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No benefit from adding GM-CSF to induction chemotherapy in transforming myelodysplastic syndromes: better outcome in patients with less proliferative disease

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In this prospective randomized multicenter trial 93 patients, median age 72 years, with RAEB-t ($n=25$) and myelodysplastic syndrome (MDS)-AML ($n=68$) were allocated to a standard induction chemotherapy regimen (TAD 2+7) with or without addition of granulocyte–macrophage-CSF (GM-CSF). The overall complete remission (CR) rate was 43% with no difference between the arms. Median survival times for all patients, CR patients, and non-CR patients were 280, 550, and 100 days, respectively, with no difference between the arms. Response rates were significantly better in patients with serum lactate dehydrogenase (S-LDH) levels $\leqslant 9.5\,\mu$kat/l, bone marrow cellularity $\leqslant 70\%$, and WBC counts $<4.0\times10^9$/l, but S-LDH was the only variable independently associated with response by logistic regression analysis. Cox's regression analysis identified four significant prognostic factors for survival: bone marrow cellularity, S-LDH, cytogenetic risk group (International Prognostic Scoring System), and age. Only bone marrow cellularity ($P=0.01$) and S-LDH ($P=0.0003$) retained statistical significance in the log-rank test. Severe adverse events were significantly more common in the GM-TAD arm ($P=0.01$). Thus, addition of GM-CSF to chemotherapy showed no clinical benefit in terms of response but carried an increased risk for side effects. We present a clinically useful tool to predict response to chemotherapy and survival in elderly patients with transforming MDS, favoring patients with features of less proliferative disease.
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Introduction

Myelodysplastic syndromes (MDS) represent a heterogeneous group of malignant hematological disorders with varying clinical course. The prognosis in an individual case of MDS can be estimated using the International Prognostic Scoring System (IPSS).[1] Patients with pronounced cytopenia, poor-risk karyotype, and more than 10% bone marrow blasts show generally poor survival and a high risk for leukemic transformation, and are often subjected to chemotherapy. However, because of the relatively poor response rates, high therapy-related toxicity and no proven survival benefit, indications for chemotherapy in high-risk MDS (HR-MDS) and acute myeloid leukemia (AML) that develops after MDS (MDS-AML) have come to vary between different centers and investigators, with the possible exception of younger MDS patients where stem cell transplantation can be an option.[2] Several studies have identified factors indicating a poor response to chemotherapy in HR-MDS and MDS-AML: adverse karyotype including chromosome 7 anomalies, higher age, and increased WBC counts and blast cell percentage.[3–6] However, these patient materials have often been heterogeneous, including elderly AML, secondary AML, and MDS patients of various age groups. A systematic analysis of prognostic factors in a homogeneous cohort of elderly patients with advanced MDS and MDS-AML who are not candidates for SCT has not been published.

In an effort to decrease the hematological toxicity of treatment and increase the remission rates, hematopoietic growth factors like granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage colony-stimulating factor (GM-CSF) have been added to standard chemotherapy regimen. Earlier studies had shown that priming with GM-CSF could recruit leukemic cells into cell cycle, both *in vitro*[7,8] and *in vivo*,[9,10] and that GM-CSF could improve myeloid recovery after high-dose chemotherapy.[11,12] A number of prospective randomized studies have shown that combined treatment with G-CSF or GM-CSF and chemotherapy in *de novo* AML indeed has a favorable effect on the duration of neutropenia, number of fever days, and incidence of infectious complications after chemotherapy but little or no effect on remission rates, remission duration and survival.[13–21] However, the results have been less conclusive in patients with HR-MDS and MDS-AML, some studies suggesting that combined treatment with hematopoietic growth factors and chemotherapy might improve the outcome, while others do not.[6,22–25]

