Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor After Chemotherapy in Patients With Acute Myeloid Leukemia at Higher Age or After Relapse

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To reduce critical neutropenia after chemotherapy (CT) for acute myeloid leukemia (AML) we administered recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) to patients over the age of 65 years with newly diagnosed AML and to patients with early or second relapse. CT was 9-day 6-thioguanine, ara-C, and daunorubicin (TAD9) in newly diagnosed AML and sequential high-dose ara-C and mitoxantrone (S-HAM) for relapse. In patients whose bone marrow was free from blasts a continuous intravenous infusion of GM-CSF 250 μg/m²/d started on day 4 after CT. Thirty-six patients entered the study and 30 of them did receive GM-CSF. For comparison, a historical control group of 56 patients was used. Complete remission rate was 50% (18 of 36) versus 32% in controls (P = .09), and early death rate was 14% versus 39% (P = .009). Treatment with GM-CSF was not associated with major adverse events. Two patients showed a marked leukemic regrowth that was completely reversible in one patient and appeared to be GM-CSF independent in the other patient. Remission duration does not seem to be reduced after GM-CSF. Under GM-CSF the blood neutrophils recovered 6 and 9 days earlier in the TAD9 (P = .009) and S-HAM (P = .043) groups associated with a rapid clearance of infections in most patients. We conclude that GM-CSF was of therapeutic benefit to our patients and this provides a basis for larger controlled trials.

DESPITE GREAT efforts in supportive care for patients with acute myeloid leukemia (AML), early death during the phase of induction treatment still remains an unsolved therapeutic problem. Multicenter trials[1-6] show early deaths in 17% to 32% of patients at all ages and 27% to 52% of those 60 years of age and older. In addition, intensive chemotherapy (CT) for relapsed and refractory AML produced up to 56% complete remissions (CR) but also 29% early deaths,[7,8] or probably more.[9] After postinduction intensification CT 5% to 20% of patients died of toxicity.[6] Infections due to neutropenia were responsible for most of the early deaths during induction therapy[1-4] and represent the major dose-limiting toxicity. Thus, reducing the phase of critical neutropenia would allow more effective antileukemic CT.

Before this first study[10,11] recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) was not applied in AML. Under various other conditions GM-CSF has been proven to effectively stimulate granulopoiesis. In primates a dramatic increase of neutrophils was induced[12,13] that similarly occurred in an animal with virus-induced pancytopenia.[12] After irradiation[14] or combined irradiation, cytostatic treatment, and autologous bone marrow transplantation,[15,16] the recovery of neutrophils was accelerated by GM-CSF. Administered to humans, GM-CSF induced an increase of neutrophils in patients with acquired immunodeficiency syndrome[17] and in patients with aplastic anemia.[18,19] The phase of therapy-induced critical neutropenia could be reduced after CT for sarcomas[20] and after CT followed by autologous bone marrow transplantation for breast cancers and malignant melanomas.[21] As preleukemic disorders, myelodysplastic syndromes have been treated now with GM-CSF[22-25] and showed an effective increase of neutrophil counts.

When considering GM-CSF as a part of treatment for AML its potential stimulatory effect on leukemic blasts has to be taken into account. In vitro leukemic blast growth in both colony assays and suspension cultures was stimulated in the presence of GM-CSF[26-32] in up to 97%[28] of AMLs. In myelodysplastic syndromes some patients receiving GM-CSF responded with an increase of blasts and even a transformation into AML.[23-25] Thus, GM-CSF in AML was restricted in this first step to patients at high risk of early death due to early or multiple relapse or higher age. The clinical and hematologic responses were evaluated in comparison with control groups not receiving GM-CSF and treated in phase II and III CT studies at the same institutions.

