A randomized comparison of immediate versus delayed application of G-CSF in induction therapy for patients with acute myeloid leukemia unfit for intensive chemotherapy

We randomized 66 elderly patients with AML unfit for conventional chemotherapy to receive G-CSF from d6 or from d12 after induction-chemotherapy with cytarabine/idarubicin. There was no difference in duration of neutropenia (17 days vs. 19 days, p=0.67) or rate of complications. Delayed treatment can reduce the administration of G-CSF without adverse consequences.

Haematologica 2007; 92:1719-1720. DOI: 10.3324/haematol.11516

Elderly AML-patients are prone to infection-related mortality. G-CSF might reduce the incidence of infections[1-3] and shorten hospitalization.[4, 5] However, the timing of G-CSF application is unclear. It is commonly given immediately after chemotherapy,[4] but there are no randomized studies evaluating the time-point of application in AML after induction-therapy. We conducted a prospective study in elderly AML-patients unfit for standard induction-therapy with G-CSF application randomized to immediate versus delayed start. If patients responded, a second cycle of induction-therapy with the same dosage was given and G-CSF applied in a cross-over design. The aim of the study was to determine the duration of neutropenia and the frequency of infections in both arms.

From November 1998 to March 2003, 66 patients (*Table 1, Supplementary Data*) were included in the study from 6 hospitals. Induction-chemotherapy consisted of cytarabine 100 mg/m^2 as continuous intravenous infusion (civ) days 1-5 and idarubicin 5 mg/m^2 civ days 1-5. For G-CSF, patients were randomized as follows: Group A received filgrastim (Amgen, Munich, Germany) from day 6 and group B from day 12 until the leukocyte count reached >4 G/L or a bone marrow puncture (BMP) confirmed blast-persistence. The dose was 480 µg/d if >75 kg and 300 µg/d if ≤75 kg. A control BMP was performed after regeneration of the peripheral blood count or on day 40. Complete remission (CR) and partial remission (PR) were defined according to standard criteria.

Statistical analyses were performed using SPSS (version 12.0 for Windows, Munich). ANOVA, Fisher's exact, the χ^2 and Mann-Whitney tests were used to evaluate any differences, a two-sided p value <0.05 was considered significant. Survival was analyzed using the Kaplan-Meier method, the log-rank test used to evaluate any differences. 95% confidence intervals were calculated using CIA. The study was powered to detect a 10% difference with 63 cycles included (power 80%, α=0.05). Compared with studies including fit elderly patients,[6] few patients died early (n=14; 21%). Seventeen patients had blast-persistence (26%), 24 (36%) achieved a CR, 3 (5%) a CR with incomplete recovery of neutrophils/platelets, and 7 (11%) a PR after one cycle of therapy (one patient lost to follow-up). Thirty-three patients received another cycle of chemotherapy (16 patients with G-CSF from day 6 and 17 patients from day 12). Here, another 6 patients achieved a CR leading to an overall CR rate of 45%. The median overall survival for those in CR was 14 months (95%CI 11-17). There was no significant difference in response between the two groups. Duration of G-CSF application was reduced by five doses in the group with delayed adminis-

Table 1. Patient characteristics and eligibility criteria.

Inclusion criteria	*Exclusion criteria*
Diagnosis of AML *de novo* or secondary or relapsed if 1st CR > 6 months.	Life expectancy < 6 weeks
Age > 18 years	Refractory AML
Not suitable for conventional more aggressive induction therapy because of age, ECOG performance status or organ dysfunction[#]	Incompatibility with cytarabine, idarubicin or filgrastim
Approval of local ethics committee and written informed consent	Severe organ dysfunction incompatible with myelosuppressive chemotherapy
	AML M3

Patient characteristics	*Group A*	*Group B*	*All*
Male; n/N (%)	13/30 (43)	25/36 (69)	38/66 (58)
Age; median (IQR)	68 (65-72)	70 (63-74)	69 (64-73)
Relapsed AML; n/N (%)	7/30 (23)	7/36 (29)	14/66 (21)
Reason for inclusion; n/N (%):			
age/reduced performance status	15/30 (50)	15/36 (41)	30/66 (46)
concomitant disease*	13/30 (43)	19/36 (53)	32/66 (48)
infection	2/30 (7)	2/36 (6)	4/66 (6)