In this prospective randomized study, patients with MDS-AML and RAEB-t were given a single-line standard chemotherapy and were allocated combined treatment with GM-CSF or no additional treatment. The hypothesis was that GM-CSF could improve remission rate, overall survival (OS) and remission duration, and decrease the hematological toxicity. Moreover, we wanted to utilize a prospectively collected homogeneous cohort of elderly patients with advanced MDS or MDS-AML to define clinical variables with an impact on outcome of therapy and survival. Even though no clinical benefit of additive treatment with GM-CSF could be demonstrated in our study, we were able to define a group of clinico-pathological features clearly associated with outcome to therapy. Patients with lower than normal white blood cell (WBC) counts, bone marrow cellularity 70% or less and normal serum lactate dehydrogenase (S-LDH) levels appeared to have significantly better response rates and survival after induction chemotherapy. The prognostic impact of these variables was higher than that of karyotype. The variables could easily be used in clinical practice to aid therapeutic decision-making in elderly patients with advanced myelodysplastic disorders.

Material and methods

Patients

Patients with a diagnosis of MDS-AML, that is, AML preceded by a myelodysplastic phase of at least 2 months' duration, and

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patients with a diagnosis of RAEB-t for at least 2 months were eligible for this randomized nonplacebo-controlled, multicenter study. The diagnosis of MDS and AML was made on blood and bone marrow specimens according to the FAB criteria classification.[26,27] Bone marrow cellularity was estimated as described by Öst *et al*.[28] Patients with cardiac failure of NYHA grade III and IV, renal failure (serum creatinine >400 mmol/l), liver failure (serum bilirubin more than three times the normal value), a diagnosis of rheumatoid arthritis or SLE or previous anaphylactic reaction to human protein were excluded from the study. There was no upper age limit for inclusion, instead the attending physician made a general judgment of performance status and comorbid conditions. Chromosome analyses were performed using standard techniques and the findings were classified according to IPSS into good, intermediate- and poor-risk-based cytogenetic subgroups.[1] Individual IPSS score values were not assigned since the majority of patients had MDS-AML, for which the IPSS system is not validated. In all, 97 patients from 15 participating centers were included in the study between February 1994 and June 1998. The final evaluation was carried out on 1st April, 2001. The study followed the guidelines of the national Ethical committee and all patients gave their informed consent before randomization.

Study design

The induction chemotherapy consisted of a standard TAD (2+7) regimen: daunorubicin 60 mg/msq i.v. days 1 and 2, cytarabine 100 mg/msq × 2 i.v. day 1–7, thioguanine 200 mg/msq p.o. day 1–7. Patients were randomized to no additional treatment (control arm, TAD) or to additional treatment with GM-CSF (molgramostim; Schering-plough AB, Stockholm) (experimental arm, GM-TAD). GM-CSF, in a dose of 200 μg per day, was given subcutaneously. Treatment started 2 days before chemotherapy in patients with WBC $<50\times10^9$/l, and concomitantly with chemotherapy in those with WBC $\geqslant50\times10^9$/l. GM-CSF therapy was continued for a maximum of 3 weeks, or until ANC reached $>1.0\times10^9$/l in the recovery phase after chemotherapy. GM-CSF therapy was withdrawn in case of serious adverse events like pleuritis, pericarditis, thromboembolic disorders, and capillary-leak syndrome. The dose of GM-CSF was reduced by 50% in case of moderate adverse events that could be controlled by the use of corticosteroids, while it was not changed in case of nonsevere adverse events that could be controlled by antipyretic drugs and antihistamine. If the WBC counts reached $>50\times10^9$/l during the first 2 days of GM-CSF administration, chemotherapy was started immediately while GM-CSF was continued. Common criteria for evaluating fever and the use of i.v. antibiotics during the neutropenic phase were used throughout the study. Prophylactic treatment with standard dose acyclovir and fluconazole was given during neutropenia.

Patients entering complete remission (CR) were eligible to receive a maximum of three consolidation courses with TAD (1+5), with or without GM-CSF subject to the initial randomization. Treating physicians could, however, withdraw patients from one or more consolidation courses if the patient developed serious or life-threatening complications to the previous treatment. Refractory and relapsing cases received further treatment according to local guidelines.

