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G-CSF and GM-CSF in Clinical Trials

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Hematopoietic growth factors have now been purified, cloned, and produced in bacteria and yeast. Those that are currently in clinical study include erythropoietin, GM-CSF, G-CSF, M-CSF (also called CSF-1), and multi-CSF (also called interleukin 3). Growth factors appear likely to enhance the recovery and function of circulating white cells after standard-dose cancer therapy and high-bone-dose cancer therapy with marrow transplant and to restore leukocyte numbers and competence in the acquired immune deficiency syndromes and myelodysplastic syndromes. Phase I, II trials in AIDS, in cancer patients receiving chemotherapy, in cases of myeloproliferative disease, and after bone marrow transplant have been published. The results of phase III studies are just becoming available.

REGULATION OF NORMAL WBC PROLIFERATION AND FUNCTION

In Vitro *Studies*

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a major hormonal regulator of human granulopoiesis [1,2,3]. GM-CSF enhances both proliferation of myeloid precursor cells and the function of mature peripheral blood neutrophils and mononuclear phagocytes. (Refer to Table 1.) GM-CSF is a protein that acts in picomolar concentrations to stimulate colonies of differentiated granulocytes and monocytes in semisolid media [3,13]. Complementary DNA clones encoding GM-CSF have been isolated, and recombinant human (rh) GM-CSF produced [13]. This material possesses biologic activity for the development of granulocytes, mixed granulocyte-macrophage, pure eosinophil, and multipotent mixed cell progenitor colonies from both normal bone marrow and human myeloid leukemia cell lines, HL-60 and KG-1 [14,15]. GM-CSF also stimulates the growth of human erythroid burst-forming units (BFU-E) in the presence of erythropoietin when adherent and E-rosette forming cells are removed from preparations [14,16]. GM-CSF is a weak but consistent inducer of differentiation in HL-60 cells, resulting in increased numbers of cells displaying monocytic and eosinophilic characteristics [15].

GM-CSF has neutrophil migration-inhibition activity and has been previously described as a neutrophil migration-inhibition factor from T-lymphoblast cell lines [3,17]. In functional studies, GM-CSF stimulates superoxide anion generation in response to the bacterial chemoattractant, N-formyl-methionyl-leucyl-phenylalanine [17]. Thus, GM-CSF stimulates growth of myeloid precursor cells and augments neutrophil oxidative metabolism important in neutrophil microbicidal and tumoricidal activities [16].

GM-CSF induces cellular activities after binding with specific high-affinity recep-

Abbreviations: See Appendix 1.

TABLE 1
Laboratory Studies with Clinical Implications of G- or GM-CSF on Granulocyte Function

First Author	No.	Observation	Reference
Baldwin		Produces functionally active PMNs	[4]
Mayani		Greater response of myeloid cells	[5]
Socinski		Greater CD11b cell surface protein	[6]
Sullivan		Greater acidity within PMN	[7]
Sullivan	7	Greater granulocyte superoxide generation after *in vitro* stimulation	[8]
Peters		Fluid migration into a sterile field (skin window response)	[9]
Linch	4	Skin window responses present in two of three patients	[10]
Addison	8	Skin window responses fluid 30 percent in four of nine patient studies	[11]
Tobler		Vitamin D decreases GM-CSF production	[12]

No., number of patients studied

tors on the plasma membrane of responding granulocytes and macrophages. Specific binding to high-affinity saturable cell surface receptors occurred on two human cell lines that exhibit proliferative responses to GM-CSF (KG-1, an acute myelocytic leukemia [AML] cell line, and HL-60, a promyelocytic cell line.)

Thus, granulocytes exposed to granulocyte colony-stimulating factor (G-CSF) or GM-CSF appear to be primed for activation and more efficient in killing bacteria. In some patients, migration into a sterile skin window appears to be suboptimal after GM-CSF but not during G-CSF administration.

In Vivo *Primate Studies*

Recombinant human (rh) GM-CSF, administered intravenously (iv) or subcutaneously over seven to 30 days to non-human primates [18], have demonstrated dose-dependent increases in total peripheral white blood cell (WBC) counts (predominantly increases in the absolute numbers of mature neutrophils, neutrophilic basophils, and eosinophils, with less consistent increases in platelets and occasionally lymphocytes).

Depending upon the method of administration, the total peripheral WBC has increased as early as 48 to 72 hours after beginning administration of GM-CSF, associated with bone marrow hyperplasia of the appropriate cell lines. In one study, peripheral blood neutrophils obtained during treatment with GM-CSF exhibited morphologic and functional changes associated with cellular priming for activation (increased superoxide anion generation and enhanced phagocytosis of opsonized *E. coli*).

With the exception of cutaneous flushing in some animals, fever in one animal during and immediately after administration, and the development of specific antibodies to human GM-CSF, no clinically significant adverse reactions were noted in any of the non-human primate studies. Doses ranged from 2–176 μg/kg/day of protein (4–300 μg/kg/day of glycoprotein) equivalent to 0.06–7.2 × 105 units/kg/day of activity (measured as the stimulation of 3H-thymidine uptake by peripheral blood cells from patients with chronic myelocytic leukemia [CML].

