COMMENTARY

Should hematopoietic growth factors routinely be given concurrently with cytotoxic chemotherapy?

Alexandra J. Croockewit, MD, Peter P. Koopmans, MD, and Ben E. de Pauw, MD

Recombinant human (rh) hematopoietic growth factors (HGFs), such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF), have been shown to accelerate significantly neutrophil recovery after conventional and high-dose chemotherapy or radiotherapy. Furthermore, the effects of HGFs are not restricted to the induction of proliferation, but they include effects on differentiation, priming of the oxidative response in neutrophils, as well as enhanced phagocytosis and other cellular functions. More than 25 years ago it was shown in patients undergoing therapy for leukemia that there was a correlation between the occurrence of severe infections and the duration and severity of neutropenia.

Consequently, it was hypothesized that the use of HGFs would result in a decrease of the incidence of infections and would also allow more optimal dosing of cytotoxic chemotherapy. Trials to explore the latter question are still investigational. This commentary addresses the influence of HGFs, given as primary prophylaxis, on the reduction of incidence of infections in patients with therapy-induced granulocytopenia on the basis of both phase II and III studies that have appeared in the literature. The number of days with fever, number of febrile neutropenic days, use of antibiotics, the number of documented infections, and the duration of hospitalization were analyzed as parameters of putative efficacy. In several phase II studies the incidence of infections in patients treated with HGF was decreased compared with historic controls, but the value of such observations is limited because the supportive care, including the use of antimicrobial agents, has changed considerably over time.

ADMINISTRATION OF HGF AFTER STANDARD-DOSE CHEMOTHERAPY

Several phase III studies concerning HGF administration in patients treated with chemotherapy
Table I. Influence of HGF administration after conventional/dose chemotherapy on the infection rate in phase III placebo/controlled trials

<table>
<thead>
<tr>
<th>Author</th>
<th>n (HGF/placebo)</th>
<th>Disease</th>
<th>Cytoxic regimen</th>
<th>Reduction in HGF/placebo groups of ANC &lt;1000/μl No. of days</th>
<th>% of patients</th>
<th>Documented infections (% of patients)</th>
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</thead>
<tbody>
<tr>
<td><strong>G-CSF</strong></td>
<td></td>
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<tr>
<td>Crawford et al.10</td>
<td>95/104</td>
<td>SCLC</td>
<td>CDE</td>
<td>Complete data†</td>
<td>6/15</td>
<td>7/13</td>
</tr>
<tr>
<td>Kotake et al.11</td>
<td>32/38</td>
<td>Urogenital cancer</td>
<td>M-VAC</td>
<td>Complete data†</td>
<td>1/7*</td>
<td>Not given</td>
</tr>
<tr>
<td>Trillet-Lenoire et al.12</td>
<td>65/64</td>
<td>SCLC</td>
<td>CDE</td>
<td>Not given</td>
<td>6/15</td>
<td>20/33</td>
</tr>
<tr>
<td>Pettengell et al.13</td>
<td>41/39</td>
<td>NHL</td>
<td>VAPEC-B</td>
<td>Not given</td>
<td>57/85*</td>
<td>17/13</td>
</tr>
<tr>
<td><strong>GM-CSF</strong></td>
<td></td>
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<tr>
<td>Kaku et al.14</td>
<td>31/31</td>
<td>NHL</td>
<td>CHOP</td>
<td></td>
<td>52/73*</td>
<td>13/26</td>
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<tr>
<td>Gerhartz et al.15</td>
<td>91/91</td>
<td>NHL</td>
<td>COP-BLAM</td>
<td></td>
<td>19/33*</td>
<td>27/45§</td>
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<tr>
<td>de Vries et al.16</td>
<td>9/9</td>
<td>Ovarian cancer</td>
<td>CAR, CTX</td>
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</table>

HGF, Hematopoietic growth factors; ANC, absolute neutrophil count; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage CSF; CTX, cyclophosphamide; CAR, carboplatin; CDE, cyclophosphamide, doxorubicin, etoposide; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; COP-BLAM, cyclophosphamide, doxorubicin, bleomycin, vincristine, procarbazine, prednisolone; M-VAC, methotrexate, vinblastine, doxorubicin, cisplatin; VAPEC-B, doxorubicin, cyclophosphamide, vincristine, bleomycin, etoposide, prednisolone; NHL, non-Hodgkin's lymphoma; SCLC, small-cell lung cancer.

*Statistically significant difference (p < 0.05) in favor of HGF; **statistically significant difference (p < 0.05) in favor of control.
†Data only for first chemotherapy cycle.
‡Fever defined as temperature >37.5°C
§Analysis for the subgroup receiving at least 70% of study medication.