Evaluation of outcome

Patients were evaluated on an intention-to-treat basis. CR was defined as a bone marrow with <5% blast cells, stable hemoglobin level over 4 weeks without transfusion need, WBC $>1.5\times10^9$/l (with a normal differential count), and platelets $>100\times10^9$/l. If CR was not achieved after the first induction course, a second identical course was given. Patients who failed to achieve CR after the second course of TAD were taken off the study and only followed for survival. Patients who were given a bone marrow transplant in CR1 were censored at the time for transplant in the statistical evaluation of relapse-free survival (RFS) and OS.

RFS in CR1 was calculated from the date of CR till the date of confirmed relapse in AML/RAEB-t, or death in CR1, whatever the reason. OS was calculated from date of randomization until date of death. Pretreatment duration of MDS was calculated from date of MDS diagnosis to date of inclusion.

Statistical methods

The study was designed to detect a 30% difference in CR rate at the 5% level with 1-β $\geqslant$80%. 95% confidence intervals were calculated for ratios. Student's *t*-test and the Mann–Whitney *U*-test were used for comparison of continuous variables, whenever appropriate and χ^2 analysis (with continuity correction) was used to compare categories. Kaplan–Meier plots were used to describe curves for survival and duration of response and the log-rank test was used to compare curves. We utilized Cox's regression analysis for the multivariate analysis of predictive factors for survival and duration of response, and logistic regression to analyze variables with an impact on the achievement of CR, and on the events of early death and severe cardiac toxicity.

Results

Randomization

In all, 97 patients were included in the study. Four patients were excluded after randomization; one patient refused to participate, one had heart failure NYHA grade III, and two were considered unsuitable for chemotherapy for other reasons. Of the remaining 93 patients, 47 were randomized to chemotherapy alone (TAD) and 46 to chemotherapy in combination with GM-CSF (GM-TAD). Of these, 32 patients had MDS-AML and 15 RAEB-t in the TAD group, while the GM-TAD group comprised 36 MDS-AML and 10 RAEB-t. The median age was 72 years (35–88 years) in the TAD group and 73 years (56–90 years) in the GM-TAD group. There were no significant differences in clinical and hematological characteristics between the two arms (Table 1).

Remission induction

CR was achieved in 40 (43%, CI 33–52%) of the 93 patients. In all, 32 (34%) patients reached CR after one induction course. Of the remaining 61 patients, 28 were given a second induction course and eight (29%) of them responded with CR. The median time to achieve CR was 38 days (range: 19–141). A total of 11 patients (12%) died early, that is, within 4 weeks after start of chemotherapy, in 10 cases following the first induction course, and in one case after the second. The immediate causes of early death are shown in Table 2.

In the TAD group, 20 of 47 patients (43%, CI 30–57%) entered CR (16 after one course), 23 showed resistant disease, and four were early death. The corresponding figures for the 46

Table 1 Description of 93 evaluable patients treated with TAD alone, or TAD in combination with GM-CSF

Variable	*TAD* (*n*=47)	*GM-TAD* (*n*=46)
Sex (M/F)	28/19	24/22
Age (years)[a]	72 (35–88)	73 (56–90)
MDS duration (days)[a]	153 (17–3479)	135 (0–6019)
Cytogenetic risk groups[b] (good/intermediate/poor/ND)	16/9/17/5	20/5/18/3
RAEB-t	15	10
All AML	32	36
M0	3	0
M1	10	5
M2	9	19
M4	5	7
M5	4	3
M6	0	1
M7	1	0
NUD	0	1
Hemoglobin (g/l)[a]	85 (65–117)	85 (59–115)
WBC (10^9/l)[a]	4.2 (0.8–219)	5.0 (0.1–140)
ANC (10^9/l)[a]	1.2 (0.1–22)	1.1 (0.1–54)
Platelets (10^9/l)[a]	53 (0–232)	49 (6–212)
S-LDH (μkat/l)[a]	9.7 (3.4–54)	9.5 (3.5–70)