Dose-response was evaluated by administration of 0 (vehicle only), 5, 15, 30, or 60 μg/kg GM-CSF (two or three animals per dose level) twice a day intravenous bolus for five consecutive days. Significant increases in WBC counts were observed in all animals within one week, with the maximal WBC observed at 15 μg/kg. Both subcutaneous

TABLE 2
CSFs Currently Undergoing Clinical Trials

Factor	Company	Produced in	Institution	Phase I		Phase II
				Dose μg/Day	Schedule	Dose
GM-CSF	Sandoz	CHO	Duke	2–32/kg	24-hour CI	<32
			DFCI	4–64/kg	24-hour CI	<32
			NEDH	.3–45/kg	24-hour CI	<32
GM-CSF	Schering	*E. coli*	Christie	3–10/kg	24-hour CI	
GM-CSF	Immunex	Yeast	MDAH	30–500/m^2	24-hour CI	30
C-CSF	AmGen	*E. coli*	MSKCC	1–60/kg	30 minutes daily	
			Manchester	1–10/kg	24-hour CI	
			UCLA	1–6/kg	Subcutaneous daily	
			MDAH	1–3/kg	Subcutaneous daily	
G-CSF	Kirin	*E. coli*	Tokyo	50–1,600/m^2		

DFCI: Dana-Farber Cancer Institute
MDAH: M.D. Anderson Hospital, Houston
MSKCC: Memorial Sloan-Kettering Cancer Center, New York City
NEDH: New England Deaconess Hospital
UCLA: University of California, Los Angeles

and intravenous administration resulted in comparable increases in WBC count. (Refer to Table 2.)

The optimal schedule of GM-CSF seems to be 5 μg/kg/day subcutaneously twice a day. Intravenous bolus schedules are associated with poor efficacy. High peak levels are associated with shortness of breath at the initial treatment. Higher doses result in an increased incidence of pericarditis [19,20].

LEUKEMIA

Growth factors are being studied as agents to synchronize leukemic cells in patients with refractory acute myelocytic leukemia (AML) prior to high-dose cytarabine [21]. In other studies, GM-CSF is being given after reinduction therapy in refractory patients [22] or in newly diagnosed AML patients at high risk [22,23] in order to attempt to decrease the period of aplasia. One patient treated with GM-CSF for idiopathic neutropenia normalized his WBC and was found to have hairy cell leukemia [24]. (Refer to Table 3.)

The results of clinical trials so far suggest that GM-CSF should enhance the activity of a phase-specific cytotoxic drug against AML. In subsets of patients with AML, G- and GM-CSF result in an earlier than expected recovery compared to historical controls. Whether the fraction of AML patients who have regrowth of leukemic cells after induction is increased by treatment with GM-CSF or G-CSF is not known. One randomized trial of 98 patients describes a significantly shorter recovery after induction treatment, significant decrement in the number of infections, and a complete response rate of 50 percent in the group receiving GM-CSF (versus 38 percent complete responses in the group randomized to placebo). G-CSF alone and with interferon has been used in patients with hairy cell leukemia and neutropenia with substantial increases in granulocyte count. The white count in one patient treated with GM-CSF for a diagnosis of aplastic anemia increased from 1,700 to 5,600 with the appearance of hairy cells (presumably the etiology of his prior neutropenia).

TABLE 3
CSF Studies in Leukemia

First Author	Response	Reference
	Laboratory	
Ciaiolo	GM-CSF enhances methotrexate cytotoxicity	[25]
Cannistra	GM-CSF enhances cytarabine cytotoxicity	[21]

First Author	No.	Dose μg/Day	Response	Reference
			Clinical	
GMCSF				
Zuehlsdorf	24		Shortened aplasia; 3 with AML regrowth	[22]
Estey	12	120/m²	4 died, 6 CRs; "4 earlier than expected recovery"; 1 APML regrowth	[23]
Schuster	1	3/kg	Rx for "AA"; WBC 1.7 to 5.6; hairy cells	[24]
Gattringer	8	10/kg	1/8 relapsed after a delay	[26]
G-CSF				
Glaspy	4	1–6 μg/kg	PMN in 3/4 with hairy cell/neutropenia <900 to >4,000/μl	[27]
Glaspy[a]	6	3–6 μg/kg	PMN in 5/5 with hairy cell/enutropenia <827 to >6,856/μl	[28]
Ohno[a]	98	200/m²	Significantly shorter recovery, infections 5 versus 15 percent CR 50 versus 38 percent	[29]
Teshima	8	50–200/m²	ANC recovery in <10 days	[30]

[a]With interferon
AA: aplastic anemia
APML: acute promyelocytic leukemia
CR: complete response

APLASTIC ANEMIA

In aplastic anemia, the number of patients with WBCs "responding" to GM-CSF has ranged from one in four patients to ten of 11. Increased white counts ranged from 1.6- to tenfold increase in improvement. In the only randomized trial, a small study of seven patients, the four patients randomized to GM-CSF responded. The three control patients also responded when they were crossed over after failure to respond to placebo. (Refer to Table 4.)

MYELODYSPLASIA

Significantly increased leukocytes, granulocytes, monocytes, lymphocytes, and eosinophils were observed (as well as platelets and reticulocytes in a few) in patients treated with GM-CSF generally for at least two weeks. Toxicity includes bone pain as well as sporadic fever, chills, myalgias, headache, and anorexia. (Refer to Table 5.)

