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The evaluation of low-dose cytarabine in the treatment of myelodysplastic syndromes: a phase-III intergroup study*

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Summary. One hundred and forty one patients were treated in a combined Eastern Cooperative Oncology Group and Southwest Oncology Group phase-III study evaluating low-dose cytarabine (LDAC) versus supportive therapy for the treatment of myelodysplastic syndrome (MDS). Patients were randomized to either cytarabine 10 mg/m^2 subcutaneously BID or supportive therapy. Central pathology review was required. All patients were classified according to the FAB criteria for MDS. The overall concordance rate for the MDS subtype was 52%, and 25 patients were pathology exclusions, including 20 with AML. The overall response rate to a single cycle of LDAC was 32%, with 11% complete and 21% partial responses. The median duration of response was 5.9 months, with a range of 1.4–33.5 months. Responses were seen in all subtypes. Infections were more common in the LDAC arm. There was no difference in the time to progression or the overall survival for patients treated with LDAC or supportive therapy. The incidence of leukemic transformation was similar in both arms at 15%, but it differed according to the MDS subtype. Patients receiving LDAC had a decreased transfusion requirement after 3 months. There was a significant correlation between the degree of cytoreduction after receiving a single cycle of LDAC and survival. This survival difference was most marked in patients with the RAEB and RAEB-T subtypes. Although LDAC produced responses in all subtypes of the MDS, there was no effect on overall survival or transformation to AML. However, selected patients benefited from a single cycle of LDAC with durable responses. A cytoreductive effect appears to be required for a durable response. Future studies should include pathology review and must address the clinical and biological heterogeneity of MDS.

Key words: Low-dose cytarabine – Myelodysplastic snydrome

Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of stem cell disorders characterized by impaired proliferation and maturation of hematopoietic progenitor cells, resulting in symptomatic anemia, leukopenia, and thrombocytopenia. Morphological and functional abnormalities involving more than one cell line are common. Elderly patients are most often affected. The clinical course is variable, ranging from a stable, mildly symptomatic disorder to one that progresses rapidly to overt acute leukemia. Recurrent infections and/or bleeding are the most frequent causes of mortality and morbidity.

The most appropriate treatment of these disorders is controversial. The current standard approach to the care of the majority of these patients is supportive, consisting of red cell transfusions and symptomatic treatment of infections or bleeding. Although intensivce therapy, including bone marrow transplantation, has been tried in selected patients, the majority of patients with MDS are elderly and tolerate cytotoxic therapy poorly [3, 9, 21]. Alternatively, chemotherapy at low doses has been administered to selected patients: low-dose cytarabine (LDAC) has been reported to induce responses in both high-risk patients with acute leukemias and in myelodysplastic syndromes [25]. Whereas standard-dose cytarabine acts by inhibiting DNA replication, at low doses it may act by a completely different mechanism. The mechanism of action of LDAC is unclear; LDAC induces both histologic and functional differentiation in vitro [13]. Some investigators have postulated that it may induce clinical re-

* This study was conducted by the Eastern Cooperative Oncology Group (Douglas C. Tormey, M.D., Ph.D., Chairman, CA 21115) and supported by Public Health Service grants from the NCI, National Institutes of Health, and the Department of Health and Human Services. Institutions from the Southwestern Oncology Group also participated

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sponses through cellular differentiation without the need for cytoreduction [26]. Some studies, however, have failed to demonstrate a significant clinical effect from LDAC in the treatment of MDS [6]. The morphological and clinical heterogeneity of the MDS have made the reported trials of therapy in this disease difficult to evaluate. Furthermore, these investigations have been, for the most part, nonrandomized studies performed at single institutions, and the definition of a complete remission, the entry criteria, and the subtype of the MDS have not been uniformly defined. Therefore, to determine the overall value of LDAC in the treatment of the MDS, the Eastern Cooperative Oncology Group and the Southwest Oncology Group initiated a randomized phase-III study comparing LDAC, administered subcutaneously, with observation and supportive therapy.

