Clinical Pharmacology of Filgrastim following High-Dose Chemotherapy and Autologous Bone Marrow Transplantation

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ABSTRACT
We evaluated the pharmacokinetics and pharmacodynamics of filgrastim during a Phase I study of this cytokine following high-dose chemotherapy and autologous bone marrow transplantation. Serum granulocyte colony-stimulating factor concentrations were determined by ELISA in 21 patients receiving 14-day continuous i.v. filgrastim infusions and 10 patients receiving daily 4-h infusions. Models were developed for filgrastim systemic clearance (CL) by incorporation of receptor-binding theory. Mean plasma half-life (t1/2) in the 4-h infusion group was 197 min, and the volume of distribution approximated plasma volume. WBC counts transiently fell, then rebounded immediately postinfusion, which correlated with a delay in the disappearance of serum granulocyte colony-stimulating factor. The effect of WBC concentrations on filgrastim Cls was determined in patients receiving continuous infusions by segregation of study periods based on the presence of severe neutropenia. Clearance increased in all 14 patients receiving doses of 4–32 μg/kg/day during WBC recovery. The effect of WBCs on Cls was described by a differential equation that included a static component and one component that varied with WBC concentration. These data suggest that currently used filgrastim dosing strategies following autologous bone marrow transplantation may be suboptimal.

INTRODUCTION
Clinical trials have demonstrated the therapeutic benefits of administering hematopoietic growth factors following myelosuppressive chemotherapy and ABMT, but multiple questions remain unanswered regarding the optimal therapeutic use of these proteins and their pharmacological characteristics. A limited amount of pharmacokinetic information is available for filgrastim following its administration to healthy volunteers or to patients who had received the cytokine following ABMT or standard-dose chemotherapy (1-5). These data suggest substantial interpatient variability in disposition, which seems to be related to patterns in peripheral blood granulocytic cell recovery.

This report describes the pharmacokinetic characteristics of filgrastim following high-dose chemotherapy and ABMT, in addition to evaluations that link these variables to pharmacodynamic effects.

PATIENTS AND METHODS
Patients and Therapy. All patients received filgrastim following informed consent as part of a Phase I/II clinical trial subsequent to high-dose chemotherapy and autologous bone marrow support for the treatment of stage II–IV breast cancer or metastatic melanoma. This study was approved by the Duke University Institutional Review Board for Clinical Trials in Humans. The ablative regimen consisted of cyclophosphamide (5625 mg/m²), carmustine (600 mg/m²), and cisplatin (165 mg/m²) administered over the course of 4 days (day −6 to day −3), as described previously and outlined in Fig. 1 (6). Autologous bone marrow was reinfused 4 days after the end of chemotherapy (day +1). Patients received doses of 4, 8, 16, 32, or 64 μg/kg/day of filgrastim (nonglycosylated, recombinant, human G-CSF derived from Escherichia coli; Amgen, Inc.). Note that following the completion of this trial, Amgen revised the extinction coefficient for filgrastim; thus, the doses reported here should be multiplied by 1.2 to be equivalent to the currently marketed product. The cytokine was administered by either 14-day continuous i.v. infusion or daily 4-h infusions for 21 days starting 3 h after bone marrow administration (day +1).

Sampling. Single daily serum samples were obtained during the continuous infusion regimen. Samples before and immediately after infusion were collected from the patients receiving daily 4-h infusions. In addition, samples were collected 5, 10, 15, 20, 30, 45, 60, 120, 240, and 360 min after the completion of the 4-h infusions on day +15. Urine was collected for 24 h after drug administration in a subset of patients receiving the 4-h infusion regimen on day +1 and day +15.