PATIENTS AND METHODS

Patients. The criteria of entering the GM-CSF study included (1) adult patients at all ages with early relapse occurring in the first 6 months of remission and with multiple relapse, and (2) patients 65 years of age and older with newly diagnosed AML or late relapse. Patients having had bone marrow transplantation before they relapsed and secondary leukemias were included in the GM-CSF study. A written informed consent was obtained from each patient. All investigations were performed after approval by the local ethical committee and in accordance with the Declaration of Helsinki. The historical control groups were treated at the same institutions and received the same chemotherapy.

Study design. If the bone marrow 3 days after the end of CT was aplastic with less than 5% blasts, GM-CSF 250 μg/m²/d continuous intravenous (IV) infusion started on day 4. When a neutrophil count of 2,000/mm³ was achieved and maintained for 4 days, the

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dose was reduced to 125 μg/m² for 4 days and to 50 μg/m² for another 4 days until the infusion was discontinued.

Recombinant human GM-CSF was provided by Behringwerke AG (Marburg, Germany). The recombinant protein was expressed in yeast and purified by Immunex Corp (Seattle, WA), as described.[33] Sterility, general safety, and purity studies met Food and Drug Administration standards.

Chemotherapy. Early or multiple relapses were treated with sequential HAM (S-HAM)[34] combining high-dose ara-C randomly either 1 or 3 g/m² every 12 hours by 3-hour IV infusion on days 1, 2, 8, 9, and mitoxantrone 10 mg/m²/d IV infusion on days 3, 4, 10, and 11. Only one course of S-HAM was administered to each patient. Newly diagnosed AML and AML late relapses in the higher age group were treated with TAD9[4] containing 6-thioguanine 100 mg/m² every 12 hours orally on days 3 through 9; ara-C 100 mg/m²/d continuous IV infusion on days 1 and 2 and every 12 hours IV infusion over 30 minutes on days 3 through 8; daunorubicin randomly either 30 or 60 mg/m²/d IV injection on days 3 through 5. Patients with inadequate blast clearance received a second course of TAD9. After attaining CR patients received one additional course of TAD9 for consolidation and monthly maintenance by 5-day courses of ara-C rotatingly combined with daunorubicin or 6-thioguanine or cyclophosphamide for 3 years as previously described.[4] No postremission CT was administered to patients achieving CR after relapse.

Definitions of outcome. CR was defined by a normocellular hematopoietic marrow with less than 5% leukemic cells and peripheral blood with at least 1,500/mm³ neutrophils and 100,000/mm³ platelets. Remission duration counted from achievement of CR until relapse. Adverse events were graded according to the Eastern Cooperative Oncology Group (ECOG) criteria.[35]

Laboratory tests. Complete blood counts including white and red blood cell, reticulocyte, platelet, and differential counts were performed daily. Bone marrow aspirates and biopsies were obtained before and after CT and after GM-CSF when CR criteria in blood counts were achieved or in case of persistent cytopenia. Bone marrow microscopy included quantification of cellularity, percentage of blasts and normal hematopoietic cells, and classification of leukemic cells according to French-American-British (FAB) criteria.[36] DNA histograms from bone marrow cells were obtained by flow cytometry as previously described.[37,38] DNA aneuploidy was defined by a clonal deviation of at least 5% of the cellular DNA content from admixed normal blood reference cells.[39]

RESULTS

Therapeutic response. Between September 1987 and December 1989, 36 consecutive patients entered the GM-CSF study; 30 of the patients received GM-CSF and are listed in Table 1. GM-CSF was infused over a median of 18 (range 10 to 48) days. Of the patients receiving GM-CSF, 18 (60%) attained a CR, three (10%) were early deaths in the first 6 weeks, seven patients (23%) died later in bone marrow hypoplasia with no blasts, and two patients (7%) in

Table 1. Characteristics, Chemotherapy, Neutrophil Recovery Time, and Outcome in Patients Receiving GM-CSF