Patients and methods

Patients at least 18 years of age with one of the FAB-defined MDS including refractory anemia (RA), refractory anemia with ringed sideroblasts (RAS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML) were eligible [4]. Submission of the diagnostic bone marrow aspirate and biopsy slides was required prior to study entry. All pathology slides were reviewed by two observers (JMB and DRH) using the FAB criteria [4]. They confirmed the diagnosis and the FAB subtype of MDS and evaluated the overall cellularity in the aspirates and biopsies. Follow-up bone marrow biopsies to determine response were also submitted for central review. In addition to the pathological diagnosis of an MDS, patients were required to have one or more of the following criteria for entry into this study: (a) A documented transfusion requirement over a 3-month period prior to entering the study; (b) a platelet count of less than 100 000/mm^3; or (c) a granulocyte count of < 1000/mm^3. Patients with the MDS subtypes RA and RAS were required to have at least two of the above criteria to enter the study, while patients with RAEB, CMML, and RAEB-T were required to demonstrate only one.

Patients who had received chemotherapy or radiation therapy less than 2 months prior to entering the study were ineligible, as were patients with impaired hepatic or renal function (bilirubin $\geq$ 3 mg/dl or creatinine $\geq$ 2.0 mg/dl). All patients were required to have an ECOG performance status of less than 4 and to be able to self-administer, or have administered to them daily, subcutaneous injections. All patients were required to give written local IRB-approved informed consent.

Treatment regimen

Patients were randomized to either LDAC or supportive therapy. On the supportive therapy arm, patients received red cell and platelet transfusions as needed. Bone marrow aspirates and biopsies were performed every 3 months. Patients went off study if they progressed to acute leukemia according to standard criteria ($> 30\%$ blast forms) [5]. Patients on the supportive therapy arm were permitted to cross over to the LDAC arm if they had progressive disease after 3 months of observation. Patients in the supportive therapy arm did not receive chemotherapy, androgens, or corticosteroids while on study.

In the LDAC arm, cytarabine was self-administered in a dosage of 10 mg/m^2, subcutaneously, every 12 h for 21 consecutive days. There was no dose modification. Patients were monitored with weekly blood counts. Bone marrow aspirates and biopsies were performed on days 14 and 29 after the start of LDAC and then every 3 months. All bone marrow aspirates and biopsies were reviewed centrally, as described above.

After completing therapy, patients who achieved a complete or partial response were followed up without further treatment until relapse or progression. Patients who progressed to acute leukemia were taken off study (progressive disease). Patients with stable or progressive disease following LDAC were followed up for survival. Patients who responded to LDAC but relapsed after receiving therapy were entitled to be retreated with a 21 day course as previously described.

Measurement of effect

A complete remission (CR) was devined as a morphologically normal bone marrow with normal cellularity and less than 5% blast forms, a platelet count of greather than 100 000/mm^3, a granulocyte count of greater than 1500/mm^3, and a hematocrit maintained without transfusions at greater than 30 vol%. A complete remission required all of these criteria.

A partial response (PR) was defined as a sustained improvement, for at least 2 months, over the pretreatment condition as demonstrated by one or more of the following: (a) A decrease in the monthly transfusion requirement by 50%; (b) an increase in the hemoglobin of 2 gm/dl; (c) an increase in the platelet count by greater than 30 000/mm^3 if the pretreatment platelet count was less than 75 000/mm^3; (d) an increase in the granulocyte count by greater than 500/mm^3 if the pretreatment granulocyte count was less than 1000/mm^3; or (e) a decrease in blasts by 50%.