In laboratory studies of granulocytes from patients with myelodysplasia, G-CSF and GM-CSF stimulated proliferation; however, the percentage of blasts decreased in most cases because of the increased absolute number of granulocytes. In clinical studies, one-half to three-quarters of the patients exhibited an improvement in white blood cell count response, but 10 percent to 25 percent of the patients had an increased absolute number of peripheral blood blasts. To attempt to decrease the risk of leukemic transformation, some investigators have added low-dose cytarabine during the GM-CSF infusion. In one randomized study of 48 patients, 27 of 28 patients responded to

TABLE 4
CSF Studies in Aplastic Anemias

First Author	Institution	No.	Dose μg/Day	WBC Response	Reference
Nissin		4	4–32/kg	In 1/4 patients	[31]
Vadhan	MDAH	10	60–500/m^2	↑1.6–10 times	[32, 33]
Antin	BWH	15	15–480/m^2	In 6/8 patients	[34]
Champlin	UCLA	15	4–64/kg	In 10/11 evaluable patients	[35]
Rifkin	Arizona	16	15–960/m^2	Mean 8.5 times	[36]
Schuster[a]	N Shore	7	3/kg	4/7 (failures crossed over)	[37]

[a]Randomized
BWH: Brigham and Women's Hospital
MDAH: M.D. Anderson Hospital, Houston
N Shore: North Shore Hospital, New York
UCLA: University of California, Los Angeles

GM-CSF. One patient each in the GM-CSF group and the placebo group developed leukemia.

IDIOPATHIC NEUTROPENIA/AGRANULOCYTOSIS

Growth factors used in patients with various neutropenias (idiopathic, cyclic, and congenital) seem responsive to even long-term use of G-CSF. Patients treated for three to 15 months continue to respond with significantly increased granulocytes and resolution of prior infection. (Refer to Table 6.)

SOLID TUMORS

There are a number of studies of GM-CSF with and without chemotherapy. Pharmacokinetic studies suggest that efficacy correlates with dose and area under the curve. Subcutaneous administration appears to avoid some toxicities associated with iv administration. In animal models, both G- and GM-CSF increase speed of recovery after common cytotoxic drugs. Laboratory studies have suggested that a few fresh solid tumors and cell lines are moderately stimulated by GM-CSF; however, more are distinctly inhibited, and most were unaffected. There are now anecdotes of patients with malignancy-associated leukemoid reactions found to have high serum growth factor level, presumably of tumor origin.

A number of investigators have delivered GM-CSF alone (with no chemotherapy) in order to attempt to modulate monocyte function. One sarcoma has partially responded. Since there have been over 100 patients entered in such studies, the significance of this response is difficult to assess. (Refer to Table 7.)

Multiple studies of G- and GM-CSF after chemotherapy for specific tumors or miscellaneous malignancies suggest a decreased duration of neutropenia with either growth factor. GM- or G-CSF without chemotherapy generally results in a dose-dependent rise in WBC and granulocytes (to >20,000 WBC in a mean of four days). The WBC nadir after chemotherapy is generally significantly shallower and shorter than after historical controls. The total duration of granulocytopenia (polymorphonuclear leucocyte [PMN] <500/μl) is generally significantly shorter. Fever occurs in about half the patients receiving GM-CSF, and arthralgias, mild headaches, and skin

TABLE 5
CSF Studies in Myelodysplasia

First Author	Response	Reference
	Laboratory	
Tohyama	GM-CSF stimulated proliferation but decreased the percentage of blasts in 5/6 cases	[38]
Carlo	CFU-GM growth was markedly improved in 15/16 patients	[39]

First Author	Institution	No.	Dose μg/Day	WBC Response	⇑ Blasts		Reference
				Clinical			
Antin	BWH	15	15–480/m^2	5/7 patients	2/7		[34]
Ganser	Frankfurt	11	15–150/m^2	10/11	4/11		[40, 41]
Vadhan	MDAH	8	30–500/m^2		0/8		[42]
Vadhan	MDAH	1		"Complete response"	0/1		[43]
Gradishar	Chicago	9	60–500/m^2	7/8 evaluable patients	3/9 (+3 lymphoma)		[44]
Thompson	Seattle	16	.3–10/kg	11/13	1/16		[45]
Hoffken[a]	Essen, FRG	12	250/m^2	5/12	2/12		[46]
Ganser[a]	Frankfurt	5	250/m^2	3/5	0/5		[47]
Herrmann		4	Varied	4/4	At doses >500/m^2		[48]
Hoelzer[a]	Frankfurt	10	15–150/m^2	9/10; 1 inc platelets	"Some"; ↯ LD ara-C		[49]
Schuster[b]	N Shore	48	3/kg	27/28	1/28; 2/48		[37]
G-CSF							
Kobayashi	Tokyo	Kirin	4	50–1,600/m^2	4/4	Two to three times in BM	[50]
Negrin	Stanford	AmGen	12	.1–3/kg	10/12 five times ⇑ PMN	Transiently	[51]

[a]Plus low-dose cyarabine
[b]Randomized
BWH: Brigham and Women's Hospital
FRG: Federal Republic of Germany
MDAH: M.D. Anderson Hospital, Houston
N Shore: North Shore Hospital, New York

rash in many patients at doses of 4–32 mg/kg/day. A syndrome of transient hypoxia and neutropenia immediately after the first dose of GM-CSF results from increased granulocyte adhesion proteins (CD11b) and congregation of granulocytes in the lungs. At high doses (e.g., 64 mg/kg/day), however, thromboses around central lines, pulmonary emboli, and 5–10 kg weight gain associated with pleural and pericardial effusions (capillary leak syndrome) as well as atrial arrhythmias have been reported. Morstyn et al. [93] reported a study of a sequence of schedules of G-CSF after 25 mg/m^2 of Melphalan. Occasional bone discomfort was the only side effect. G-CSF could be started as late as eight after chemotherapy and did not need to be continued more then seven days [94].

