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COMMENTARY

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

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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.[1] 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.[2] 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.[3] 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,[4-9] but the value of such observations is limited because the supportive care, including the use of antibiotic agents, has changed considerably over time.

ADMINISTRATION OF HGF AFTER STANDARD-DOSE CHEMOTHERAPY

Several phase III studies[10-16] concerning HGF administration in patients treated with chemotherapy

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Table I. Influence of HGF administration after conventional/dose chemotherapy on the infection rate in phase III placebo/controlled trials

Author	*n (HGF/ placebo)*	*Disease*	*Cytotoxic regimen*	*Reduction in HGF/placebo groups of*		
				ANC <1000/μl		*Documented infections (% of patients)*
				No. of days	*% of patients*	
G-CSF						
Crawford et al.[10]	95/104	SCLC	CDE	Incomplete data†	Incomplete data†	7/13
Kotake et al.[11]	32/38	Urogenital cancer	M-VAC	1/7*	Not given	Not given
Trillet-Lenoir et al.[12]	65/64	SCLC	CDE	6/15	Not given	20/33
Pettengell et al.[13]	41/39	NHL	VAPEC-B	Not given	37/85*	17/13
GM-CSF						
Kaku et al.[14]	31/31	NHL	CHOP	Not given	52/73*	13/26
Gerhartz et al.[15]	91/91	NHL	COP-BLAM	Not given	19/33*	27/45§
de Vries et al.[16]	9/6	Ovarian cancer	CAR, CTX	Not given	Significant difference	Not given

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, vincristin, procarbazine, prednisolone; M-VAC, methotrexate, vinblastin, doxorubicin, cisplatin; VAPEC-B, doxorubicin, cyclophosphamide, vincristine, bleomycine, 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

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

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 allogeneic bone marrow transplantation.
‡Total number of patients.
§Number of positive blood cultures.

in standard dosages have been published (Table I). In only one large study[15] 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

Reduction in HGF/placebo groups of		
Fever (neutropenic) (% of patients)	*Antibiotic use*	
	No. of days	*% of patients*
40/77*	1/2 per cycle	Not given
Not given	Not given	37/58
26/53*	Not given	37/58*
23/44*‡	Not given	22/31
13/2**	Not given	Not given
41/56§	3/8*§	
Not given	Not given	Not given

Reduction in HGF/placebo groups of		
Fever (neutropenic)		*Antibiotic use (No. of days)*
No. of days	*% of patients*	
3/5*	66/70*	15/19*
8/8	97/97	24/27*
Not given	79/77	19/19
Not given	Not given	Not given
Not given	Not given	Not given
4/2	27/13	19/22
Not given	Not given	Not given
Not given	No significant difference	No significant difference
8/6	Not given	8/3.5
Not given	100/100	Significant difference

other infection-related parameters such as days with fever or the use of antibiotics, provided that data on these parameters were given.[10-14,16] 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[17-19] showed a reduced incidence of documented infections in patients treated with HGF. Nemunaitis et al.[17] reported that 65 patients with lymphoid malignancies who were receiving rhGM-CSF (250 mg/m^2/day) after ABMT had statistically significant fewer infections than 63 placebo-treated patients (17% versus 30%). Similarly, Link et al.[18] 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[20-26] 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.[27] However, fever can be due to many causes, such as the administration of rhGM-CSF

itself, a possible relation to enhanced host defense,[28] 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[9,17,19,22] HGF administration appeared to offer cost saving in the range of 25% to 35% in patients undergoing an ABMT.[29] 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.[25] 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.[1,18,25] 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.[17] and Link et al.,[18] 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,[30] 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.[31] 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 and kind of underlying disease, and supportive strategies used. To allow a final assessment of the putative clinical benefit of HGFs, further data on 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