Progressive disease was defined as a change from the pretreatment values, characterized by one or more of the following: (a) A sustained increase in the monthly transfusion requirement by greater than 50%; (b) a decrease in the platelet count by 30 000/mm^3 or 50%, whichever is greater; (c) a decrease in the granulocyte count in the neutropenic patient to less than 1000/mm^3, (d) an increase in the percentage of blasts in the bone marrow according to the following schedule: for patients with initial blast counts of less than 5%, an increase to greater than 10% blasts, or for patients with initial blast counts greater than 5%, a 100% increase in the blast count; (e) progression to a prognostically less favourable FAB category (RA or RA-S to RAEB: or RAEB to RAEB-T). Transformation to acute leukemia was defined by the FAB criteria, with the appearance of $> 30\%$ blast forms in the bone marrow [5].

Statistical methods

For comparison of toxicities, the exact Kruskal and Wallis test for ordered categorical data was used. The transfusion requirement was compared with a generalized estimating equation [17]. Objective response rates were analyzed using Fisher's exact test, survival data by the log rank test of Mantel to find individual prognostic factors associated with response and survival data [19]. The survival distributions for the survival time and the time to progression were estimated by the method of Kaplan and Meier [14]. The logistic regression model was used for analysis of response and Cox's proportional hazards model was used for analysis of failure-time data [7, 8].

Results

Patient characteristics

One hundred forty-one patients were entered into the induction step of this study, and 102 were analyzable. One patient was canceled and ten patients were ineligible; three had a revised diagnosis of AML at the registering institution and seven did not meet the eligibility criteria. Twenty-six were excluded from analysis after pathology review: 19 had AML, five had no pathology material submitted for review, and two had inadequate pathology

material submitted for diagnosis. Two further patients were excluded from the analysis due to loss to follow-up. Fifty percent of all the AMLs were reclassified as FAB M6, 15% as hypocellular AML, and 20% as either FAB M1 or M2. Of the 22 patients with AML, the majority – 12 – had the initial entry diagnosis of refractory anemia with excess blasts, nine were thought to have refractory anemia with excess blasts in transformation, and one was entered with the diagnosis of refractory anemia.

There were 33 patients registered for the cross-over/reinduction step of the study. Twelve patients received LDAC initially and relapsed following a response (reinduction) and 21 progressed on the supportive therapy arm (cross-over). Of these 33 patients, ten were excluded from the analysis; five patients were not evaluable for induction analysis, four were found to be AML at the time of cross-over, and one had no bone marrow biopsy performed.

The distributions of some of the important patient characteristics by treatment arm for the 102 analyzable patients are summarized in Table 1. The majority (71%) were male; the median age was 70.4 years, with a range of 19.2–85.5 years. Eleven patients had received prior chemotherapy or radiotherapy. All patients had an ECOG performance status of 3 or less, and 96% of the patients had a performance status of 2 or less. According to the review diagnosis, the MDS subtypes of the 102 analyzable patients were RA 12, RA-S 5, RAEB 52, RAEB-T 20, and 13 with CMML. The two arms were well balanced with regard to diagnosis, age, and prior therapy. The diagnosis provided at the time of study entry by the local pathologist was confirmed by central review in only 52% of the cases. The entry and review diagnosis of the subtypes of MDS is presented in Table 2. The concordance between the two pathology references (JMB and DRH) was 94% for diagnosing MDS versus AML and 75% for the recognition of the FAB-defined subtype. Eighty-three percent of these disagreements were the result of differences in the estimate of the percent of blasts, resulting in over or under calling of the FAB subtypes (e.g., RA to RAEB or RAEB to RA).

Table 1. Distribution of patient characteristics by induction treatment

Patient characteristic	Treatment	
	Supportive	LDAC
Age in years		
Median	70	70
Range	34–85	19–85
Gender (%)		
Male	71	70
Female	29	30
Prior XRT/chemotherapy (%)		
No	92	92
Yes	8	8
Performance status (%)		
Fully active	31	25
Ambulatory/capable of light work	45	58
In bed < 50% of time	18	15
In bed > 50% of time	6	2

Table 2. Entry diagnosis vs review diagnosis

Entry diagnosis	Review diagnosis (*n*)				
	RA	RA-S	RAEB	CMML	RAEB-T
RA	9	3	11	1	2
RA-S	0	1	5	0	0
RAEB	3	0	30	2	13
CMML	0	0	1	8	0
RAEB-T	0	1	5	2	5

