorial in nature. Red cell production may be affected by a variety of pathophysiologic mechanisms, including diminished hormonal signals (erythropoietin), an abnormal hematopoietic microenvironment (caused by the presence of tumor infiltration or the effects of prior chemotherapy or radiation therapy), direct chemotherapy-induced myelosuppression, diminished or absent nutritional stores, and the classical reticuloendothelial blockade of the anemia of chronic disease. Although patients with solid tumors have been shown to have lower basal EPO levels and a blunted EPO response to the presence of anemia, the multifactorial nature of anemia in these patients would not surprisingly lead to demonstration of only small to moderate treatment effects with EPO.

Clinical trials of EPO in patients with malignancy have demonstrated the ability of EPO to increase the hematocrit in patients receiving nonmyelosuppressive chemotherapy, in patients with primary marrow disease such as multiple myeloma, and in patients receiving myelosuppressive chemotherapy. One series of randomized, double-blind, controlled trials looked at the effect of EPO in three types of cancer patients: (1) those not undergoing chemotherapy, (2) those undergoing non-cisplatin-containing chemotherapy, and (3) those undergoing cisplatin-based chemotherapy. In all three groups, hematocrit was increased over baseline by a small but statistically significant amount (2.8 percent to six percent, absolute increase, P<0.004) in EPO-treated patients compared with placebo after eight to twelve weeks of therapy. Combining both chemotherapy groups, the absolute transfusion requirements after three months were slightly less for the EPO-treated group (1.04 units blood per patient in the treated group versus 1.81 units blood per patient in the placebo group, P=0.009). Of all treated patients, significant increments in hematocrit (six percent or more) were seen in only about 50 percent of patients. Perhaps not surprisingly, patients responsive to EPO reported significant improvements in quality-of-life measures from baseline to final evaluation compared with placebo-treated patients.

Another randomized trial of EPO in
patients with metastatic ovarian cancer undergoing cisplatin-based chemotherapy did not demonstrate any significant difference in transfusion requirements between the EPO-treated and the conventionally supported groups. However, only 30 patients were randomized in the study, and as such, a small difference in transfusion requirements would not have been detectable with any certainty.

Given that only about 50 percent of cancer patients are significant responders to EPO, that relatively small increments in hemoglobin are seen in these patients, and that the risks of red cell transfusion remain relatively low, it is difficult to recommend EPO as a cost-effective alternative to conventional transfusion therapy in cancer patients without the benefit of formal economic analyses.

Promotion of Myeloid Recovery in Solid Tumors

Studies using G-CSF in standard-dose chemotherapy regimens have consistently demonstrated a decrease in length and severity of neutropenia, a decrease in the incidence of neutropenic fever, and an increase in the ability of patients to receive full-dose therapy on schedule. The relevant outcome measures of health care delivery in this patient population include the ability to decrease the incidence of complications of neutropenia (by shortening both the duration of risk and absolute neutrophil nadir) and the ability to offset financial aspects of the resulting hospitalization.

At least five potential strategies can be identified that have the potential to address these issues: (1) treat all patients (preemptive therapy) in whom the regimen-related risk of febrile neutropenia exceeds a predefined threshold (e.g., 40 percent or more); (2) treat all patients in whom the occurrence of febrile neutropenia can be reliably predicted (risk-adjusted therapy); (3) treat patients in whom febrile neutropenia has occurred with a growth factor during subsequent treatment cycles to hopefully minimize the risk of further febrile neutropenic episodes; (4) begin a growth factor on admission for patients with febrile neutropenia (reactive therapy); and (5) discharge low-risk patients on home antibiotic therapy with or without growth factors. The first and third strategies are in accordance with the guidelines from the American Society for Clinical Oncology for the use of hematopoietic growth factors. The first four strategies can be thought of as potentially having both cost and outcome implications, and the fifth is basically a cost-minimization strategy.