Analytic Procedure. Immunoreactive G-CSF was measured in our laboratory using a double-antibody sandwich technique (Amgen Diagnostics, Thousand Oaks, CA). Microtiter plates were precoated with polyclonal rabbit antibody specific for G-CSF. One hundred μl of test samples were added and incubated for 4 h at 37°C. Serum was removed and 100 μl of anti-G-CSF monoclonal antibody-horseradish peroxidase conjugate was added and incubated for 2 h in the well during a 2-h incubation at 37°C. After further washing, 100 μl of dilute tetramethylbenzidine was added and oxidized by enzyme to
yield a blue complex during a 30-min room temperature incubation. Addition of 100 μl of 0.5 N sulfuric acid stopped the reaction and yielded a yellow color. Absorbance was determined by an ELISA plate reader with a 450-nm interface filter, using 650 nm as the reference wavelength. The standard curve concentrations were in the range of 1–25 ng/ml. Unknowns containing >25 ng/ml G-CSF were diluted to appropriate concentrations using sample diluent. Optical densities corresponding to the standards were fit by linear regression, and unknown values were calculated. Assays were always conducted with standards to minimize interrun variation; however, the inter- and intraday coefficients of variation were <10% for both high and low quality control samples. All samples obtained during continuous infusions were analyzed in the same run for individual patients to eliminate any potential bias.

**Pharmacokinetic Analysis.** Selection of the appropriate pharmacokinetic model and initial parameter estimation for each patient receiving a 4-h infusion was performed by curve stripping (RSTRI P V.4.03; MicroMath, Salt Lake City, UT). Subsequent evaluations of individual data sets were conducted using nonlinear least-squares regression (PCNONLIN V.3.0.; Statistical Consultants, Lexington, KY). Systemic drug clearance was determined in those patients receiving filgrastim by continuous i.v. infusion using noncompartmental methods as described by the following equation: clearance = infusion rate/concentration.

**Statistical Analysis.** The Wilcoxon test was used for paired analyses, and the Mann-Whitney U test was used for nonpaired group comparisons. Modeling of clearance changes during continuous infusion was based on pharmacokinetic theory. A differential equation relating pharmacokinetic theory to concentration-time data was developed. This relationship was approximated by a linear equation to expedite analysis.

**RESULTS**

**Patient Population.** Twenty-eight patients were evaluable for pharmacokinetic purposes. The mean patient age was 40 years, and females with the diagnosis of breast cancer made up 89% of the study group. The therapeutic response (i.e., acceleration of WBC recovery) to filgrastim was not clearly dose related, with maximum hematopoietic response found at doses of 8, 16, and 32 μg/kg/day, as reported previously (7, 8). Patients receiving only 4 μg/kg/day had discernably less hematopoietic response, and those at a dose of 64 μg/kg/day also manifested lower WBC counts throughout therapy. Three patients receiving continuous infusions of 64 μg/kg/day (patients 231, 233, and 234) were taken off the study drug prematurely due to suspected toxicity. Other clinical results have been reported previously (7, 8).

**Intermittent Infusions.** To investigate the acute effects of filgrastim administration on the WBC count, seven patients had WBCs counted at the same time points as the postinfusion pharmacokinetic samples (Fig. 2). WBC counts fell precipitously in the first hour following the 4-h filgrastim infusion and then climbed steadily over the next 4–5 h. Interestingly, serum concentrations of G-CSF did not decay significantly during the first hour following infusion (Fig. 2). We selected the three patients who had day +15 WBC counts of >4 x 10^6 cells/ml to evaluate the relationship between G-CSF and WBC concentrations with linear regression analysis. A linear inverse relationship between WBC concentration postinfusion and G-CSF concentration postinfusion was noted in each patient (r^2 = 0.84, 0.92, and 0.93 for patients 231, 233, and 234, respectively; n = 8 and P < 0.001 for each).