Transfusion requirements

A majority of patients in both arms ($n = 102$) had received RBC transfusions prior to entering the study, 84% on the supportive therapy and 87% on the LDAC arm. At the first 3-month follow-up ($n = 77$), 78% on the supportive therapy and 75% on the LDAC arm required transfusion support. At 6 months ($n = 43$), 77% on the supportive therapy and 67% on LDAC continued to require transfusion; at 9 months ($n = 22$), 75% on the supportive therapy and 40% on the LDAC arm where receiving transfusion support. At 12 months ($n = 20$) 75% on the supportive therapy arm and 56% on the LDAC arm continued to require transfusions. There was a decrease in the transfusion requirement after 3 months of follow-up on the LDAC arm; however, it was not significantly different from the support group.

Toxicity

The incidence of the treatment arm-related toxicities are summarized in Table 3. The majority of the severe toxicities were infectious complications. Serious and life-threatening infectious complications occurred on both the supportive therapy and LDAC treatment arms. However, LDAC treatment was associated with a significantly increased risk of serious infectious complications ($p < .01$). A total of 102 21-day courses of LDAC were administered, 69 induction and 33 cross-over/reinduction courses, and there were two lethal, seven life-threatening, and 14 severe infectious complications. The toxicity rate for grade 3 or greater infectious complications for all courses of LDAC was 22.5%.

Response to treatment

The response to treatment is summarized in table 4. The overall objective response to LDAC was 32%, with 11% complete and 21% partial responses. The median duration of response to a single course of LDAC was 5.9 months, with a range of 1.4–22.5 months. In the suppor-

Table 3. Treatment arm-related toxicity

	ECOG grade					
	None	Moderate	Mild	Severe	Life-threat.	Lethal
LDAC arm						
Hematologic	0	1	2	6	60	
Infection	31	3	17	10	6	2
Bleeding	40	17	9	3		
Respiratory	68				1	
Vomiting	49	7	12	1		
Hepatic	62	3	3	1		
GU	52	9	8			
Skin/mucous membranes	58	5	6			
Diarrhea	61	6	2			
GI (other)	66	2	1			
Neurologic	67	1	1			
Other	63	1	4	1		
Supportive therapy arm						
Hematologic	3		1	25	38	
Infection	45	2	14	3	2	1
Bleeding	48	9	4	3	3	
Vomiting	65	2				
Hepatic	62	1	2	2		
GU	64	3				
Neurologic	63	2	1	1		
Other	66	1				

Table 4. Response by induction treatment

Treatment	Supportive		LDAC	
	n	%	*n*	%
Complete response	0	0	6	11
Partial response	0	0	11	21
Stable disease	9	18	20	38
Progressive disease	36	73	15	28
Unevaluable	4	8	1	2
Total	49	100	53	100

Table 5. Response to cross-over reinduction LDAC by MDS subtype

MDS subtype	CR	PR	% Response
RA	1	1	67
RAEB	2	2	31
CMML	0	0	0
RAEB-T	2	1	60
Total	5	4	39

tive care arm 73% of the patients progressed while on study, while 28% progressed on LDAC ($p < .01$). The objective responses for the LDAC cross-over/reinduction patients are provided in Table 5. Among the 23 evaluable patients in the cross-over and reinduction arms, there were five complete and four partial responders, for an overall response rate of 39%. The response rate was 67% (four complete and two partial responses) for patients who initially responded to LDAC and relapsed and were then retreated. Patients who progressed on the supportive therapy arm and then crossed over had a meaningfully lower overall response rate of 21%. The overall response to LDAC, including both the patients treated in induction and at the time of cross-over was 30%: 10% CR and 20% PR. The response to LDAC induction by MDS subtype is summarized in Table 6. Responses were noted in each subtype. Patients with the RA and RAEB-T subtypes had the best response to LDAC, with overall response rates of 43% and 42% respectively. Patients with RAEB had a 32% response rates of 43% and 42% respectively. Patients with RAEB had a 32% response rate those with RA-S a 25% response rate, and those with CMML a 13% response rate.