1. Metcalf D. The colony-stimulating factors: discovery, development and clinical applications. Cancer 1990; 65:2185-95.
2. Peters WP. The effect of recombinant human colony-stimulating factor on hematopoietic reconstitution following autologous bone marrow transplantation. Semin Hematol 1989;26(suppl 2):18-23.
3. Bodey GP, Buckley M, Sathe US, et al. Quantitative relationships between circulating leukocytes and infections in patients with acute leukemia. Ann Intern Med 1966;64:328-40.
4. Brandt SJ, Peters WP, Atwater SK, et al. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on hematopoietic reconstitution after high dose chemotherapy and autologous marrow transplantation. N Engl J Med 1988;318:869-76.
5. Blazar BR, Kersey JH, McGlave PB, et al. In vivo administration of recombinant human granulocyte/macrophage colony-stimulating factor in acute lymphoblastic leukemia patients receiving purged autografts. Blood 1989;73:849-57.
6. Gulati S, Bennett C, Phillips J, Van-Poznak C. GM-CSF as an adjunct to autologous bone marrow transplantation. Stem Cells (Dayt) 1993;11:20-5.
7. Sheridan WP, Wolf M, Lusk J, et al. Granulocyte colony-stimulating factor and neutrophil recovery after high dose chemotherapy and autologous bone marrow transplantation. Lancet 1989;2:491-5.
8. Taylor KM, Jagannath S, Spitzer G, et al. Recombinant human granulocyte colony-stimulating factor hastens granulocyte recovery after high dose chemotherapy and autologous bone marrow transplantation in Hodgkin's disease. J Clin Oncol 1989;7: 1791-9.
9. Tokahasmi S, Asano S, Masaoka T, et al. Clinical evaluation of recombinant human granulocyte colony-stimulating factor (rhG-CSF) in autologous bone marrow transplantation. Jpn J Clin Hematol 1991;32:221-6.
10. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced chemotherapy in patients with small cell lung cancer. N Engl J Med 1991;315:164-70.
11. Kotake T, Miki T, Akaza H, et al. Effect of recombinant granulocyte colony-stimulating factor (G-CSF) on chemotherapy induced neutropenia in patients with urogenital cancer. Cancer Chemother Pharmacol 1991;27:253-7.
12. Trillet-Lenoir V, Green J, Manegold C, et al. Recombinant granulocyte colony-stimulating factor reduces the infectious complications of cytotoxic chemotherapy. Eur J Cancer 1993;29A:319-24.
13. Pettengell R, Gurney H, Radford JA, et al. Granulocyte colony-stimulating factor to prevent dose-limiting neutropenia in non-Hodgkin's lymphoma: a randomized controlled trial. Blood 1992;80:1430-6.
14. Kaku K, Takahashi M, Moriyama Y, et al. Recombinant human granulocyte macrophage colony-stimulating factor (rhGM-CSF) after chemotherapy in patients with non-Hodgkin's lymphoma: a placebo-controlled double-blind phase III trial. Leuk Lymphoma 1993;11:229-38.
15. Gerhartz HH, Engelhard M, Meusers P, et al. Randomized, double-blind, placebo-controlled, phase III study of recombinant human granulocyte-macrophage colony-stimulating factor as adjunct to induction treatment of high-grade malignant non-Hodgkin's lymphomas. Blood 1993;82:2329-39.
16. de Vries EGE, Biesma B, Willemse PHB, et al. A double-blind controlled study with granulocyte macrophage colony-stimulating factor during chemotherapy for ovarian cancer. Cancer Res 1991;51: 116-22.
17. Nemunaitis J, Rabinowe SN, Singer JW, et al. Recombinant granulocyte macrophage colony-stimulating factor after autologous bone marrow transplantation for lymphoid cancer. N Engl J Med 1991;324:1773-8.
18. Link H, Boogaerts MA, Carella AM, et al. A controlled trial of recombinant human granulocyte macrophage colony-stimulating factor after total body irradiation, high dose chemotherapy, and autologous bone marrow transplantation for acute lymphoblastic leukemia or malignant lymphoma. Blood 1992;80:2188-95.
19. Advani R, Chao NJ, Horning SJ, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) as an adjunct to autologous hemopoietic stem cell transplantation for lymphoma. Ann Intern Med 1992;116: 183-9.
20. Gisselbrecht C, Prentice HG, Bacigalupo A, et al. Placebo-controlled phase III trial of lenograstim in bone-marrow transplantation. Lancet 1994;343:696-700.
21. Bennett CL, Greenberg P, Gulati SC, Advani R, Bonnem E. GM-CSF decreases duration of cytopenia and hospitalization and in-hospital costs in patients with Hodgkin's disease treated with high dose chemotherapy and autologous bone marrow transfusion (ABMT) [Abstract]. Blood 1990;76(suppl 1):132.
22. Gorin NC, Coiffier B, Hayat M, et al. Recombinant human granulocyte-macrophage colony-stimulating factor after high-dose chemotherapy and autologous bone marrow transplantation with unpurged and purged marrow in non-Hodgkin's lymphoma: a double-blind placebo-controlled trial. Blood 1992;80:1149-57.
23. Advani R, Greenberg P, Gulati S, Hoglund M, Bonnem EM. Randomized placebo controlled trial of granulocyte-macrophage colony-stimulating fac-

tor in patients undergoing autologous bone marrow transplantation [Abstract]. Blood 1990;76(suppl 1): 525.
24. Rabinowe S, Freedman A, Demetri G, et al. Randomized double blind trial of rhGM-CSF in patients with B-cell non Hodgkin's lymphoma undergoing high dose chemoradiotherapy and monoclonal antibody purged autologous bone marrow transplantation [Abstract]. Blood 1990;76(suppl 1):161.
25. Khwaja A, Linch DC, Goldstone AH, et al. Recombinant human granulocyte-macrophage colony-stimulating factor after autologous bone marrow transplantation for malignant lymphoma: a British National lymphoma investigation double-blind placebo controlled trial. Br J Haematol 1992;82:317-23.
26. Gulati SC, Bennett C. Granulocyte macrophage colony-stimulating factor (GM-CSF) as adjunct therapy in relapsed Hodgkin's disease. Ann Intern Med 1992;116:177-81.
27. Donnelly JP, de Pauw BE. Current infectious complications and their management in acute leukemia and bone marrow transplantation. Int J Antimicrob Agents 1994;3:245-50.
28. Vreugdenhil G, Preyers F, Croockewit A, Sauerwein R, Swaak AJG, de Witte T. Fever in neutropenic patients treated with GM-CSF representing enhanced host defence. Lancet 1992;339:1118-9.
29. Goa KL, Bryson HM. Recombinant granulocyte-macrophage colony-stimulating factor (rGM-CSF): an appraisal of its pharmacoeconomic status in neutropenia associated with chemotherapy and autologous bone marrow transplant. PharmacoEconomics 1994;5;56-77.
30. Gerson SI, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. Ann Intern Med 1984;100: 345-51.
31. Yamamoto Y, Klein TW, Friedman H, Kimura S, Yamaguchi H. Granulocyte colony-stimulating factor potentiates anti-Candida albicans growth inhibitory activity of polymorphonuclear cells. FEMS Immunol Med Microbiol 1993;7:15-22.