Patient	Age (y)	Diagnosis		Special History	CT	Days From GM-CSF Start to 500 Neutrophils/mm³	Outcome*
1	65	AML (M1)†	1st relapse		S-HAM	14	ED
2	44	AML (M4)	1st relapse		S-HAM	21	CR
3	61	AML (M2)	1st relapse	Tumor CT	S-HAM	14	NR
4	54	AML (M5)	1st relapse		S-HAM	11+	CR
5	75	AML (M2)	1st relapse		S-HAM	15	CR
6	64	AML (M2)	1st relapse		S-HAM	12	CR
7	61	AML (M4)	2nd relapse		S-HAM	10	CR
8	34	AML (M2)	2nd relapse	Auto BMT	S-HAM	32	CR
9	35	AML (M5)	2nd relapse	Allo BMT	S-HAM	26	Hypoplasia
10	27	AML (M1)	2nd relapse	Auto BMT	S-HAM	19+	ED
11	77	AML (M2)	1st relapse		TAD9	6	CR
12	65	AML (M5)	Newly diagnosed		TAD9	5+	ED
13	77	AML (M2)	Newly diagnosed		TAD9	8	CR
14	75	AML (M2)	Newly diagnosed		TAD9	7	CR
15	70	AML (M1)	Newly diagnosed		TAD9	11	NR (regrowth)
16	84	AML (M6)	Newly diagnosed		TAD9	10	CR
17	75	AML (M3)	Newly diagnosed		TAD9	9	CR
18	66	AML (M2)	Newly diagnosed		TAD9	6	Hypoplasia
19	83	AML (M2)	Newly diagnosed		TAD9	20+	Hypoplasia
20	68	AML (M1)	Newly diagnosed		TAD9	26+	Hypoplasia
21	72	AML (M4)	Newly diagnosed		TAD9	12	CR
22	69	AML (M5)	Newly diagnosed		TAD9	15	CR
23	68	AML (M1)	Newly diagnosed		TAD9	10	CR
24	65	AML (M4)	Newly diagnosed	Tumor CT	TAD9	19	Hypoplasia
25	78	AML (M5)	Newly diagnosed	MDS	TAD9	10	CR after regrowth
26	75	AML (M5)	Newly diagnosed	MDS	TAD9	11	Hypoplasia
27	67	AML (M1)	Newly diagnosed		TAD9	8	CR
28	67	AML (M2)	Newly diagnosed		TAD9	16	CR
29	69	AML (M5)	Newly diagnosed		TAD9	8	CR
30	73	AML (M1)	Newly diagnosed		TAD9	9	Hypoplasia

*CR, complete remission; ED, early death; NR, definite nonresponse.

†FAB classification.

whom AML persisted were classified as definite nonresponders. One of the nonresponders (patient 3) showed a 30% reinfiltration of his bone marrow 4 weeks after cessation of GM-CSF. The other nonresponder (patient 15) developed a marked leukemic regrowth under GM-CSF as described later. Six patients remained untreated by GM-CSF due to persistent bone marrow blasts after two induction courses (two patients) or after one course (four patients) with contraindications against further CT. All six patients had newly diagnosed AML and were included in the calculation of response data in comparison with the controls. The control groups comprised 56 sequential patients treated by the identical chemotherapy at the same situations between 1985 and 1987 as parts of phase II and III studies of the AML Cooperative Group.[4,34] Patient characteristics in the GM-CSF and control groups are compared in Table 2. Table 3 shows the response data for the whole GM-CSF group in comparison with the control group.

Adverse events and toxicity. After CT all patients in the GM-CSF and control groups exhibited grade 4 neutropenia and thrombocytopenia according to ECOG toxicity criteria.[35] Nonhematologic adverse events are listed in Table 4.