Table 6. Response to induction LDAC by MDS subtype

MDS subtype	CR	PR	Total	% Response
RA	2	1	7	43
RA-S	0	1	4	25
RAEB	2	5	22	32
CMML	0	1	8	13
RAEB-T	2	3	12	42
Total	6	11	53	32

Time to progression and survival

The time to progression was measured from the date of randomization to the date of progression or to relapse (Fig. 1). Progression was defined as progressing to AML or another MDS type, an increase in the transfusion requirement, or progressive pancytopenia as previously noted. The median time to progression for patients initially treated with LDAC, and excluding patients who crossed over or received reinduction, was 5.6 months on LDAC versus 2.9 months on the supportive therapy arm.

Overall, the incidence of leukemic transformation was similar in both arms at 15%. The frequency of transformation to acute leukemia differed according to the MDS subtype and ranged from a high of 28% in RAEB-T to a low of 0% in RA-S (Table 7). THere was no difference in the time to leukemic transformation in the two arms. Overall survival time, measured from the time of randomization, was not significantly different in the two arms; 5.1 months versus 6.8 months for the supportive care and LDAC arms, respectively (Fig. 2). However, due to the cross-over design of this study we were not able to specifically address the overall survival benefit of LDAC treatment. The median survival of the 23 patients in the cross-over reinduction arm was 10.6 months.

The majority (82%) of patients in the study died of complications related to thrombocytopenia, infection, or anemia. After a median follow-up of 40 months, 97% of the analyzable patients in the study had died.

Percent cytoreduction

Percent of cytoreduction following LDAC was determined by comparing the overall cellularity of the pretherapy bone marrow with the bone marrow obtained after 21 days of treatment. All measurements were performed prospectively by the central reviewer, without knowledge of the clinical events. A ratio of post-therapy cellularity

Table 7. Leucemic transformation by MDS subtype

MDS type	Leukemic transformation (%)
RA-S	0
RA	9
RAEB	14
CMML	15
RAEB-T	29
Total	15

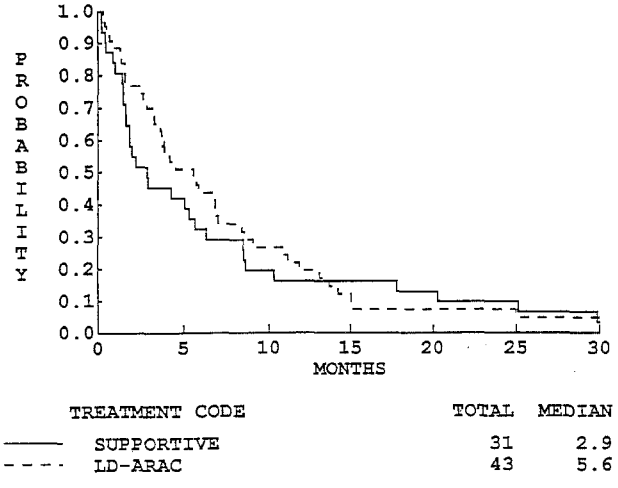

Fig. 1. Time to progression measured from the date of randomization to the date of progression or to relapse. Progression was defined as progressing to AML or another MDS type, as an increase in the transfusion requirement, or as pancytopenia. *LD-ARAC*, LDAC