Randomized trials are now just being reported, including a study by Crawford et al. [83] including 126 patients with small-cell lung cancer treated with repeated cycles of

TABLE 6
CSF Studies in Neutropenia

Author	No.	Response	Reference
		Laboratory	
Wright	4	Stimulation of CFU-GM required ten times GM-CSF than normals	[52]

First Author	Institution	Product	No.	Dose μg/Day	WBC Response	Reference
				Clinical		
GM-CSF						
Ganser	Frankfurt	Immunex	4	150–1,000/m^2	↑ in 4/4; resolution of infection	[53]
G-CSF						
Congenital agranulocytosis						
Bonilla	MSKCC	AmGen	5	3–60/kg	5/5 PMN <100 to 1,300–9,500/μl 9–13 months	[54]
Cyclic neutropenia						
Hammond	Seattle	AmGen	6	3–10/kg	Nadir PMN 17/μl to 1,393/μl; 3–15 months	[55]
Chronic idiopathic neutropenia						
Jakubowski	MSKCC	AmGen	1	1–3/kg	PMN 40/μl to >1,500/μl	[56]

MSKCC: Memorial Sloan-Kettering Cancer Center, New York City

cyclophosphamide, adriamycin, and etoposide with significant differences in duration of neutropenia, infections, and hospital days. A smaller randomized study from Osaka draws similar conclusions.

BONE MARROW TRANSPLANTATION

Myelosuppression is the dose-limiting toxicity for many chemotherapy regimens; however, for many tumors, optimum response cannot be achieved without exceeding the dose of chemotherapeutic agents, which causes unacceptable myelosuppression. The concept of removal and storage of sufficient numbers of hematopoietic stem cells to re-establish normal marrow function is well established in both animal models and many human trials. In tumors such as lymphomas and Hodgkin's disease, high-dose chemotherapy with autologous marrow "rescue" appears to result in prolonged disease-free survival, compared to treatment with standard chemotherapy regimens for patients failing standard therapy. The role of autografting in solid tumors is less well defined at present, but considerable laboratory and clinical evidence suggests that sensitive but incurable tumors are appropriate for investigation of high-dose chemotherapy.

The major morbidity of high-dose chemotherapy results from myelosuppression. While anemia and thrombocytopenia can be treated by transfusion, no effective method restores granulocyte and monocyte-macrophage levels. The incidence of bacterial and fungal infection correlates with both duration and severity of neutropenia. The first polymorphonuclear leucocyte (PMN) appears on complete blood counts obtained on day 9 to 11. An absolute neutrophil count (ANC) >500 is achieved at a median of 18 to 26 days after transplant with platelet transfusion independence at a

TABLE 7
CSF Studies in Malignancy

First Author	No.	Response	Reference
		Laboratory Trials	
Efficacy			
Cebon	33	GM-CSF in humans: Efficacy α dose, AUC; SQ > IV. Toxicity α dose.	[19]
O'Reilly		GM-CSF in primates: Rapid WBC recovery after 5 FU	[57]
Ono		G-CSF in mice: Rapid WBC recovery after cyclophosphamide	[58]
Effect of GM-CSF on tumor (fresh or cell lines)			
Dedhar		⇑ growth, 2 osteosarcomas, 1 breast, fibroblasts	[59]
Salmon	33	19, stable; 10, growth inhibition (marked in 3); 4, moderate stimulation	[60]
Ohwade	1	A patient with 71,300 WBC and prostate cancer had serum G-CSF levels three times normal	[61]
Monocyte function			
Wing		⇑ monocyte numbers and function (cytotoxicity, TNF, IF)	[62]
Kleinerman		GM-CSF increases monocyte numbers; activated for tumor lysis in 1/7 No IL-1 or TNF production	[63]
Cannistra		GM-CSF increased tumor lysis after *in vivo* exposure	[64]

First Author	Institution	No.	Dose μg/Day	Tumor	Observations	Reference
			Clinical Trials			
GM-CSF alone (no chemotherapy)						
Antman	DFCI	16	4–64/kg	Sarcomas		[65]
Avashia	Cleveland	13	60–250/m^2	Lung	Monocyte modulation	[66]
Phillips		10	100–500/m^2	Miscellaneous		[67]
Steward		20	.3–60/kg	Miscellaneous	1PR sarcoma; 7 SD	[68]
Wing			100–500/m^2	Refractory		[62]
Linch		4		Miscellaneous	Kinetic/skin window studies	[10]
Lieschke	Melbourne	21	.3–30/kg	Miscellaneous		[69]
Herrmann		30	120–1,000/m^2	Miscellaneous	No responses	[70]
Aglietta		9	8/kg	Miscellaneous	⇓ S phase bone marrow cells after drug dcd	[71]
Hoogmoed	NYU	16	30–150/m^2	Refractory	8 patients > four times monocyte cytotoxicity	[72]

First Author	Institution	No.	Dose μg/Day	Tumor	Drugs	Reference
GM-CSF with chemotherapy						
Gerhartz[a]	Munich	40	2–32/kg	Lymphoma+	Chemotherapy	[73]
Ajani	MDAH	20	250–500/m^2	Esophagus	VP-16, ADR, DDP	[74]
Antman	DFCI	16	4–64/kg	Sarcomas	ADR, Ifos, DTIC	[65]
Rusthoven	Ontario	7	10/kg	Ovarian	CPA, 400–800 carboplatin	[75]
Fox	Melbourne			Miscellaneous	(CBDCA and VP-16) × 3	
Neidhart	New Mexico	23	250–1,000/m^2	Miscellaneous	CPA, VP-16, DDP	[76]
Shea	San Diego	12	5–10/kg	Miscellaneous	HD carboplatin	[77]
Speyer	NYU	9	15/kg	Miscellaneous	50–72 mg/m^2 ADR	[78]
Stitt	Wisconsin	8		Miscellaneous	HDCPA, VP-16, DDP	[79]
Hartmann[b]	Mayo Clinics	33	10–20/kg	Miscellaneous	1 gm CPA, 225–600 CBDCA	[20]
Gattringer		5	10/kg	Miscellaneous	Miscellaneous	[26]
Lowenberg	Rotterdam		216 mg/bid	Miscellaneous	Repeated cycles	[80]