The overall frequency of weight gain not specified for different grades was higher in patients with GM-CSF than in the controls ($P = .007$), while edema, effusions, and higher-grade weight gain did not differ significantly. The GM-CSF group showed a higher overall frequency, including all grades of decrease in serum protein ($P = .02$), prothrombin ($P = .02$), and pseudo-cholinesterase levels

Table 2. Patient Characteristics

	GM-CSF Group	Controls	P*
Patients	36†	56	
Age, median (range)	68 (27-84)	68 (19-80)	
FAB subtype			
M1	7 (19%)	10 (18%)	
M2	10 (28%)	19 (34%)	
M3	1 (3%)	1 (2%)	
M4	4 (11%)	10 (18%)	
M5	10 (28%)	10 (18%)	
M6	1 (3%)	3 (5%)	
M7	1 (3%)	0	
Hybrid AML/ALL	2 (5%)	1 (2%)	
Unknown	0	2 (3%)	
Newly diagnosed AML age 65+	25	41	
Age	70 (65-84)	70 (65-80)	
Prior tumor chemo/ radiotherapy	1	1	
AML after preleukemia	2	3	
Relapsed AML	11	15	
Age	61 (27-77)	46 (19-65)	
Early 1st relapse (within 6 months)	6	2	.038
Late 1st relapse	1	6	
2nd relapse	4	7	
Prior tumor chemo/ radiotherapy	1	1	
Prior bone marrow transplant	3	0	
AML after preleukemia	0	3	
Hybrid AML/ALL	2	1	

*Fisher's exact test.

†Including six patients not receiving GM-CSF due to persistence of blasts in bone marrow after CT.

Table 3. Therapeutic Response to Induction

	GM-CSF Group	Controls	P*
Patients	36†	56	
CRs	18/36 (50%)	18/56 (32%)	.09
In newly diagnosed AML	11/25 (44%)	12/41 (29%)	
In relapsed AML	7/11 (64%)	6/15 (40%)	
Early deaths (within 6 wk)	5/36 (14%)	22/56 (39%)	.009
In newly diagnosed AML	3/25 (12%)	18/41 (44%)	.007
In relapsed AML	2/11 (18%)	4/15 (27%)	
Later hypoplastic deaths	7/36 (19%)	7/56 (13%)	
In newly diagnosed AML	6/25 (24%)	6/41 (15%)	
In relapsed AML	1/11 (9%)	1/15 (7%)	
Definite nonresponse	6/36 (17%)	9/56 (16%)	
In newly diagnosed AML	5/25 (20%)	5/41 (12%)	
In relapsed AML	1/11 (9%)	4/15 (26%)	

*Chi squared test.

†Including six patients not receiving GM-CSF due to persistence of blasts in bone marrow after CT.

Table 4. Adverse Events: Grading According to ECOG Criteria

		Patients With Events/ Patients Evaluable		
		GM-CSF	Controls	P
Fever	Grade 1-2	18/25	30/50	.3
	Grade 3-4	7/25	19/50	.4
Infections	Clinically or microbiologically documented	18/25	41/49	.2
	Microbiologically documented	10/25	24/49	.5
	Pneumonia	14/25	21/49	.3
Effusions	Pleural with pneumonia	4/28	6/48	.8
	Pleural without pneumonia	2/28	5/48	.6
	Pericardials, ascites	2/28	1/48	.2
Edema		4/25	6/47	.7
Weight gain	Grade 1	6/26	3/45	.045
	Grade 2-3	3/26	1/45	.1
Cardiac events	Grade 1	0/28	3/47	.2
	Grade 2-3	2/28	10/47	.1
	Grade 4-5	4/28	10/47	.5
Serum bilirubin elevation	Grade 1-2	2/25	12/48	.08
	Grade 3-4	10/25	19/48	.97
Serum GOT/GPT elevation	Grade 1-2	5/25	32/48	.000
	Grade 3-4	1/25	5/48	.3
Serum PCHE decrease to U/L	1,500-750	12/25	6/26	.06
	<750	4/25	1/26	.1
Serum protein decrease to g/L	5.9-5.0	10/25	18/47	.9
	4.9-4.0	11/25	13/47	.2
	<4.0	2/25	1/47	.2
Prothrombin time prolongation	Grade 1-2	16/25	21/43	.2
	Grade 3	5/25	4/43	.2
	Grade 4	1/25	1/43	.7
Neurocortical events	Grade 1-2	4/28	2/43	.2
	Grade 3	2/28	2/43	.6
	Grade 4-5	0/28	7/43	.025