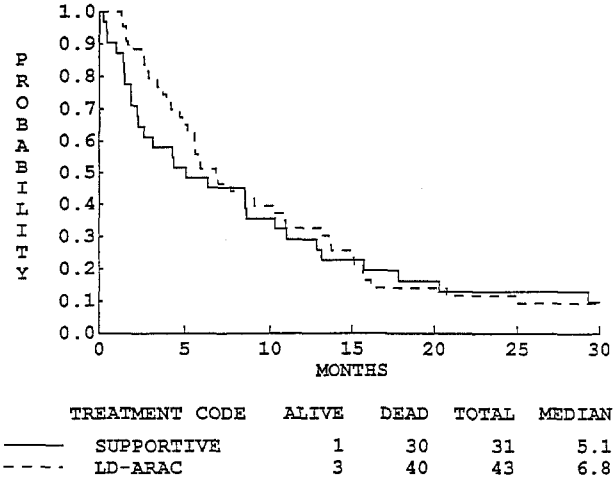

Fig. 2. Overall suvival time from time of randomization. *LD-ARAC*, LDAC

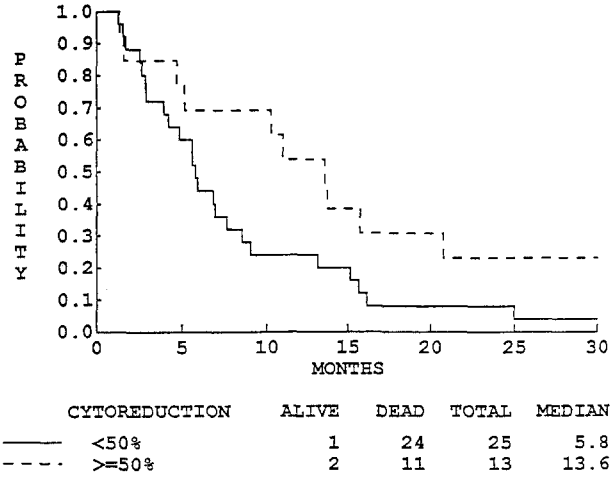

Fig. 3. Percent cytoreduction and overall survival for patients treated with LDAC. Cytoreduction was determined by comparing pretreatment bone marrow with bone marrow obtained after 21 days of therapy

to the pretherapy cellularity was used for the analysis. There was a correlation with the percent of cytoreduction and the response to treatment; patients with 50% or greater cytoreduction survived 13.6 months versus 5.8 months for those with less than 50% cytoreduction ($p = .0517$, Fig. 3). For patients with the RAEB and the RAEB-T subtypes, the degree of cytoreduction significantly correlated with the overall survival: 5.9 months versus 13.6 months for less or more than 50% cytoreduction, respectively ($p < .05$). In contrast, for patients with the RA and RAS subtypes there was no correlation with the percent cytoreduction and response to treatment. However, there were only seven analyzable patients in this group.

Discussion

The treatment of patients with one of the myelodysplastic syndromes remains controversial [18]. Intensive cytotoxic chemotherapy, low-dose therapy, bone marrow transplantation, differentiating agents, and growth factors have been investigated in selected studies [1,2,10,11,16,20,22]. While each of these therapies has been effective in limited numbers of patients, the use of supportive therapy remains the standard of care. Cytarabine administered at low doses, either intermittently by subcutaneous injection or by continuous intravenous or subcutaneous infusion, has been reported as effective in some patients with a myelodysplastic syndrome or overt AML [25]. In selected studies, patients have attained complete remissions of varying duration. However, as in this study, the majority of patients have had only partial responses with improvement in peripheral blood counts and reduced transfusion requirements. The mechanism of action of LDAC is also controversial. Although many patients experiences marrow hypoplasia, it has been suggested that LDAC may act by inducing cellular differentiation without the need for cytoreduction [26]. The present study was designed to address the role of low-dose cytarabine in the treatment of the myelodysplastic syndromes.

The MDSs are clinically heterogeneous, with varying presentations, natural history, and response to treatment. The present study attempted to carefully define the entry and response criteria of these disorders. Morphological and clinical evidence of dysplasia and clinical evidence of cytopenias involving more than one cell line were required. Moreover, central pathological review for diagnosis and response was mandatory. Twenty-six percent of the patients entered in the study did not have one of the myelodysplastic syndromes. The majority of these patients had the M 6 variant of AML [5]. The FAB criteria for the diagnosis of MDS was used throughout this study to identify and classify patients [4]. On central pathology review, 51% of the patients were reclassified to a different MDS subtype. The FAB criteria separate the MDSs into prognostically and clinically distinct subtypes [12,15,27]. This review process may have accounted for the low leukemic transformation rate of 15% observed in this study.