The pharmacokinetic parameters for 10 individuals receiving filgrastim by 4-h i.v. infusion are shown in Table 1. Only samples collected at 0, 1, 2, 4, and 6 h postinfusion were included due to high variability in serum G-CSF concentration and WBC counts immediately following infusion, as described above. A one-compartment model with zero-order input and a first-order elimination process best described these data in all cases. Calculated parameters included an average half-life (t_1/2) of 198 min and volume of distribution (V_d) of 0.06 liter/kg, approximating plasma volume. Mean systemic exposure, as

| Day from Marrow Infusion | -8 | -6 | -4 | -2 | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 |
|--------------------------|----|----|----|----|---|---|---|---|---|----|----|----|----|----|----|----|
| Cyclophosphamide         |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| (1875 mg/m²/day)         |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| Cisplatin                |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| (55/mg/m²/day)           |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| Carmustine               |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| (600 mg/m²)              |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| Bone Marrow Infusion     |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| Filgrastim Infusions     |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| 14-day continuous IV     |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| (4 - 64 μg/kg/day)       |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| or                      |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| 21-day four hour QD IV   |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |
| (4 - 64 μg/kg/day)       |    |    |    |    |   |   |   |   |   |    |    |    |    |    |    |    |

*Fig. 1* Treatment administration scheme.
measured by area under the curve (AUC) or $C_{\text{max}}$, rose with dose; however, interpatient variability in clearance was large (coefficient of variation, 151%). These values should be considered apparent because current analytical methods cannot distinguish between endogenously produced G-CSF and exogenously administered drug.

Twenty-four-h urine samples collected on day +1 and day +15 from five patients showed that no detectable G-CSF was present in urine. Known G-CSF concentrations added to urine were detectable.

**Continuous Infusions.** Patients receiving continuous i.v. infusions also manifested large interpatient variability in clearance. Pharmacokinetic and laboratory data for individuals receiving continuous i.v. infusion are shown in Table 2. Clearance estimates are divided into values obtained at an early point in the infusion regimen (day +4 to day +8) when the WBC count was $<250$ cells/mm$^3$ in all patients and those obtained on the final few days of infusion (day +13 to day +15) when hematopoietic recovery was in progress. Serum G-CSF concentrations reached an equilibration point ($<20\%$ daily fluctuation) by day +4 in all patients receiving $<64 \mu g/kg/day$. However, patients receiving $64 \mu g/kg/day$ continued to accumulate serum G-CSF before hematopoietic recovery. Median increase in G-CSF concentration from day +4 to day +8 was over 100%, from 700 to 1500 ng/ml in these patients. Conversely, the CIs for the other patients increased slightly over this time period. Two of the three patients who had therapy discontinued early due to toxicity manifested rapidly increasing G-CSF concentrations before the end of infusion. The third patient had her infusion stopped on day +3 before a G-CSF serum sample was drawn.

Systemic clearance increased during hematopoietic recovery compared to early in therapy for all patients receiving $<64 \mu g/kg/day$ by continuous infusion (Table 2). The median increase in clearance was 27% ($P = 0.001$). Clearance increased $\geq20\%$ for six of seven patients with final WBC counts of $>1 \times 10^9$ cells/ml and three of seven with final WBC counts of $<1 \times 10^9$ cells/ml. Only one patient (patient 272) experienced hepatic dysfunction (total bilirubin, $>5.0$ mg/dl) during filgrastim infusion, whereas six patients developed renal dysfunction (serum creatinine, more than twice baseline value during therapy; Table 2). Three of these patients had pharmacokinetic studies conducted and did not demonstrate altered disposition compared to

![Fig. 2 Mean serum G-CSF (---) and WBC (- - -) concentrations from seven patients following the 4-h filgrastim infusions. Concentrations were normalized to a dose of 16 $\mu g/kg$ for comparison.](image-url)