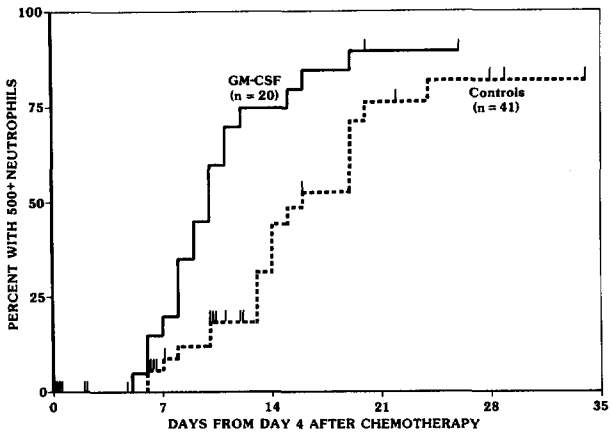

Fig 1. Kaplan-Meier test of blood neutrophil recovery time in patients receiving TAD9 CT (logrank test $P = .009$). Tick marks represent patients without neutrophil recovery at their last possible update.

($P = .008$), with no significant difference in higher-grade deficiencies in the three parameters. In the controls, elevation of serum transaminases was more frequent overall ($P = .008$) and in lower-grade elevations. Controls showed more frequent cardiac events ($P = .018$), not significant within the different grades. There were more severe neurocortical events due to cerebral hemorrhage in the control groups. Infections overall were more frequent in patients after S-HAM CT in the control group ($P = .05$). There were no other differences in adverse events between TAD9 and S-HAM CT.

Hematologic response. The recovery time to achieve 500/mm^3 blood neutrophils from start of GM-CSF is given in Table 1. Neutrophil recovery time after GM-CSF is compared with that in the control group in Figs 1 and 2 for the two chemotherapeutic regimens used. The medians are 10 versus 16 days ($P = .009$) after TAD9 and 15 versus 24 days ($P = .043$) after S-HAM. Median recovery time of platelets to 20,000/mm^3 after TAD9 was 15 days in the GM-CSF group and 11 days in the controls ($P = .28$). After S-HAM corresponding medians were 16 versus 20 days ($P = .64$). Platelet recovery time to 50,000 equally failed to show a significant effect of GM-CSF after TAD9 ($P = .75$)

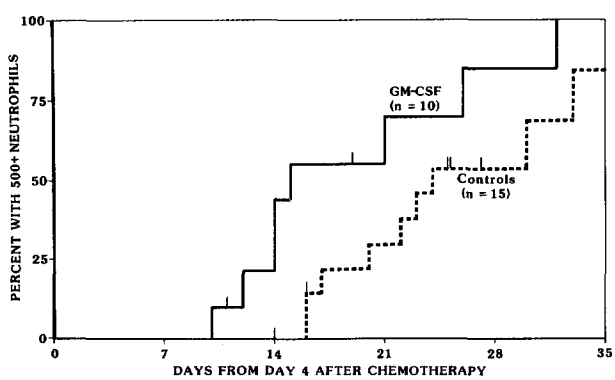

Fig 2. Neutrophil recovery time in patients receiving S-HAM chemotherapy ($P = .043$) (see also Fig 1).

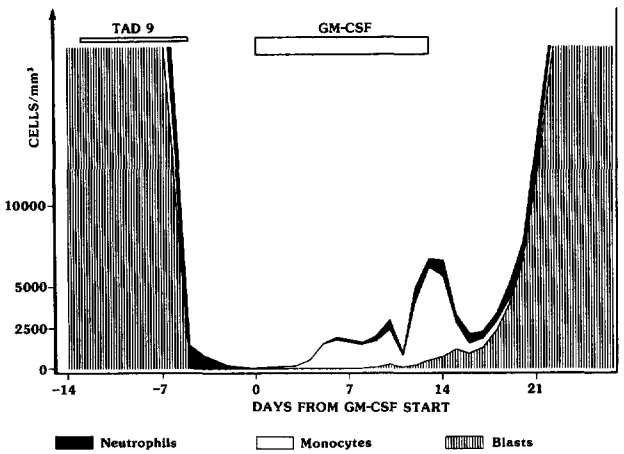

Fig 3. Absolute counts of different white blood cells in patient 15 with AML M1 during TAD9 CT followed by GM-CSF. After cessation of GM-CSF monocytosis is reversible while regrowth of leukemic blasts continues uneffectedly.