The majority of the patients entered in this study died as a direct consequence of their myelodysplastic syndrome, due to bleeding or infections. Ninety-seven percent of the patients died after a median follow-up of 40 months. This observation supports the concept that the MDS are a separate diagnostic group with an overall very poor prognosis [23,24].

Patients treated with LDAC had a delay in the time to progression when compared with those on the supportive care arm. Moreover, patients on the LDAC arm had a decrease in their transfusion requirement. However, this delay in the time to progression and decreased need for transfusions did not translate into an overall significant effect on survival. While it was not possible to address the effect of LDAC on survival by itself in this study, due to the cross-over design, there was no difference in survival between the patients treated with LDAC and those receiving supportive therapy alone. Moreover, only 14 evaluable patients from the supportive therapy arm did cross over and receive LDAC as part of this study.

The response rate to LDAC was 30% overall, with 10% complete responders and 20% partial responders. This response rate is similar to the aggregate of patients in the literature treated with LDAC [6]. The response rates were not equal for all the MDS subtypes. As noted previously, the best responses were seen in patients with the RAEB-T subtype [6,25]. While we did observe meaningful responses in patients with RA, there were only 12 patients with this subtype in the study.

The rate of transformation to acute leukemia was similar in both the LDAC and the supportive therapy arms and differed only according to the MDS subtype. The highest rate of transformation was seen in patients with RAEB-T subtype (29%) and the lowest for RA and RAS, 9% and 0%, respectively.

Interestingly, we found an association between the cytoreductive effects of LDAC and survival in the more proliferative subtypes of MDS – RAEB and RAEB-T. These two subtypes are characterized by an increased number of blasts in the bone marrow and an increased incidence of leukemic transformation. Our data suggest that in these subgroups a cytoreductive effect is required for a favorable response. While our data do no rule out a differentiating effect from LDAC, we found no evidence to support this possibility. Other studies have also questioned the clinical importance of cytarabine-induced in vitro differentiation [25]. Our failure to demonstrate a similar finding in patients treated with RA and RA-S may be due to the small numbers of patients with these subtypes evaluated or may reflect the clinical and biological heterogeneity of these disorders. Our data suggest that alternative types of therapy may be warranted in these subtypes of MDS.

This study demonstrates that LDAC can induce clinical complete and partial responses in a meaningful number of patients with one of the MDSs, but that it does not significantly affect overall survival. Responders did have a significantly longer survival. The meaning of this observation is unclear, but it suggests that selected patients may benefit from treatment with LDAC.

LDAC is not superior to supportive therapy for every subtype of MDS. However, patients with RAEB may benefit from treatment with LDAC, and those patients

who respond to a single course and relapse are more likely to benefit from retreatment. Whether or not a more intensive cytoreductive regimen may be more effective in MDS is unclear. Other investigators have administered more intensive regimens with varying results [20, 21]. In our study, however, patients treated with LDAC had significantly more infectious complications and thus may not have tolerted more intensive therapy.

In summary, this study did not demonstrate that a single cycle of LDAC prolonged overall survival in patients with one of the MDSs. LDAC began to decrease the transfusion requirement after 3 months of follow-up, and a meaningful number of patients had a prolonged transfusion response to treatment. A cytoreductive effect of LDAC was associated with a favorable response in patients with RAEB and RAEB-T, but it was not associated with a favorable response in patients with RA and RA-S. Considering the overall poor prognosis of this disease, other forms of therapy are needed. Future prospective trials need to include central pathology review and should address the marked differences in the biology of the MDS subtypes with regards to response, progression to AML, and overall survival.

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