[a]median (range).
[b]Cytogenetic risk-based subgroups according to IPSS.[1]
ND: not done.

patients in the GM-TAD group were 20 CR (43%, CI 30–58%) (16 after one course), 19 resistant disease, and seven early deaths. There was no significant difference in time to achieve CR or in the number of early deaths ($P=0.33$) between the two arms. Continuous and category variables associated with response to treatment are shown in Tables 3 and 4. Peripheral blood blast counts, S-LDH, bone marrow cellularity, WBC counts, and percentage of bone marrow blasts were significantly associated with a response to treatment in the univariate analysis. S-LDH levels ($\leqslant$ or $>9.5\,\mu$kat/l), bone marrow cellularity ($\leqslant$ or $>70\%$), and WBC counts ($<$ or $\geqslant 4.0\times 10^9$/l) were significantly associated with response to treatment when used as category variables (Table 4). Logistic regression analysis including both continuous variables and category variables showed that the only variable independently associated with response to treatment was S-LDH, $\leqslant$ or $>9.5\,\mu$kat/l ($P<0.0001$).

Follow-up of CR patients

At the time of follow-up 34 months after the inclusion of the last patient, 33 patients had relapsed (16 of 19 (84%) patients in the TAD group and 17 of 20 (85%) in the GM-TAD group), while two patients in each arm had died in CR1. There was no significant difference in RFS between TAD (median 330 days; range: 23–2171+) and GM-TAD (median 364 days; range: 76–2478+), $P=0.45$. RFS of >1 year was seen in 19 patients, nine in the TAD, and 10 in the GM-TAD group, respectively. One more patient in the TAD group was alive at follow-up after 2148 days. She had received a bone marrow transplant after 4 months in CR1 and was censored for the analyses of OS and RFS.

The number of consolidation courses during CR1 varied between patients, but not between arms. In all, 17 patients received 0–1 consolidation courses (eight in the TAD group and nine in the GM-TAD group), and 23 cases received two to three courses (11 and 12 in the respective arms). Median RFS did not differ between patients receiving 2–3 and 0–1 consolidation courses, respectively (352 *vs* 302 days, $P=0.99$). Interestingly, variables predicting for CR did not predict for duration of CR.

Table 2 Serious adverse events recorded in association with induction therapy in 93 patients treated with TAD or GM-TAD

	TAD	*GM-TAD*
Infectious events	29	24
Septicemia	18	12(3)
Systemic fungal infection	2	4
Pneumonia	3(1)	0
Fever NUD	6	8
Hemorrhages	3	2
Cerebral bleedings	3(2)	0
Intravascular coagulation	0	2
Cardiac events	7	14
Myocardial infarction	0	6(3)
Cardiac failure	6	6(1)
Arrythmias	1	1
Pericarditis	0	1
Fluid retention	1	14
Capillary leak syndrome	1(1)	3
Pulmonary edema	0	2
Weight gain, edema	0	9
Thromboembolic events	2	0
Pulmonary emboli	1	0
Deep venous thrombosis	1	0
Other events	5	7
Exanthema	2	6
Miscellaneous[a]	3	1

[a]Ulcerative esophagitis, renal failure, abdominal pain, hyperglycemia.
The number of patients who died early, that is, within 4 weeks after start of induction therapy, are shown within brackets.

Table 3 Continuous variables in CR and non-CR patients (mean±s.d.)

Variable	*CR* (*n*=40)	*Non-CR* (*n*=53)	*P-value*
Age (years)	71±9	71±10	0.87
MDS duration (days)	326±387	579±1037	0.15
Hemoglobin level (g/l)	88±13	86±12	0.29
WBC count (10^9/l)	8.9±13.1	32.2±46.1	0.004
ANC count (10^9/l)	2.55±7.3	5.3±9.0	0.13
Platelet count (10^9/l)	62.3±42.7	55.4±45.8	0.46
Peripheral blood blasts (%)	7.1±16.0	27.4±31.9	0.0005
Bone marrow cellularity	66.8±23.3	81.3±19.1	0.001
Bone marrow blasts (%)	37.9±15.2	48.2±21.4	0.012
S-LDH	8.2±5.9	19.7±16.2	0.0001

Instead, the multivariate analysis identified platelet count before start of treatment as the only clinical or hematological pretreatment variable significantly associated with the duration of CR1 ($P=0.01$).