or S-HAM ($P = .55$). There was no difference in neutrophil or platelet recovery time according to the randomized two different doses of daunorubicin and ara-C. Under GM-CSF we also observed increases in blood eosinophils to 1,176 to 2,725/mm^3 in six patients, monocytes to 2,544 to 8,160/mm^3 in seven patients, and lymphocytes to 3,843/mm^3 in one patient. All multilineage responses were found to be rapidly reversible.

Response of infections. After recovery of neutrophils under GM-CSF to at least 500/mm,^{3} temperature returned to normal within 2 days in 41% and within 7 days in 73% of patients. Other signs of infections responded in ⅔ of the patients and persisted longer in some fungal infections. This pattern of response was similar to that in the control group after recovery of neutrophils.

Leukemic regrowth. Two patients under GM-CSF showed a marked regrowth of their blood blasts. In patient 15 this was associated with a monocytosis. As shown in Fig

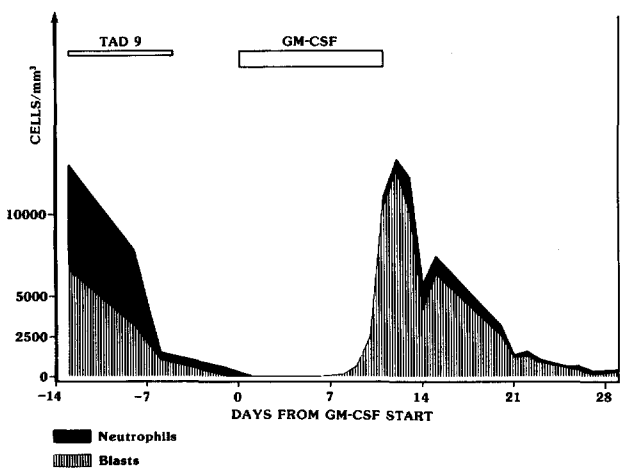

Fig 4. Absolute counts of different white blood cells in patient 25 with AML M5 during TAD9 CT followed by GM-CSF. Leukemic regrowth is reversible after GM-CSF cessation.

3, monocytosis was rapidly reversible after cessation of GM-CSF whereas the blasts uneffectedly continued to increase. This patient died in progression of her AML. In patient 25, who suffered from an AML M5, there was an increase of blood monocytes and promonocytes up to 11,600/mm^3 under GM-CSF (Fig 4). The bone marrow became highly hypercellular and infiltrated by 95% immature and mature monocytic cells. Pretherapeutically, no Auer rods, DNA aneuploidy, or cytogenetic markers were present in this case. After GM-CSF cessation the leukemic regrowth reversed. The patient went into CR and is still free from relapse after 3 years without any further treatment.

Remission duration. Remission duration after GM-CSF is shown in Figs 5 and 6 and compared with that in the controls. Remission duration after GM-CSF in the patients treated for relapse compared with the duration of the preceding remissions shows no difference in the medians. In patients 7 and 8 the duration of the new remissions (by June 1991) is 40+ and 39+ months versus 8 and 13 months previously.

DNA aneuploidy. Data on bone marrow DNA aneuploidy are shown in Table 5. Hyperdiploid cell populations were found in 5 of 22 patients. Aneuploid cells were no longer detectable in 3 of 4 cases investigated after CT. In patient 13, 8% aneuploid cells with a DNA index of 1.19 were still identified at the start of GM-CSF infusion, during which time they disappeared both in bone marrow and blood.