Table II. Influence of HGF administration after autologous bone marrow transplantation on the infection rate in phase III placebo-controlled trials

<table>
<thead>
<tr>
<th>Author</th>
<th>n (HGF/placebo)</th>
<th>Disease</th>
<th>Reduction in HGF/placebo groups of ANC &gt;500/μl No. of days</th>
<th>Documented infections (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G-CSF</strong></td>
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<tr>
<td>Gisselbrecht et al.20</td>
<td>163/152†</td>
<td>Non-myeloid cancer</td>
<td>14/20*</td>
<td>26/26</td>
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<tr>
<td><strong>GM-CSF</strong></td>
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<tr>
<td>Nemunaitis et al.17</td>
<td>65/63</td>
<td>Lymphoid malignancies</td>
<td>19/26*</td>
<td>17/30*</td>
</tr>
<tr>
<td>Link et al.18</td>
<td>39/40</td>
<td>ALL, NHL</td>
<td>14/18*</td>
<td>46/70*</td>
</tr>
<tr>
<td>Advani et al.19</td>
<td>36/66</td>
<td>NHL, HD</td>
<td>12/16*</td>
<td>3/18*</td>
</tr>
<tr>
<td>Bennett et al.21</td>
<td>27/22</td>
<td>HD</td>
<td>13/20</td>
<td>68/53</td>
</tr>
<tr>
<td>Gorin et al.22</td>
<td>41/47</td>
<td>NHL</td>
<td>14/21*</td>
<td>39/47</td>
</tr>
<tr>
<td>Advani et al.23</td>
<td>231‡</td>
<td>NHL, HD, solid tumors</td>
<td>16/19</td>
<td>No significant difference</td>
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<tr>
<td>Rabinowe et al.24</td>
<td>24/23</td>
<td>NHL</td>
<td>20/27*</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Khwaja et al.25</td>
<td>29/29</td>
<td>NHL, HD</td>
<td>14/20*</td>
<td>14/13§</td>
</tr>
<tr>
<td>Gulati et al.26</td>
<td>12/12</td>
<td>HD</td>
<td>Not given</td>
<td>17/8</td>
</tr>
</tbody>
</table>

HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma; SCLC, small-cell lung cancer.

*Statistically significant difference (p < 0.05) in favor of HGF.
†Includes patients undergoing autologous bone marrow transplantation.
‡Total number of patients.
§Number of positive blood cultures.

In standard dosages have been published (Table I). In only one large study15 in patients treated with COP-BLAM polychemotherapy for non-Hodgkin's lymphoma (consisting of cyclophosphamide, doxorubicin, bleomycin, vincristine, procarbazine, and prednisolone), a reduction of documented infections was observed in conjunction with a decreased number of days with fever and antibiotics. All other randomized studies showed neither a decrease of documented infections nor a consistent reduction of
other infection-related parameters such as days with fever or the use of antibiotics, provided that data on these parameters were given. The reason for the discrepancy between effects on duration of granulocytopenia and effects on documented infections is unknown but could be related to insufficient statistical power of the studies or to the individual characteristics of the patients and their underlying disease. Indeed, it should be emphasized that most chemotherapy schedules for nonleukemic disorders have been developed in an attempt to minimize the incidence and severity of neutropenia and are therefore rarely complicated by clinically or microbiologically documented infections.

ADMINISTRATION OF HGF AFTER HIGH-DOSE CHEMOTHERAPY

The potential of HGF to reduce the incidence of infections can be assessed more adequately in the context of conditioning regimens for an autologous bone marrow transplantation (ABMT), inasmuch as ABMT usually results in relatively long periods of profound granulocytopenia. Moreover, a more reliable assessment of the incidence of infections can be made because the patients are hospitalized and are available for adequate daily monitoring. Surprisingly, the results of studies concerning HGF administration in patients treated with high-dose therapy are almost as conflicting as those obtained in patients with less severe granulocytopenia. It can be postulated that a significant decrease of the incidence of documented infections represents convincing evidence for reduction of the incidence of infections attributable to accelerated neutrophil recovery. In light of this, only three phase III placebo-controlled studies in patients undergoing an ABMT showed a reduction of documented infections in patients treated with HGF. Nemunaitis et al. reported that 65 patients with lymphoid malignancies who were receiving rhGM-CSF (250 mg/m²/day) after ABMT had statistically significant fewer infections than 63 placebo-treated patients (17% versus 30%). Similarly, Link et al. observed infective events in 46% of patients treated with rhGM-CSF in comparison with 70% in the group of patients treated with placebo. However, most other studies on this subject did not corroborate these findings (Table II). Moreover, none of the phase III studies could establish a lower treatment-related mortality, a reduction in extramyeloid toxicities, an enhanced tumor response, or a better survival for patients treated with HGF.