Overall survival

The median survival from date of randomization was 284 days: 623 days (range: 56–2507+) for CR patients and 103 days (range: 1–553) for non-CR patients. No significant differences in survival were observed between TAD and GM-TAD ($P=0.95$, Figure 1). Five patients were alive at the time of follow-up, two in the TAD group at 1081 and 2229 days, and three in the GM-TAD group at 1248, 1442, and 2507 days, respectively. Cox's regression analysis identified four significant independent prognostic factors for survival: bone marrow cellularity

Table 4 Category variables in CR and non-CR patients

Variable	*Favorable group*	*Response rate* (%)	*Unfavorable group*	*Response rate* (%)	*P-value*
Sex (M/F)	Male	46	Female	39	0.49
Type of MDS (prim./sec.)	Primary	45	Secondary	36	0.53
Diagnosis (AML/RAEB-t)	RAEB-t	52	MDS-AML	40	0.29
Karyotype (N/A)	Normal	50	Abnormal	40	0.72
Cytogenetic risk group (Good/intermediate/poor)	Good/intermediate	48	Poor	37	0.60[a]
WBC (10^9/l)	⩽4.0	60	>4.0	28	χ^2=9.94**
Bone marrow cellularity (%)	⩽70	60	>70	30	χ^2=8.27**
S-LDH (μkat/l)	⩽9.5	71	>9.5	13	χ^2=30.0***

[a]*P*-value calculated on three groups.
**$P<0.01$.
***$P<0.001$.

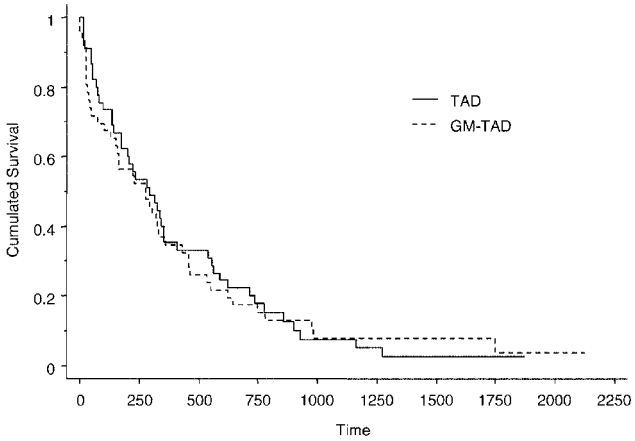

Figure 1 OS in days from date of randomization according to assigned treatment group. No significant difference was seen between the two treatment arms TAD and GM-TAD, respectively.

($P=0.006$), log S-LDH ($P=0.001$), cytogenetic risk group ($P=0.003$), and age ($P=0.03$). Using the above-described cutoff values to subcategorize these variables, cellularity and S-LDH retained statistical significance in the log-rank test. Moreover, leukocyte count that did not retain significance as a continuous variable in the Cox model was highly significant as a categorized variable (< or ⩾4.0×10^9/l, $P=0.005$) (Figure 2a–d). It was not possible to find a cutoff for age that showed significance in the log-rank test.

Hematological toxicity, infections and fever during induction therapy

The mean number of days with ANC $<0.5\times 10^9$/l was 20 ± 12 in the whole material, 21 ± 14 in the TAD group, and 18 ± 9 in the GM-TAD group ($P=0.21$). The mean number of days with fever >38°C was 7.8 ± 8.0 in the whole group, 8.7 ± 8.3 in the TAD group, and 6.8 ± 7.7 in the GM-TAD group ($P=0.26$). In addition, the mean number of days in hospital during the first 90 days from start of chemotherapy was comparable between the two treatment groups; 33 ± 15 days for TAD *vs* 30 ± 16 days for GM-TAD ($P=0.30$).