The benefits of preemptive therapy have been well described and include significant decreases in the incidence of febrile neutropenia, the number of culture-confirmed infections, and the duration of both neutropenia and hospitalization. Unfortunately, preemptive therapy produces a potentially significant increase in the overall cost of therapy. Using decision analysis and assuming that the use of G-CSF would decrease the number of days of hospitalization by 45 percent, Nichols et al have determined that the required risk of hospital admission would have to be 40 percent or more to offset the cost of 10 days of preemptive G-CSF use per cycle. For this reason, subsequent strategies might best be directed at trying to predict and treat those likely to be at high risk of febrile neutropenia (risk-adjusted therapy) or to treat only those who develop febrile neutropenia (suppressive therapy).

The effects of suppressive therapy have been measured and reported in at least three published randomized trials. A randomized, double-blind, placebo-controlled trial of G-CSF in patients with febrile neutropenia demonstrated a one-day median reduction in both the number of neutropenic days (P=0.005) and days of neutropenic fever (P=0.01) for treated patients, although the number of days of hospitalization...
were not significantly reduced when compared with controls. Therefore, no significant cost savings were realized. There was no demonstrable decrease in morbidity or mortality in the treated group.

A second smaller randomized study using G-CSF/GM-CSF was able to demonstrate a greater reduction in median duration of severe neutropenia (one day versus three days) and hospitalization (five days versus eight days) compared with placebo. A third randomized, placebo-controlled trial of GM-CSF in 132 patients with solid tumors or hematologic malignancies with febrile neutropenia revealed a one-day median reduction in duration of neutropenia (three days versus four days) for the group receiving GM-CSF, but no significant difference in duration of fever or hospital days in the group treated with GM-CSF.

From the above studies, it seems apparent that a relatively small benefit is obtained by treating patients using the suppressive approach. The use of growth factors with antibiotics in febrile neutropenic patients with documented infection or clinical deterioration is reasonable and in accordance with accepted guidelines for colony-stimulating factor use, although benefit under these circumstances has not definitely been proven.

Intermediate between the preemptive approach and the suppressive approach lies the risk-adjusted approach (treating patients in whom the occurrence of febrile neutropenia can be reliably predicted). By targeting high-risk patients, this model might be more cost-effective, but as described by Nichols et al, it would probably need to predict patients with a risk of admission of 40 percent or more for febrile neutropenia. From a mathematical/statistical standpoint, such a model would likely be difficult to generate and validate because of the relatively low number of febrile neutropenic events in most chemotherapy regimens for solid tumors and the difficulties inherent in retrospectively measuring and reliably quantitating various potential risk factors, such as performance status, extent of disease, and extent of prior therapy. If fever and neutropenia can be included as a predictor of further episodes of the same, indirect evidence from the trial of Crawford et al would suggest that the use of G-CSF in such patients may be associated with a decrease in febrile neutropenic episodes in subsequent chemotherapy cycles.

Finally, studies evaluating the outcome of home antibiotic use for selected low-risk patients have demonstrated this to be a safe and viable option. Ideally, this requires a model that can reliably predict low-risk patients, but this approach is attractive from the point of view of simplicity and potential cost savings. If resolution of neutropenia is no longer the rate-limiting step to hospital discharge, other clinical endpoints such as measures of morbidity may be the required outcome measures in future studies of hematopoietic growth factors in this particular therapeutic setting.

Promotion of Myeloid Recovery in Acute Leukemia

Because of the potential to stimulate leukemic cells through cytokine exposure, there was initial reluctance to explore the use of these agents in dis-
eases such as acute leukemia. A number of randomized, placebo-controlled trials have now reported on the use of G-CSF or GM-CSF to promote myeloid recovery after induction or consolidation chemotherapy in acute myelogenous leukemia.\textsuperscript{131-138} Four of these studies were designed to specifically address the benefit of this strategy in elderly patients.\textsuperscript{133-135,138} All of these studies demonstrated a significant reduction in the duration of neutropenia; three reported a decrease in the duration of fever or fever/neutropenia and duration of antibiotic use,\textsuperscript{132,137,138} and one reported a decrease in the incidence of documented infections for patients randomized to receive growth factors.\textsuperscript{136} The complete-remission rate for patients treated with growth factors was improved in one study (70 percent for treated versus 47 percent for placebo, \(P=0.002\)),\textsuperscript{135} and a trend toward the same was observed in two others.\textsuperscript{133,136} The reasons for this are not immediately clear, because growth factor was given only after completion of chemotherapy. Overall, therapy-related toxicity was reportedly less in