Criteria used for the estimation of the presence of infections in various trials—fever, use of antibiotics, and hospital stay—were not always irrefutable parameters of infection. The policy to institute antibiotic treatment in most studies when fever occurs in granulocytic patients after high-dose chemotherapy is justifiable. However, fever can be due to many causes, such as the administration of rhGM-CSF
itself, a possible relation to enhanced host defense, and other drugs. Some studies reported that the duration of antibiotic treatment and hospital stay were significantly shorter in the group of patients treated with HGF. However, this is debatable as true evidence of infection because antibiotics were given mostly for fever only. The reason the duration of use of antibiotics cannot be used as a parameter of infection is the correlation between duration of granulocytopenia and use of antibiotics: in most studies antibiotics were discontinued when absolute neutrophil count (ANC) rose above 500 per microliter. In some studies HGF administration appeared to offer cost saving in the range of 25% to 35% in patients undergoing an ABMT. This was achieved mainly by reducing the duration of hospitalization, a major cost factor in the management of neutropenia. Considering the possibility of the occurrence of an overwhelming infection in patients with profound granulocytopenia, most physicians will keep these patients hospitalized. Therefore the duration of a hospital stay is directly correlated with the presence of neutropenia, but it is questionable whether HGF is truly saving cost, considering the fact that the incidence of documented infections was not reduced in the vast majority of studies. Improved diagnostic facilities to discriminate patients with an infection from those with a noninfectious cause of fever, as well as better home care with easy access to a hospital, may offer better prospects to reduce costs.

**DISCUSSION**

The reasons for the apparent discrepancy between the positive effect of HGFs on granulocyte recovery and objective clinical benefits, such as a reduction in the incidence of documented infections, remain ambiguous in most studies. Factors that might be responsible for the apparent lack of clinical benefit and factors that obscure a possible clinical efficacy should be recognized. First, infections after ABMT are most likely to occur during the time period when ANC is <100/μl. Khwaja et al. showed that 96% of positive blood cultures were isolated during the period when ANC was <100/μl after ABMT and that HGFs have no major impact on the duration of the episode of severe granulocytopenia. HGFs do not promote earlier engraftment but rather accelerate myelopoiesis once it is initially established, causing a more rapid increase in the number of the neutrophils after a period of severe neutropenia. Second, patients treated with chemotherapy and radiotherapy are prone not only to infections as a result of granulocytopenia. Numerous other factors, such as those related to their underlying immunocompromised state, the use of antibacterials and immunosuppressive drugs, the destruction of physical barriers, and the use of indwelling intravascular catheters, enhance the risk of infections. The occurrence of mucositis is associated with both radiotherapy and chemotherapeutic regimens, particularly anthracyclines, high-dose methotrexate, and high-dose cytarabine.

There are no convincing data from the phase III trials that HGFs selectively decrease the incidence of gram-negative infections. On the other hand, one should take into account that the use of prophylactic antibacterial agents has diminished and curtailed the incidence of gram-negative infections during neutropenia. Therefore the size of the trials done is probably too small to disclose a beneficial influence. In the trials of Nemunaitis et al. and Link et al. the difference in infection rate was attributable to differences in infections caused by gram-positive bacteria. The number of fungal infections encountered was too low to allow any conclusion, but in patients with a high risk for fungal infections the use of hematopoietic growth factors is attractive from a theoretical point of view. The risk for fungal infections increases with prolonged neutropenia, and it is known that antifungal therapy is more effective after neutrophil recovery. Furthermore, in vitro studies show that G-CSF potentiates anti-candida growth inhibitory activity of polymorphonuclear cells. It must be concluded that, besides granulocytopenia, numerous factors determine the risk of infection in patients treated with chemotherapy and radiotherapy, for example, mucosal damage, central venous catheters, environment, state of the underlying disease, and supportive strategies used. To allow a final assessment of the putative clinical benefit of HGFs, further data on 1 hard end points such as documented infection are ultimately required. This warrants carefully designed randomized clinical trials that have to be balanced with respect to the major risk factors, which may necessitate stratification, particularly if the number of patients to be entered is expected to be limited. It is mandatory that adequate trials on the options and limitations of the use of HGFs are performed.
References

23. Advani R, Greenberg P, Gulati S, Hoglund M, Bonnem EM. Randomized placebo controlled trial of granulocyte-macrophage colony-stimulating fac-

**STATEMENT OF ANNOUNCEMENT**

**Accreditation of programs**

The American Board of Clinical Pharmacology announces that it will now accredit training programs in Clinical Pharmacology. The Board certification process for individuals in Clinical Pharmacology began in 1991. Since that time 240 physicians, clinical pharmacists, and medical scientists have been certified. The process of accreditation of programs will formalize the training requirements for Clinical Pharmacology. These requirements are detailed in the application for accreditation. Accredited programs must be located at an appropriately accredited institution, and accreditation will provide trainees with a minimum of two years of training in Clinical Pharmacology.

**Registration of programs**

The Board realizes that many institutions do not have all the components of a formal training program currently in place. For programs that do not meet all requirements, there will be a process by which programs may register with the Board so that the trainees in the program may be eligible to take the Board examination. Until the year 2000, programs may register for a five-year period, informing the Board annually of the progress the program is making toward satisfying the accreditation requirements. After that time, the registration period will be for a maximum of three (3) years.

After 1997, most candidates for the Board examination will be required to have successfully completed a fellowship in a registered or a fully accredited program. The Board is prepared to review applications for accreditation or registration.

Program directors may obtain information and application forms from the administrative office of the American Board of Clinical Pharmacology, Inc., by writing to: PO Box 40278, San Antonio, TX 78229-1278 or by fax (210)567-8509 or by phone (210)567-8505.