TABLE 7—*Continued*

First Author	Institution	No.	Dose μg/Day	Tumor	Drugs	Reference
G-CSF						
Bronchud	Manchester	12	1–40/kg	SCLC		[81,82]
Crawford[a]	Duke	126		SCLC	CPA, ADR, VP-16	[83]
Eguchi	NCC, Tokyo	39	50–800/m^2	Lung	Miscellaneous	[84]
Ogawara[a]	Osaka	60	75/kg	Lung	Miscellaneous	[85]
Takada	Osaka	40	2/kg	NSCLC	Mit C, VDS, DDP	[86]
Toki	Japan	4	2/kg	Lymphoma	CHOP	[87]
Ema	Japan	4	100–800/m^2	Lymphoma	Miscellaneous	[88]
Bronchud	Manchester	17	10–5/kg	Breast, ovary	ADR	[89]
Gabrilove	MSKCC	27	1–60/kg	Bladder	Methotrexate, ADR, VBL, DDP	[90,91]
Fukutani	JCF, Tokyo	17	25–800/m^2	Miscellaneous	Miscellaneous	[92]
Morstyn	Melbourne	15	1–60/kg	Miscellaneous	Melphalan	[93]
Morstyn	Melbourne	22	.3–10/kg	Miscellaneous	Melphalan	[94]
Neidhart	New Mexico			Miscellaneous	CPA, VP-16, DDP	[95]
Stitt	Wisconsin	13	60/kg	Miscellaneous	HDCPA, VP-16, DDP	[79]

[a]Randomized
[b]5/33 patients developed atrial fibrillation while receiving GM-CSF at the highest dose level.
ADR: adriamycin
CBDCA: carboplatin
CPA: cyclophosphamide
DFCI: Dana-Farber Cancer Institute
DDP: cisplatin
DTIC: dacarbazine
HDCPA: high-dose cyclophosphamide
IF: interferon
Ifos: ifosfamide
IL-1: interleukin 1
JCF: Japan Cancer Foundation
MDAH: M.D. Anderson Hospital, Houston
MSKCC: Memorial Sloan-Kettering Cancer Center, New York City
NCC: National Cancer Center
NYU: New York University, New York City
TNF: tumor necrosis factor
VBL: vinblastine
VDS: vindesine
VP-16: etoposide

median of 21 to 28 days. A median of 30 to 50 inpatient days is required for autologous bone marrow transplant (ABMT). The psychological effect of prolonged isolation and hospitalization and hospital costs are substantial. The major cause of the 4–25 percent mortality for ABMT remains infection or bleeding during the three- to four-week period of profound myelosupression. More rapid hematologic reconstitution would substantially reduce mortality, morbidity, and the expense of high-dose therapy.

GM-CSF levels have been found to be elevated between days 7 and 21 after bone marrow reinfusion, and increased serum levels are also measured in patients with graft-versus-host disease (GVHD). Transient cyclic neutropenia has been reported following the use of GM-CSF after an allograft for chronic granulocytic leukemia (CGL). (Refer to Table 8.)

TABLE 8
CSF Studies in Bone Marrow Transplantation

First Author	Response	Reference
	Laboratory	
Yamasaki	ABMT:GM-CSF in produced day 7–21	[96]
Kanamaru	⇑ Serum levels of GM-CSF produced in GVHD	[97]
Atkinson	Monokines recover early; lymphokines late	[98]
Meagher	Growth factors affect marrow cells in long-term culture	[99]
Gluckman	Transient cyclic neutropenia following GM-CSF after AlloBMT for CGL	[100]
Haas	GM-CSF in long-term marrow culture expands neutrophil progenitors	[101]
Geissler	Growth factor levels initially fall, then rise, peaking at day 8–14	[102]

			Days to PMN > 500		
GM-CSF	Institution	No.	GM-CSF	Control	Reference
		Clinical			
Historical Controls					
Brandt	Duke	19	16	19	[103]
Nemunaitis	Seattle	15	14	25	[104]
Blazer	Minnesota	25	24	23	[105]
Herrmann	Mainz	28	"Significant difference"		
Link	Hanover, FRG	11	14	20	[106]
Linkesch	Vienna	4	15	24	[107]
Michon	Paris	21	18	26	[108]
Lazarus	Cleveland	12	14	22	[109]
Devereaux	London	12	18	25	[110]

			Response		
First Author	Institution	No.	Yes	No	Reference
Poor Graft Function					
Klingeman	Vancouver	9	6	3	[111]
Nemunaitis	Seattle	37[b]	21	16[b]	[112]
Vose	Nebraska	12	9	3	[113]
Randomized					
Philip[a]	Lyon	20			[114]
Nemunaitis[a]	Seattle	30	16	17	[115]

			Days to PMN > 500		
G-CSF	Institution	No.	G-CSF	Control	Reference
Historical Controls					
Masaoka	Japan	13	21	Significantly longer	[116]
Mukaiyama	Japan	10	"Significant difference"		[117]
Teshima	Japan	7	11	27	[30]
Sheridan	Melbourne	15	11	20	[118]