Infections were documented in 48 (52%) of the 93 patients. There were 30 episodes of bacterial septicemia, six invasive fungal infections or fungal septicemia, three pneumonia, and nine cases with infections of unknown origin (Table 2). Four patients died early (<4 weeks) as a result of infection.

Two patients died of cerebral hemorrhages, and three others suffered major bleeding complications associated with thrombocytopenia and disseminated intravascular coagulation (Table 2), with no differences between treatment groups.

Nonhematological toxicity

In all, 50 episodes of clinically significant nonhematological adverse events were recorded in association with the induction therapy; 15 in the TAD group and 35 in the GM-TAD group (Table 2). Fluid retention, that is, capillary-leak syndrome, pulmonary edema, or weight increase was observed in 14 patients receiving GM-TAD, while only one patient showed such symptoms after TAD. Six of eight patients with exanthema had received GM-CSF. In total, 21 events involved cardiac complications, seven (33%) after TAD, and 14 (67%) after GM-TAD ($P=0.01$). All six patients who suffered acute myocardial infarction belonged to the GM-TAD group. Other thromboembolic events included one case with deep venous thrombosis and another with pulmonary emboli, both in the TAD group.

Discussion

The present study was designed with the purpose to improve outcome of treatment in MDS-AML and RAEB-t. An earlier small pilot study in MDS-AML had suggested that the addition of GM-CSF to standard chemotherapy might improve the outcome of treatment substantially,[29] and we wanted to test this hypothesis in a prospective study. We also aimed at defining pretreatment variables with a predictive value for the outcome of therapy. The results showed that the overall CR rate was 43%, the median RFS 11.3 months, and the median OS 9.5 months, with no differences between the two arms. Thus, we were unable to confirm our initial report that addition of GM-CSF to a standard TAD (2+7) regimen could improve the outcome of chemotherapy in MDS-AML and RAEB-t. Since the start of our study, only a few comparable randomized studies in transforming MDS have been published. Bernasconi *et al*[23] randomized 105 patients to receive G-CSF or not as an adjuvant after chemotherapy and found significantly better response rates (CR+PR) after G-CSF therapy, but no effect on survival, unless stem cell transplantation was performed. A HOVON study reported a nonsignificant trend towards a higher CR rate and longer OS in patients who were treated with G-CSF during and after chemotherapy.[24] Estey *et al*[25] found an increased CR rate, but no effect of the addition of G-CSF to chemotherapy on RFS or OS. In addition, two smaller randomized studies combining GM-CSF with chemotherapy failed to show improved response