*Group A: G-CSF from day 6 onwards, Group B: G-CSF from day 12 onwards. [#]Organ dysfunction was defined as follows: creatinine >1.5xnormal value, bilirubine/AST/alkaline phosphatase >2xnormal value, FEV1<50% of expected value, left-ventricular ejection fraction <50% or pre-existing malignant disease. Patient exclusion from standard conventional induction because of age and reduced performance status was left to the physician's discretion. *Concomitant disease included (patients could have more than 1): COPD/lung fibrosis in 10 (15%) patients, coronary artery disease/ chronic heart failure in 13 (20%) patients, liver cirrhosis / hepatitis in 3 (5%) patients, renal failure in 4 (6%) patients and diabetes mellitus in 7 (11%) patients. Ten (15%) patients had had a malignant disease prior to the diagnosis of AML (8 epithelial cancer, 2 lymphoma).*

Table 2. Duration of G-CSF treatment, duration of neutropenia and infectious complications for the first cycle.

	Early G-CSF Median (IQR)	*Late G-CSF Median (IQR)*	*p ANOVA*
First cycle			
Duration of G-CSF treatment (days)	17 (12-20)	12 (7-16)	0.005
Duration of neutropenia (days)	17 (11-21)	19 (10-23)	0.67
Number of febrile days	2 (1-5)	1 (0-4)	0.97
Number of days with antibiotic therapy	11 (7-15)	9 (0-19)	0.67
Second cycle			
Duration of G-CSF treatment (days)	17 (14-25)	13 (10-18)	0.18
Duration of neutropenia (days)	10 (5-15)	11 (9-13)	0.79
Number of febrile days	0 (0-2)	1 (0-2)	0.69
Number of days with antibiotic therapy	0 (0-10)	7 (0-10)	0.33

Early G-CSF first cycle n=30; late G-CSF first cycle n=36; early G-CSF second cycle n=16; late G-CSF second cycle n=17; IQR: interquartile range.

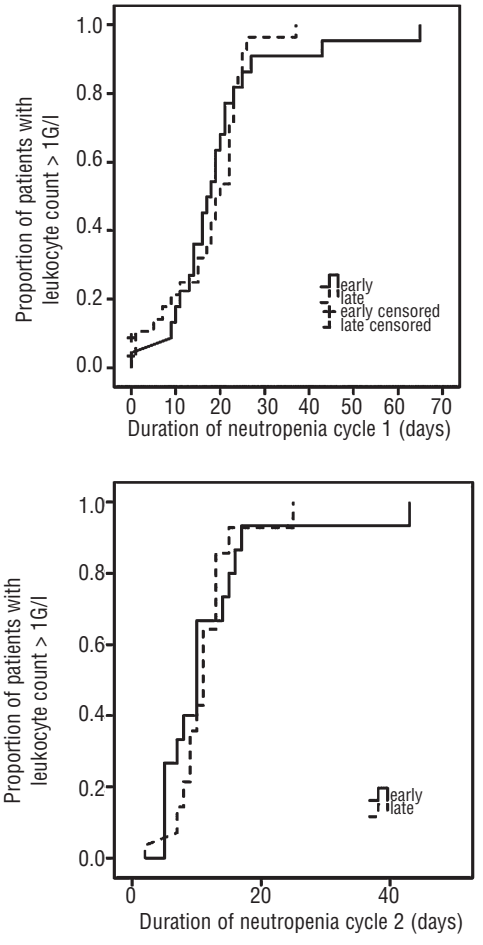

Figure 1. Duration of neutropenia after early or late G-CSF. Neutropenia is defined as leukocyte counts <1 G/L. A: cycle 1, B: cycle 2.

tration (Table 2). This saves 770 € (German hospital pharmacy 2006 prices including 16% VAT) per patient. There was no difference in the duration of neutropenia between groups (median duration of neutropenia for all patients: 19 days, 95%CI 15-21). Twenty-five patients in group A and group B respectively (83% *vs.* 69%, p=0.22) had an episode of neutropenic fever with no significant difference in duration (Table 2). No significant differences were detected in the frequency of pneumonia or any chemotherapy-induced toxicity. Early deaths were comparable in both groups (group A: 8, group B: 6 patients, p=0.25). After the second cycle, duration of neutropenia and infectious complications were lower for both groups. Again, there was no significant difference between immediate and delayed application of G-CSF (Figure 1).