TABLE 8—*Continued*

First Author	Institution	No.	Response		Reference
			Yes	No	
Poor Graft Function					
Takaue	Japan	1	1		[119]
Randomized					
Masaoka[a]	Japan	66	"Significant difference"		[120]

[a]Randomized
[b]Including 7/7 purged marrows
AlloBMT: allogenic bone marrow transplant
FRG: Federal Republic of Germany

Of the nine studies of GM-CSF after bone marrow transplant with historical controls, there was modest but statistically significantly decreased time to re-engraftment in eight, with fewer episodes of bacteremia or organ toxicity in the majority of studies. In the ninth, which used purged marrows, those patients who had the highest levels of colony-forming units granuloyte-macrophage (CFU-GM) reinfused had a markedly shorter time to recovery. Dose correlated with peak WBC. Platelets are inconsistently affected. Significant shortening of time to >500 PMNs, >20,000 platelets, and duration of hospitalization are reported in some series. Patient variability appears considerably related to prior chemotherapy. Toxicity includes myalgias, transient rash, peripheral edema, minor abdominal cramps, bone pain, and low-grade fever. At higher doses (~30 μg/kg/day), a capillary leak syndrome with pleural and pericardial effusions becomes dose-limiting.

There are three studies of GM-CSF used in patients with poor graft function after autologous or allogeneic bone marrow. One-half to two-thirds of patients are reported to benefit from GM-CSF. Noteworthy again was the poor response of patients who received purged marrow.

There are two randomized placebo-controlled trials of GM-CSF after bone marrow transplant. While the study from Seattle shows no significant difference in duration of neutropenia, the number of the infectious complications and hospital days were significantly decreased in the arm receiving GM-CSF. Fewer trials have studied G-CSF after transplant, but more rapid engraftment in these trials has been reported as well. One patient received G-CSF for poor graft function. The only randomized trial reports a significantly shorter period of neutropenia in the group receiving G-CSF but does not provide the actual days of neutropenia.

Butturini and colleagues in Brazil used GM-CSF in eight patients suffering from serious radioactive cesium overdose after an abandoned therapeutic radiotherapy source was inadvertently opened by curious villagers, exposing many in the community [121].

PERIPHERAL BLOOD PROGENITOR CELLS (PBPC)

Preclinical Studies

There is no clear understanding of why peripheral blood contains progenitor cells or of the regulation of progenitor cell number. The circulating progenitor cell population is apparently quite immature compared to marrow cells, is in Go (not in cell cycle), and does not actively contribute to hematopoiesis. Stem cells collected from the

peripheral blood of laboratory animals by cytapheresis have successfully reconstituted myelopoiesis following marrow lethal treatment [122,123].

Clinical Studies

Weiner et al. demonstrated that human PBPC could be collected via established techniques for harvesting platelets [123]. Between five and eight leukophereses are required for adequate stem cell collection in humans [124,125]. Methods of collection using density gradient, counterflow centrifugation (surge), or methods to collect granulocytes and mononuclear cells could influence the duration of aplasia [126].

Initially, studies of patients with chronic myelogenous leukemia (CML) determined that their blood contains an order of magnitude more granulocyte-macrophage committed colony-forming units (CFU-GM) than that of normal individuals. Goldman demonstrated engraftment after delivery of autologous PBPC collected in CML patients by demonstrating a return to the chronic phase of disease [125].

Juttner et al. (Adelaide, Australia) reported good early engraftment in four AML patients receiving PBPC collected after induction [124]. Late poor bone marrow function developed prior to relapse of AML in three, but did not occur in the fourth patient, who received four times the number of nucleated cells. Engraftment in AML required significantly more progenitor cells than in non-AML malignancies [127].

Kessinger and colleagues have refined the technical collection of PBPCs and documented successful engraftment in 34 breast cancer and Hodgkin's disease patients treated with cyclophosphamide, total body irradiation, and cisplatin [128].

Adequacy and speed of recovery appears related in part to the number of stem cell dose reinfused [28,29]. Although the actual pluripotent stem cell cannot be measured in humans, reinfusion of $>4 \times 105$ CFU-GM/kg body weight (15- to 50-fold that required for ABMT recovery) results in reliable reconstitution. While lower doses yield less consistent engraftment, variable results may in part result from institutional differences in colony assay techniques and reagents. The larger number of CFU-GM required for PBPC compared to ABMT may reflect a lower ratio of pleuripotent to committed stem cells in peripheral blood or to the few stromal cells transplanted. Hematopoietic reconstitution using PBPC has been reviewed in leukemia, lymphoma, and various solid tumors [129,130].

Advantages of PBPC compared to ABMT: PBPC appear to be a reliable source of stem cells for reconstitution of myelopoietic function, although the concentration of hematopoietic progenitor cells in the blood is 10- to 100-fold less than in the bone marrow. The concentration of true "stem" cells is not measurable in the human (because of lack of an assay), but it is common practice to measure the number of progenitor cells committed to myeloid (granulocyte/monocyte) and to erythroid maturation (measured as CFU-GM and BFU-E, respectively). Preliminary data suggest that the presence of a neoplasm may increase the number of circulating CFU-GM [131].

1. Leukapheresis is an outpatient procedure similar to platelet donation. Marrow donation currently involves hospitalization, general anesthesia, and aspiration of 500–1,000 ml of marrow from pelvic bones.

2. Using the apheresis technique, adequate numbers of stem cells may be collected from patients with hemipelvectomies, tumor involving the pelvic bones, or after pelvic irradiation.

3. Granulocyte reconstitution may be faster, possibly due to reinfusion of larger number of committed mononuclear cells.

4. Recovery of immune function appears faster and more complete, possibly due to increased numbers of reinfused lymphocytes.