DISCUSSION

The results of this clinical study in patients with AML at high risk of early death provide good evidence that GM-CSF was of therapeutic benefit for the patients. This is reflected by the 60% CRs after GM-CSF with a comparatively low early death rate of 10%. The median age of responders was as high as 69, ranging up to 84 years. Even when including the six patients with persistent blasts who did not receive growth factor, the GM-CSF group compares favorably with the historical control group by its CR rate of 50% versus 32% and an early death rate of 14% versus

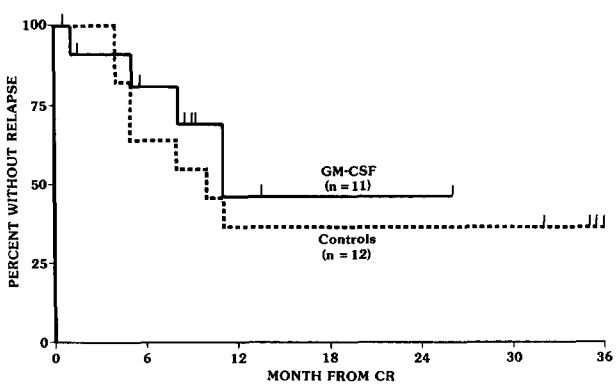

Fig 5. Kaplan-Meier test of remission duration in newly diagnosed AML. Tick marks represent patients in CR at last update.

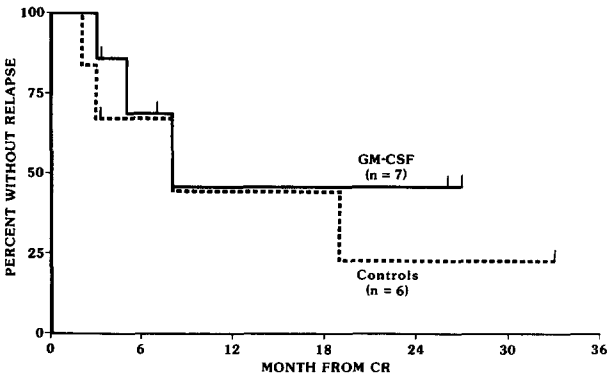

Fig 6. Remission duration in patients treated for relapse (see also Fig 5).

39%. This effect is more pronounced in newly diagnosed AML over the age of 65 years than in the relapses, where the GM-CSF group included three prior bone marrow transplantations and more early relapses.

Table 5. Bone Marrow DNA Aneuploidy During the Course of Treatment in Patients Receiving GM-CSF

Patient	DNA Index Before CT	DNA Index After CT	DNA Index After GM-CSF
1	1.0	1.0	
2			
3			
4	1.0		
5	1.0		
6	1.0	1.0	1.0
7	1.11	1.0	1.0
8			
9	1.0		
10			
11	1.0	1.0	1.0
12	1.0	1.0	
13	1.25	1.19	1.0
14			
15	1.0	1.0	
16	1.0	1.0	1.0
17	1.0	1.0	1.0
18	1.0		1.0
19	1.0		
20	1.0	1.0	
21			
22	1.0		
23	1.18	1.0	1.0
24			
25	1.0	1.0	1.0
26	1.0	1.0	1.0
27			
28	1.0		
29	1.08	1.0	
30	1.11		

The clonal DNA content measured by flow cytometry is expressed as DNA index with 1.0 for admixed normal diploid reference cells. In patients with aneuploidy only the DNA index of the aneuploid clone is given.

The reduction in the early death rate mainly accounts for the improved response rate and is explained by a marked acceleration of the recovery from critical neutropenia. The median neutrophil recovery time was reduced by about 1 week after both the TAD9 and the more intensive S-HAM induction regimen. After recovery of neutrophils under GM-CSF to 500/mm^3, signs of documented infections or fever of unidentified origin reversed immediately or within a few days in most patients. We conclude that by reducing the phase of risk more patients survive their infections.