A pooled comparison of all patients receiving immediate G-CSF (n=46) versus delayed G-CSF (n=53) after the first or the second course of chemotherapy confirmed no difference: duration of neutropenia was 14 days (IQR 9-19 days) after immediate and 15 days (IQR 9-22 days) after delayed application of G-CSF (p=0.75). The number of febrile days was 2 (IQR 0-4 days) after immediate and 1 (IQR 0-4 days) after delayed treatment (p=0.77).

This study evaluated the timing of the start of G-CSF administration on duration of G-CSF use, duration of neutropenia and number of febrile days in AML patients unfit for conventional chemotherapy. Supportive therapy with growth factors seems useful in this high-risk group of patients who can still achieve a reasonable response with a low early death rate. In conclusion, administration of G-CSF can be delayed to five days after the end of chemotherapy without a prolonged duration of neutropenia or other adverse effects.

Marie von Lilienfeld-Toal, Corinna Hahn-Ast,* Hartmut Kirchner,° Dimitri Flieger,# Gottfried Dölken,@ Axel Glasmacher**

**Medizinische Klinik und Poliklinik I, Universitätsklinikum Bonn, Bonn; °Klinikum Region Hannover, Siloah, Medizinische Klinik III, Hannover; #GPR Klinikum, I. Medizinische Klinik, Rüsselsheim; @Ernst-Moritz-Arndt-Universität Greifswald, Klinik und Poliklinik für Innere Medizin C, Diagnostikzentrum, Greifswald, Germany*

Funding: this study was supported by unrestricted grants from the Leukämie-Initiative Bonn, AMGEN and Pharmacia.

Acknowledgments: we would also like to thank the nursing staff and the doctors involved in the treatment of the AML patients included in this study for providing excellent clinical care. In particular, we would like to thank Dr. Peter Ehscheidt, Dr. Eckhardt Jaeger and Professor Dr. Klaus Rieche for presenting patients and their help with study management.

Correspondence: Marie von Lilienfeld-Toal, Medizinische Klinik und Poliklinik I, Universitätsklinikum Bonn, Sigmund-Freud Str. 25, 53105 Bonn. Phone: international +49.22828714003. E-mail: m.lilienfeld.toal@uni-bonn.de

References

1. Godwin JE, Kopecky KJ, Head DR, Willman CL, Leith CP, Hynes HE, et al. A double-blind placebo-controlled trial of granulocyte colony-stimulating factor in elderly patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study (9031). Blood 1998;91: 3607-15.
2. Kern W, Aul C, Maschmeyer G, Kuse R, Kerkhoff A, Grote-Metke A, et al. Granulocyte colony-stimulating factor shortens duration of critical neutropenia and prolongs disease-free survival after sequential high-dose cytosine arabinoside and mitoxantrone (S-HAM) salvage therapy for refractory and relapsed acute myeloid leukemia. German AML Cooperative Group. Ann Hematol 1998;77: 115-22.
3. Bennett CL, Hynes D, Godwin J, Stinson TJ, Golub RM, Appelbaum FR. Economic analysis of granulocyte colony stimulating factor as adjunct therapy for older patients with acute myelogenous leukemia (AML): estimates from a Southwest Oncology Group clinical trial. Cancer Invest 2001;19:603-10.
4. Amadori S, Suciu S, Jehn U, Stasi R, Thomas X, Marie JP, et al. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study. Blood 2005;106:27-34.
5. Heil G, Hoelzer D, Sanz MA, Lechner K, Liu Yin JA, Papa G, et al. A randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia. The International Acute Myeloid Leukemia Study Group. Blood 1997;90:4710-8.
6. Frohling S, Schlenk RF, Kayser S, Morhardt M, Benner A, Dohner K, et al. Cytogenetics and age are major determinants of outcome in intensively treated acute myeloid leukemia patients older than 60 years: results from AMLSG trial AML HD98-B. Blood 2006;13:13.