5. A consistent feature of PBPC compared with bone marrow transplants has been rapid granulocyte reconstitution (10–16 days to >500 μl) and equivalent rates of platelet recovery (19–25 days).

Methods of increasing CFU-GM yields during leukopheresis: Previous efforts to augment circulating progenitor cell numbers have had limited success. Richman et al. [132] first observed that nine of 14 patients given cyclophosphamide and doxorubicin had a significantly increased concentration of peripheral blood CFU-GM at the time of leukocyte recovery. Initial depletion of the peripheral blood CFU-GM was followed by a rebound of up to 20-fold (median, four- to sevenfold) the baseline level. This phenomenon has been confirmed in the majority of patients receiving chemotherapy for lung, ovary, breast, and other solid tumors [133,134,135,136] or following induction chemotherapy of acute myelogenous leukemia, with leukopheresis yielding $11 \pm 2 \times 104$ CFU-GM/kg/leukopheresis. Other methods have included dextran, steroids, and endotoxin [129,130]. Nonetheless, between seven and ten leukophereses are required for adequate stem cell collection; however, ~8 leukophereses required per patient strains blood bank and cryopreservation resources and delays therapy for three weeks. Thus PBPC reinfusion is not practical as a routine source of stem cells. One interesting technique currently under investigation is positively to select CD34 cells, using monoclonal antibody bound to the inner surface of a collecting device [137].

Data from Milan suggest that the combination of both bone marrow and PBPCs collected via two to three apheresis during rebound from cyclophosphamide results in significant shorter times to granulocyte recovery >500/μl (a median of eight days in a small pilot study) in patients with breast cancer or NHL [138,139,140,141].

Effect of GM-CSF on PBPC: Of 12 patients studied during three- to seven-day continuous infusions of GM-CSF at doses of 4, 8, 16, and 64 μg/kg/day [65], Socinski et al. reported that nine had significantly increased absolute numbers of peripheral blood CFU-GM (median, 18-fold; range, 2–200; $p = 0.01$). BFU-E increased a median of eightfold. In the same patients, they observed a ten- to 100-fold increase in circulating CFU-GM after treatment with chemotherapy and GM-CSF. Immediately following chemotherapy, circulating CFU-GM were undectable. CFU-GM recovery after cycle 1 increased 30-fold (14-fold for BFU-E) compared to recovery after cycle 2 ($p = .001$). The peak levels of peripheral blood CFU-GM occurred earlier in the cycle with GM-CSF than in the cycle without GM-CSF (day 16, 16, 16 versus day 19, 22, 27). CFU-GM were increased 9- to 14-fold by the combination of post-chemotherapy rebound and GM-CSF compared with GM-CSF alone. In the bone marrow, however, CFU-GM and BFU-E did not change significantly in number [142]. In Japan, Toki et al. have evaluated G-CSF after cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in four lymphoma patients. The number of peripheral blood progenitor cells increased 37- to 221-fold over baseline and peaked about day 10 [87]. Duhrsen et al. have also shown a similar effect with G-CSF [143]. (Refer to Table 9.)

Augmentation of peripheral blood progenitor cells by GM-CSF may facilitate collection of adequate numbers of PBPC with fewer leukophereses enhancing the feasibility of PBPC autografting. If eight to 12 leukapheresis sessions are required to

TABLE 9
G- or GM-CSF Alone and with Chemotherapy: Effect on Numbers of Peripheral Blood Progenitor Cells

Factor	Day 1	Cycle 0 End	Cycle 1 +GM-CSF	Cycle 2 -GM-CSF
PB CFU-GM/ml	36	469	2,251	74
PB BFU-E/ml	68	242	1,125	80

Socinski et al. [142]

Patient No.	CFU-GM/ml		
	Day 1	Peak (Day 10)	-Fold Increase
1	22	1,584	72
2	1	106	106
3	10	370	37
4	8	1,771	221

Toki et al. [87]

obtain sufficient progenitor cells, then PBPC autografting is unlikely to replace marrow harvesting, except in special situations (e.g., known tumor involvement of the marrow); however, the use of GM-CSF with chemotherapy ± growth factor to augment progenitor cell number prior to pheresis theoretically could reduce the number of required phereses (and aliquots frozen) to one to two per patient. If that method were successful, a shorter duration of aplasia resulting from the use of PBPC or both PBPC and marrow may significantly reduce the mortality, morbidity, and the cost of high-dose therapy. Multiple groups are now testing the premise that GM-CSF can enhance collection of peripheral blood progenitor cells [138,140,144,145].

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) AND AIDS-RELATED COMPLEX

A 14-day iv infusion of rhGM-CSF (Sandoz) in 16 patients resulted in a dose-dependent increase in circulating leukocytes [146]. The peak WBC ranged from 4,575 at the lowest dose, to 48,700/μl at the highest dose. Increased circulating neutrophils, eosinophils, and monocytes occurred in all but one patient. In three patients, the increased circulating WBC observed during iv and three times daily subcutaneous administration of the same total daily dose was comparable.