**Table 1** Pharmacokinetic parameters for patients receiving filgrastim by 4-h i.v. infusion

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Dose (\mu g/kg/day)</th>
<th>AUC (\mu g/mL·min)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$V_d$ (liter/kg)</th>
<th>$t_{1/2}$ (min)</th>
<th>Cls (ml/h/kg)</th>
<th>WBCs* (\times 10^9/ml)</th>
</tr>
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<tbody>
<tr>
<td>311</td>
<td>4</td>
<td>30.3</td>
<td>81.3</td>
<td>0.061</td>
<td>160.3</td>
<td>15.8</td>
<td>1.0</td>
</tr>
<tr>
<td>287</td>
<td>8</td>
<td>37.7</td>
<td>116.0</td>
<td>0.038</td>
<td>123.4</td>
<td>12.7</td>
<td>4.3</td>
</tr>
<tr>
<td>247</td>
<td>16</td>
<td>285.0</td>
<td>499.7</td>
<td>0.025</td>
<td>303.3</td>
<td>3.4</td>
<td>3.0</td>
</tr>
<tr>
<td>255</td>
<td>16</td>
<td>119.0</td>
<td>273.4</td>
<td>0.040</td>
<td>206.6</td>
<td>8.1</td>
<td>6.3</td>
</tr>
<tr>
<td>256</td>
<td>16</td>
<td>25.8</td>
<td>84.9</td>
<td>0.095</td>
<td>105.9</td>
<td>37.2</td>
<td>3.4</td>
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<tr>
<td>261</td>
<td>16</td>
<td>121.5</td>
<td>330.4</td>
<td>0.030</td>
<td>156.7</td>
<td>7.9</td>
<td>1.3</td>
</tr>
<tr>
<td>268</td>
<td>32</td>
<td>343.2</td>
<td>734.2</td>
<td>0.031</td>
<td>229.8</td>
<td>5.6</td>
<td>1.2</td>
</tr>
<tr>
<td>269</td>
<td>32</td>
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<td>469.1</td>
<td>0.058</td>
<td>521.1</td>
<td>4.6</td>
<td>1.5</td>
</tr>
<tr>
<td>281</td>
<td>32</td>
<td>18.0</td>
<td>68.6</td>
<td>0.171</td>
<td>66.4</td>
<td>106.9</td>
<td>15.3</td>
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<tr>
<td>280</td>
<td>64</td>
<td>487.6</td>
<td>1635.1</td>
<td>0.019</td>
<td>101.4</td>
<td>7.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>0.057</td>
<td>197.5</td>
<td>0.046</td>
<td>133.5</td>
<td>31.7</td>
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<td>SD</td>
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* Measured on the day of pharmacokinetic evaluation.
others with similar WBC counts. Systemic clearance appeared to be related to dose both before and after hematopoietic recovery, as shown in Fig. 3.

Two pharmacodynamic models were considered to describe the relationship between WBC and G-CSF elimination during continuous infusion. Both models assume that G-CSF is eliminated by a first-order process in the absence of WBCs. The first (model 0) assumes that WBC-mediated elimination is zero-order. Applying the steady-state assumption in this case yields the equation:

\[
\text{Cls}_0*\text{[G]}_1 = \text{Dose} = \text{Cls}_0*\text{[G]}_1 + K_0*\text{WBC}, \quad (A)
\]

where \([G]\) represents the concentration of G-CSF and \(i\) represents the time when WBC counts were \(<250\) cells/mm\(^3\). \(\text{Cls}_i\) refers to the clearance of filgrastim in the absence of significant
Model 0

\[
\frac{[G]_1 - [G]_f}{WBC_f/\text{Cl}_1} \text{ (ng/mL)}
\]

where \( K_0 \) is the clearance of G-CSF by each WBC (first-order) in ml/h/kg per (cells × 10^6/ml). The clearance in the presence of WBC is:

\[
\text{Cl}_f = \text{Cl}_i + K_1 \cdot \text{WBC}_f.
\]

Comparison of the two models was determined by plotting log(\( \text{Cl}_f - \text{Cl}_i \)) versus log(WBC) and log([G]_1 - [G]_f) versus log(WBC/\( \text{Cl}_i \)). The alternative model (model 1) assumes first-order elimination of G-CSF by WBC. Applying the steady-state assumption in this case yields the equation:

\[
\text{Cl}_f \cdot [G]_f = \text{Dose} = (\text{Cl}_i + K_1 \cdot \text{WBC}) \cdot [G]_f.
\]