Estey et al[40] recently reported that GM-CSF failed either to improve response rates or to accelerate neutrophil recovery in 12 patients with poor-prognosis newly diagnosed AML. This discrepancy to our results may be due to a lower daily dose of 120 μg/m^2 GM-CSF in the Houston study versus 250 μg/m^2 in our study. When using this higher dose but interrupting GM-CSF for 1 week in most patients, the median neutrophil recovery time was reduced by 3.5 days when compared with controls, but differences in therapeutic outcome were not reported.[41]

GM-CSF was generally well tolerated. The same adverse events occurring in the GM-CSF group were also observed in the controls, mostly at similar incidence or even more frequently like cardiac events, elevation of serum transaminases, and severe neurocortical events. In the GM-CSF group the overall incidence of weight gain, hypoproteinemia, and prolongation of prothrombin time was increased, which was not significant for higher grades. Together with the decrease of the pseudo-cholinesterase levels, the three changes similarly reported by others[41] may reflect an impaired synthetic function of the liver. Those non–life-threatening events were reversible in part while GM-CSF was continued. Unlike others,[41] we observed similar changes in the controls. Fever reactions were mostly explained as infectious and probably not GM-CSF related.[42] No typical first-dose effect of GM-CSF as characterized by flushing, tachycardia, hypotension, musculoskeletal pain, and dyspnoe[43] was observed in our patients.

In addition to the response in neutrophil recovery, 20% of patients showed an increase in blood eosinophils and monocytes under GM-CSF. All multilineage responses were found rapidly reversible after discontinuation of GM-CSF.

This study also provides data on the risk of stimulating the progress of AML by GM-CSF. We observed a marked leukemic regrowth under GM-CSF in two instances. In patient 15 the regrowth appeared unrelated to GM-CSF because it was uneffected in its kinetics by the stop of the infusion while an additional monocytosis in this patient typically reversed rapidly. One could argue that GM-CSF in this case only triggered the regrowth by recruiting dormant leukemic stem cells into the cell cycle while not affecting proliferation. However, in the in vitro studies an increase of colony numbers in presence of GM-CSF occurred with an increase of colony size[27,30] and a selective recruitment effect has not been reported. In patient 25 the leukemic regrowth was clearly related to GM-CSF as indicated by its reversibility. In this AML M5 specific leukemic cell markers were not present. However, the selective increase of promonocytes and monocytes in blood up to 11,600/mm^3 and the 95% infiltration and hypercellularity of the bone marrow by the corresponding type of cells strongly suggest their leukemic nature. After cessation of GM-CSF and disappearance of her leukemic regrowth the 78-year-old patient is in continuous remission for 3 years without further treatment.

Those data suggest that there is only a low risk of activating minimal residual disease by GM-CSF leading to regrowth or early relapse. Indeed, remission duration after GM-CSF appears so far similar to that in the controls, and shows at least no increase in early relapses.

As shown in patient 13, a residual leukemic cell population marked by a DNA aneuploidy may persist after CT and disappear even after GM-CSF not followed by an early relapse. Furthermore, it is remarkable that two of seven responders treated for relapse have been achieving a remission duration after GM-CSF five and three times that in the preceding remission (patients 7 and 8).

Confirming numerous data obtained from in vitro experiments,[25-32] we found that in 8 of 17 patients investigated leukemic colony growth (CFU-L) was stimulated by GM-CSF in vitro.[44] However, in the in vivo situation only two patients developed a marked leukemic regrowth under the infusion of GM-CSF. The other six patients went into a CR with one early relapse and two long-term remissions. Thus, progenitor cells stimulated by GM-CSF in vitro may not be representative for the cells producing disease progression in the patient.

In conclusion, GM-CSF administered in aplasia after CT to patients with AML at high risk of early death seems to improve their therapeutic outcome by accelerating the recovery of neutrophils. Adverse effects like stimulating disease progression are less important than expected from in vitro data. The data provide a basis for larger controlled trials that are highly warranted.

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