Toxicity consisted of flushing during bolus infusions at higher doses, and fever, myalgia, and phlebitis at the peripheral iv administration site during the continuous infusion in some patients. Three patients developed a localized, macular skin rash lasting < 24 hours without relation to dose, duration of treatment, or change in WBC. Four patients with subclinical disseminated or pulmonary infection (cytomegalovirus, *M. avium* complex, *Pneumocystis carinii*) prior to treatment with rhGM-CSF developed inflammatory symptoms during treatment. A fifth patient developed fever and abnormal liver chemistries without any evident infectious agent. Of the five patients with significant symptoms, three had received 8 μg/kg/day of glycoprotein, suggesting that this amount may be the maximum tolerated dose in this patient group when GM-CSF is administered as a daily 24-hour iv infusion. No dose-limiting local or systemic toxicity was encountered in three patients who received a second course

TABLE 10
CSF Studies in AIDS

Author/Institution	Responses	Reference
	Laboratory	
Donahue	GM-CSF induces proliferation of PMN in AIDS patients	[147]
Bhalla	GM-CSF corrects AZT-mediated myelosuppression	[148]
Perno (NCI)	GM-CSF potentiates HIV viral production and AZT effect	[149]
Nimer	HTLV I or II infected T cells constitutively express GM-CSF ⇒ ?leukemia	[150]
Ganser	CFU-GM from AIDS patients require ⇑ concentration GM-CSF for maximal growth	[151]

Author	Institution	Product	No.	Dose/Day	Comments	Reference
Groopman	NEDH	Sandoz	16	1.3–20 × 10^3 u/kg	GM-CSF improves WBC	[146]

NCI: National Cancer Institute
NEDH: New England Deaconess Hospital

subcutaneously three tiines daily (1, 2, and 4 μg/kg/day of glycoprotein). (Refer to Table 10.)

MISCELLANEOUS OBSERVATIONS

There are a number of observations of the effects of G- or GM-CSF in other disease states. Urine levels of GM-CSF from patients with bilharziasis are almost twofold higher than normals [152]. Nimer and associates at the University of California, Los Angeles, found that serum cholesterol levels declined significantly in eight patients treated with GM-CSF [153].

SUMMARY

In conclusion, growth factors appear likely to enhance the recovery and function of circulating white cells after standard-dose cancer therapy or high-dose cancer therapy with marrow transplant and to restore leukocyte numbers and competence in the acquired immune deficiency syndromes and myelodysplastic syndromes. Phase I and II trials in patients with AIDS, cancer, myeloproliferative diseases, and after bone marrow transplant have been published. The results of phase III studies are just becoming available. A randomized trial of G-CSF in small-cell lung cancer demonstrates a decreased incidence of febrile neutropenia, antibiotic days, and in-hospital days [83]. Because of the crossover design of the study, they could not address any differences in complete response rate or survival. In a randomized trial of GM-CSF in patients receiving ABMT for lymphoma, there was a significantly shorter duration of time to re-engraftment (an absolute neutrophil count of $>100/\mu l$), number of antibiotic days, and time to discharge. Whether the decreased incidence of febrile neutropenia or number of antibiotic days results from earlier granulocyte recovery or from more functionally efficient neutrophils is at present impossible to assess.

The use of G- and GM-CSF in myelodysplasia and in leukemias requires caution prior to the availabilty of data from large randomized trials. Preliminary data from small randomized trials suggest that the incidence of evolution to leukemia in patients with myelodysplasia and the number of patients with regrowth of leukemia after induction treatment in relapsed patients with AML is not significantly different.

Various neutropenias (idiopathic, cyclic, and congenital) seem responsive to growth factors. Patients treated for three to 15 months continue to respond with significantly increased granulocytes and resolution of prior infection. The subcutaneous route of administration is convenient, and patients seem to accept it about as well as diabetics accept insulin injections.

Because the cost of G- and GM-CSF has not become available, it is difficult to determine at what level these drugs will be cost-effective. They may be cost-effective in the setting of intensive therapy such as bone marrow transplantation, where the reliable recovery of patients even a few days earlier would save several thousand dollars per patient. In standard-dose therapy for regimens where the incidence of hospitalization for fever and neutopenia is low, there may be little discernable cost benefit.

Thus, so far the data suggest that growth factors will be a significant addition to the clinician's armamentarium. In addition, they provide laboratory researchers with new tools for examining the process of hematopoiesis, clinically and at the molecular level.

APPENDIX 1

Abbreviations: AA: aplastic anemia ABMT: autologous bone marrow transplant ADR: adriamycin AIDS: acquired immune deficiency syndrome Allo BMT: allogeneic bone marrow transplant AML: acute myelocytic leukemia ANC: absolute neutrophil count APML: acute promyelocytic leukemia BFU-E: blast-forming units erythrocytes BWH: Brigham and Women's Hospital CBDCA: carboplatin CFU-GM: colony-forming units granulocyte-macrophage CGL: chronic granulocytic leukemia CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone CML: chronic myelocytic leukemia CPA: cyclophosphamide CR: complete response DDP: cisplatin DFCI: Dana-Farber Cancer Institute DTIC: dacarbazine FRG: Federal Republic of Germany G-CSF: granulocyte colony-stimulating factor GM-CSF: granulocyte-macrophage colony-stimulating factor GVHD: graft-versus-host disease HDCPA: high-dose cyclophosphamide IF: interferon Ifos: ifosfamide IL-1: interleukin 1 iv: intravenous JCF: Japan Cancer Foundation M-CSF: monocyte colony-stimulating factor MDAH: M.D. Anderson Hospital, Houston MSKCC: Memorial Sloan-Kettering Cancer Center, New York City N Shore: North Shore Hospital, New York NCC: National Cancer Center NEDH: New England Deaconess Hospital NYU: New York University, New York City PBPC: peripheral blood progenitor cells PMN: polymorphonuclear leucocyte rh: recombinant human TNF: tumor necrosis factor UCLA: University of California, Los Angeles VBL: vinblastine VDS: vindesine VP-16: etoposide WBC: white blood cell (count)

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