WBC counts and is assumed to be constant. The term \( K_0 \) reflects the absolute amount of G-CSF eliminated by each WBC per unit time (zero-order) in units of ng/kg/h per (cells × 10^6/ml). Parameters followed by \( f \) are those observed during hematopoietic recovery. Rearranging terms yields:

\[
[G]_1 - [G]_f = K_0 \cdot \text{WBC} \cdot \text{Cl}_1.
\]  

Model 1

\[
\frac{\text{Cl}_f - \text{Cl}_i}{WBC_f} \text{ (ml/h/kg)}
\]

\[
\text{Cl}_f = \text{Cl}_i + K_1 \cdot \text{WBC}_f.
\]

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due to the large influence of this data point. In the latter case, model 1 did not accurately describe the data set ($r^2 = 0.05$, $P = 0.4$); in contrast, model 0 yielded a significant relationship ($r^2 = 0.41$, $P < 0.02$). Including patient 246 improved both models; however, model 0 was still superior to model 1 ($r^2 = 0.63$, $P < 0.001$ versus $r^2 = 0.51$, $P = 0.004$). These data suggest that WBC elimination of G-CSF is a zero-order process. Model 0 yielded a value of $K_b = 54$ ng/h/kg per (cells × 10^9/ml). Thus, if WBC = 1 × 10^6 cells/ml, then WBC elimination of G-CSF is 54 ng/kg/h or 1.3 µg/kg/day.

**DISCUSSION**

Infusion of filgrastim following high-dose chemotherapy with ABMT can reduce the severity of chemotherapy-induced toxicities and speed hematopoietic recovery, thus this cytokine is widely used in such settings. However, relatively sparse data have been published in regard to the most appropriate dosage of filgrastim or other CSFs following ABMT. Pharmacokinetic information, such as that provided in the present study, alludes to potential differences in disposition of this cytokine in the transplant patient, perhaps due to the typically higher degree of bone marrow and peripheral blood ablation. The clinical portion of this study demonstrated that increasing filgrastim dose beyond 16 µg/kg/day did not seem to significantly improve the efficacy of therapy, whereas a dose of 64 µg/kg/day seemed to actually slow hematopoiesis in some cases (7, 8). One possible explanation for these effects, based on both in vitro and in vivo evidence, is the stimulation of an endogenous cytokine such as tumor necrosis factor α, which may down-regulate G-CSF receptor expression (9, 10). Overall, these results suggest that the efficacy of filgrastim therapy in the posttransplant setting is not limited by the dose infused but rather by the number of available G-CSF receptors and/or responsive hematopoietic cells. The critical question in dose selection appears to be the number of WBCs and their precursors present, as well as the capacity of these cells to use G-CSF.

G-CSF binds to cell surface receptors on several types of WBCs in vitro. Following binding, the G-CSF-receptor complex appears to be internalized and the receptor returned to the cell surface (11). Occupancy of only a small fraction of available receptors on a particular cell is thought to be sufficient for full biological response (12). In addition, receptor binding appears to provide a clearance mechanism, beyond suspected protease activity, for filgrastim.

The acute effects following a filgrastim infusion on the peripheral WBC concentration have been described previously and include immediate reduction in WBC followed by a rebound, as was noted in this trial (13, 14). Mechanistically, this is thought to be accounted for by alterations in neutrophil margination (15). We have noted that this reduction in WBC coincided with a transient delay in drug elimination, which persisted for approximately 1 h postinfusion. Use of multiple-concentration, time data at the end of infusion and following the 1-h time point yielded apparent clearances that were in the same range of values noted in both adult (5) and pediatric (3) patients following nonablative chemotherapy; however, this methodology will not allow for detailed investigation of nonlinear effects, as described with the continuous infusion data sets.