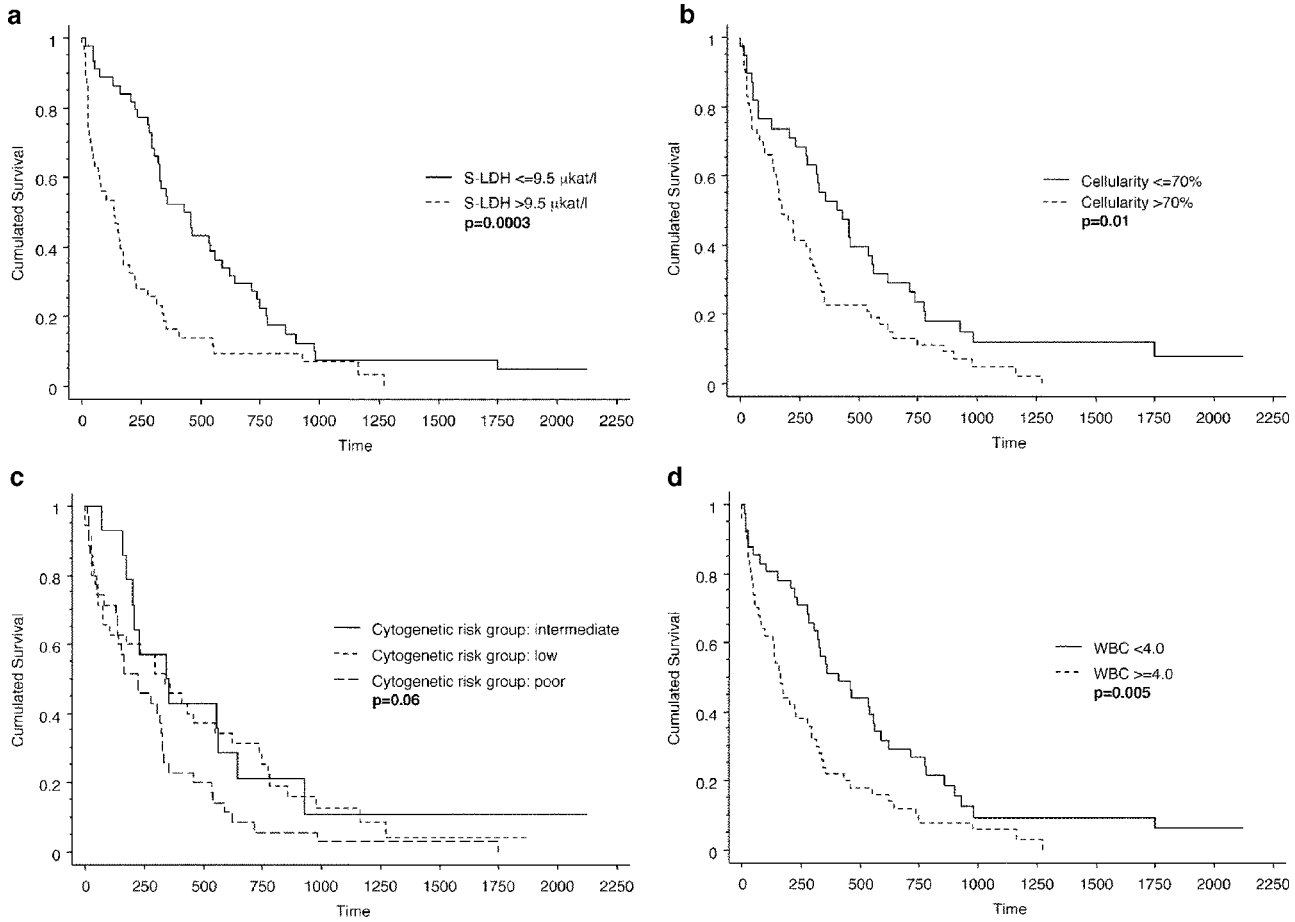

Figure 2 OS in days from date of randomization according to: (a) S-LDH levels at diagnosis – patients with $>9.5\,\mu$kat/l had significantly poorer survival ($P=0.0003$); (b) bone marrow cellularity at diagnosis – patients with $>70\%$ cellularity had significantly poorer survival ($P=0.01$); (c) cytogenetic risk-based categorization (IPSS) – no significant differences between the three risk groups ($P=0.06$); and (d) leukocyte counts at diagnosis – patients with a WBC count $<4.0\times10^9$/l showed significantly better survival ($P=0.005$). (log-rank test.)

rates in MDS-AML and HR-MDS.[6,22] Considering all controlled studies in MDS-AML and HR-MDS, including the present one, it seems unlikely that G-CSF or GM-CSF given concomitantly with or after chemotherapy can significantly improve end points like CR rate, RFS, and OS. This is in agreement with the results in *de novo* AML.[13–21]