| Potential Indications for Hematopoietic Growth Factor Use in Cancer Care |
|---------------------------------------------------------------|
| Clinical Indication for Hematopoietic Growth Factor           | Evidence of Benefit | Evidence of Harm | Cost Effectiveness | References |
| Supporting dose-intensity in standard-dose regimens for solid tumors | Limited            | No              | Unknown           | 48         |
| Primary prevention of febrile neutropenia in solid tumors     | Yes                | No              | If risk of febrile neutropenia high (\(\geq 40\%\)) | 119-123    |
| Secondary prevention of febrile neutropenia in solid tumors   | Limited            | No              | Unknown           | 120        |
| Treatment of established febrile neutropenia in solid tumors  | Limited            | No              | No               | 126-128    |
| Mobilization of progenitor cells                               | Yes                | No              | Yes              | 58, 59, 66 |
| Postrescue in high-dose therapy: Bone marrow                  | Yes                | No              | Likely           | 69-73, 76  |
| Postrescue in high-dose therapy: Peripheral blood              | Yes                | No              | Likely           | 78, 79     |
| Cell cycling in leukemias                                      | No                 | Unclear         | Unknown          | 107-109, 112|
| Promotion of myeloid recovery in acute leukemia                | Yes                | Unclear         | Unknown          | 131-138    |
only one study, but no significant differences in survival were reported in any of these studies. From these data, it would appear that the use of hematopoietic growth factors to shorten the duration of neutropenia in patients with acute leukemia results in a modest degree of clinical benefit.

Summary
Over the past ten years, the availability of pharmacologic quantities of hematopoietic growth factors has opened many avenues of study in basic science and clinical investigation. Numerous studies performed to date have demonstrated significant benefits from the use of these cytokines. The side effect profiles, particularly for "later acting" growth factors, indicate that they are generally well tolerated by most patients.

The Table summarizes the potential indications for hematopoietic growth factor use as discussed in this article, as justified by current evidence of benefit, harm, and cost effectiveness resulting from their use in various clinical settings.

It has been clearly demonstrated in standard-dose chemotherapy regimens that these agents shorten the duration of myelosuppression, reduce the incidence of significant infection, can shorten hospital stay, and reduce antibiotic use for most patients, although the cost/benefit ratio for growth factors such as G-CSF makes this a cost-effective approach only for regimens with a high (40 percent or more) incidence of febrile neutropenia. Limited indirect evidence supports the use of growth factors in patients with a prior episode of fever and neutropenia. The suppressive approach to growth factor use could potentially benefit patients with documented infection or clinical deterioration, but it has not otherwise been shown to be a particularly effective or cost-effective approach.

Administration of hematopoietic growth factors has been instrumental in facilitating both autologous and allogeneic peripheral progenitor cell mobilization and techniques such as ex vivo expansion. There is an increasing body of data supporting the use of high-dose chemotherapy regimens with progenitor cell rescue for a number of malignancies and limited data supporting the benefits of maintaining dose-intensity for certain malignancies in standard-dose settings. Although of continuing concern, clinically significant evidence of disease stimulation and recurrence has not been unequivocally demonstrated in studies to date.

A comprehensive set of evidence-based guidelines has recently been published by the American Society of Clinical Oncology. As often is the case, current studies have perhaps generated more questions than answers. Future investigation will undoubtedly focus on use of hematopoietic growth factors in conjunction with other techniques, such as outpatient-based treatment of febrile neutropenia, CD34-positive stem cell selection in autologous transplantation, selective manipulation of T-cell subsets (to decrease the incidence of severe graft-versus-host disease) in allogeneic transplantation, and high-dose therapy with stem cell transplantation.

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