Dose-related clearance of filgrastim was evident both before and after hematopoietic reconstitution, as shown in Fig. 3. Data from animals (16) and humans (1) have shown a similar relationship; however, some of the latter data are complicated by lack of knowledge of the potential influence of dose on systemic absorption due to s.c. drug delivery (3). One would suspect that metabolic clearance of filgrastim should not be dose dependent at low concentrations of the ligand; however, clearance is likely to decrease at high concentrations, as seen in this patient set. Doses greater than the elimination maximum may lead to steadily increasing serum drug concentrations during the course of therapy, as demonstrated in patients receiving 64 µg/kg/day. These escalating G-CSF concentrations appeared to be detrimental, coinciding with severe toxicities in three patients (7, 8). This suggests that high doses of filgrastim (>20 µg/kg/day) should not be routinely prescribed for patients during periods of absolute neutropenia.

The relationship between G-CSF clearance and WBCs provides evidence that developing hematopoietic cells have the potential to use only limited quantities of G-CSF. In particular, the fact that WBC clearance of G-CSF appears to be a zero-order process suggests that lower doses of the cytokine than those used in this report would be sufficient to saturate all available receptors. Using $K = 54$ ng/kg/h per (cells × 10^9/ml; based on linear regression of Eq. B) implies that in patients with WBC counts below $1 × 10^6$ cells/ml, hematopoietic elimination of G-CSF will not exceed 1.3 µg/kg/day, regardless of dose. Metabolic clearance of G-CSF is presumably first-order; therefore, doses near this theoretical optimum (e.g., $2$ µg/kg/day) can maximize the G-CSF-receptor interaction while minimizing the amount of drug eliminated by alternate mechanisms. Higher doses may be of use when the desired WBC count is $>1 × 10^6$ cells/ml. For example, if a WBC count of $1 × 10^6$ cells/ml is desired, then hematopoietic elimination could be expected to reach $13$ µg/kg/day and a filgrastim dose in the range of 15–20 µg/kg/day would be reasonable. It is important to realize that all of the clearance relationships described above were determined when filgrastim was administered by continuous i.v. infusion. One would anticipate similar effects when the cytokine is given by s.c. injection; however, these effects may occur at higher doses than those found here because the bioavailability of the latter is incomplete. These data imply that an optimal schedule of G-CSF administration may entail initiation of therapy at low doses and titration upward as reconstitution occurs, quite the opposite of what is typically practiced today. Alternatively, perhaps more consideration could be made for an earlier discontinuation of therapy altogether.

The data from this study of patients following high-dose chemotherapy confirm reports by others, which have identified a direct correlation between the apparent clearance of filgrastim and WBC counts in patients with chronic neutropenia (2) or following chemotherapy (1, 3, 4). Our approach to describing the disposition of filgrastim (Eq. C) proposes that the clearance would continue to increase with WBC count and thus is dissimilar to that of the sigmoidal relationship that was postulated by others (2).

We have evaluated previously the pharmacokinetics of an investigational recombinant granulocyte macrophage CSF product (regranestim) in patients treated with exactly the same
high-dose chemotherapy regimen (17). A similar pharmacodynamic effect between WBCs and apparent drug clearance was noted on that trial; however, patients who experienced renal dysfunction during cytokine administration via continuous infusion displayed reduced drug clearance. We postulate that the apparent lack of such effects in patients treated on the current study with filgrastim may be a result of either a relatively higher receptor affinity or availability compared with regromostim. Alternatively, dissimilar renal handling of the cytokines is possible, especially because we were not able to detect significant urinary concentrations of G-CSF. In contrast, granulocyte macrophage CSF was excreted in the urine of patients following its administration, and the extent of such excretion was less in patients who experienced renal dysfunction (17).

Further studies of filgrastim pharmacokinetics should continue to monitor the relationship between clearance, WBCs, and appropriate dosing. Sensitive and specific bioassays should be used to substantiate results obtained by ELISA. The role of secondary cytokine release in the therapeutic and toxic effects of filgrastim should also be considered. Clinical utilization of the relationship between filgrastim clearance and WBCs may help to optimize dosage regimens of filgrastim by minimizing cost and toxicity while maximizing therapeutic response.

REFERENCES