Most studies of *de novo* AML and MDS where G-CSF or GM-CSF has been used as adjunct to chemotherapy have shown positive effects on neutropenia, febrile episodes, or hospitalization.[13–25] In one study of AML, this effect was translated into a 'cost gain' that could further motivate the routine use of growth factors in combination with chemotherapy in AML and MDS.[30] In the present study, however, we did not observe any significant differences between the two arms, either with respect to days with neutropenia or fever, number of infectious events, or days spent in hospital. GM-CSF, in contrast to G-CSF, may cause fever that may blur the interpretation of this variable; however, it is still unclear as to why we, in contrast to most other investigators, did not observe an effect on ANC recovery. One explanation might be that we used a somewhat lower GM-CSF dose from the start in an effort to reduce the reported heavy nonhematological toxicity of GM-CSF.[31] In the 25% of our patients who experienced moderate to severe adverse events this dose was reduced further, which together with the measures outlined in our protocol, allowed all but four patients to continue the treatment with GM-CSF. Cardiac events were more common in the GM-TAD group, and this was largely explained by the unexpected finding of six patients suffering acute myocardial infarction in this group. Interestingly, Sugiyama *et al*[32] recently suggested that endogenous GM-CSF may play an important role in the development of acute coronary syndromes. It is conceivable that administration of exogenous GM-CSF might likewise contribute to atheroma complications. We are not aware of any earlier reports linking GM-CSF therapy to acute myocardial infarction. Perhaps the unusually high median age of our patients, 72 years, may have contributed. In view of these findings, it is probably prudent to use GM-CSF with caution in elderly patients with advanced coronary sclerosis.

Response rate, response duration, and survival are important issues for elderly patients with advanced MDS, for whom cure is exceedingly rare. The present study is one of the hitherto largest studies in which patients with MDS-AML and HR-MDS have been treated prospectively in a uniform way and followed-up for a relatively long period. Only one variable, S-LDH, was independently associated with response rate in the multivariate analysis. Patients with subnormal or normal S-LDH levels ($<9.5\,\mu$kat/l) showed a response rate of 71% compared to 13% in those with S-LDH $\geqslant 9.5\,\mu$kat/l ($P<0.0001$). An association between elevated S-LDH and poorer survival has previously been reported in AML, and in untreated cohorts of MDS patients.[33–35] As S-LDH predicted also for survival in our study, it turns into a clinically highly relevant pretreatment variable.

Karyotype, which usually has a significant impact on outcome in studies of *de novo* AML and younger MDS, was a less important variable in the present study. The CR rate was 40% for patients with an abnormal karyotype compared to 50% for those with a normal karyotype, and 37% for patients belonging to the poor cytogenetic risk group (IPSS), compared to 48% for the good/intermediate groups. Furthermore, we failed to demonstrate a difference in survival between patients with poor-risk and intermediate karyotype, while good-risk karyotype (IPSS) was associated with better OS. Our hypothesis is that the higher median age in our study has influenced the role of cytogenetics.

Interestingly, increased bone marrow cellularity and S-LDH levels were independently associated with poorer survival, indicating that these variables partly reflect different aspects of disease. Also, leukocyte count showed independent prognostic value with an optimal cutoff between low counts and normal/high counts. This is important information since it has been generally believed that MDS patients with profound pancytopenia might respond less well to chemotherapy. Platelet count was the only clinical or hematological pretreatment variable that had an independent prognostic significance for RFS in CR1, most likely reflecting residual stem cell function of the bone marrow. A similar finding was recently reported by Osterveld *et al.*[36]

Three important conclusions can be drawn from our results: (i) The addition of GM-CSF according to the described schedule did not improve the outcome of chemotherapy. An association of uncertain significance between GM-CSF therapy and acute myocardial infarction was observed, which warrants further studies. (ii) patients who appeared to have a more proliferative form of disease, with increased WBC counts, elevated S-LDH, and increased bone marrow cellularity, had the worst outcome. This set of prognostic variables is easily available in most patients, and could be a useful tool in the decision-making before treatment with induction chemotherapy. (iii) The present TAD (2+7) regimen appears well suited to treat elderly patients with HR-MDS and MDS-AML, where stem cell transplantation is not an option. It is noteworthy that half of the responding patients in our study remained in CR1 for more than a year. This may be explained partly by a relatively low mortality during CR1, which possibly was achieved by allowing for an attenuated maintenance treatment.

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