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ORIGINAL REPORT

Outcome of High-Risk Myelodysplastic Syndrome After Azacitidine Treatment Failure

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ABSTRACT

Purpose
Azacitidine (AZA) is the current standard of care for high-risk (ie, International Prognostic Scoring System high or intermediate 2) myelodysplastic syndrome (MDS), but most patients will experience primary or secondary treatment failure. The outcome of these patients has not yet been described.

Patients and Methods
Overall, 435 patients with high-risk MDS and former refractory anemia with excess blasts in transformation (RAEB-T) were evaluated for outcome after AZA failure. The cohort of patients included four data sets (ie, AZA001, J9950, and J0443 trials and the French compassionate use program).

Results
The median follow-up after AZA failure was 15 months. The median overall survival was 5.6 months, and the 2-year survival probability was 15%. Increasing age, male sex, high-risk cytogenetics, higher bone marrow blast count, and the absence of prior hematologic response to AZA were associated with significantly worse survival in multivariate analysis. Data on treatment administered after AZA failure were available for 270 patients. Allogeneic stem-cell transplantation and investigational agents were associated with a better outcome when compared with conventional clinical care.

Conclusion
Outcome after AZA failure is poor. Our results should serve as a basis for designing second-line clinical trials in this population.

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INTRODUCTION

Myelodysplastic syndromes (MDSs) are clonal disorders of the bone marrow occurring in elderly patients in a majority of instances. They are defined by ineffective hematopoiesis with peripheral-blood cytopenias and by the risk of evolution to acute myeloid leukemia (AML).[1] Until recently, conventional therapies had not demonstrated a clear survival benefit, and standard of care used supportive transfusion and growth factors, such as erythropoietin.[2] When disease progresses to leukemia, prognosis is clearly unfavorable, with chemotherapy-resistant disease and an overall survival (OS) of less than 1 year.

In past years, significant advances have been made with the demonstration of the implication of epigenetic regulation in disease pathogenesis, especially during disease progression.[3] Epigenetic regulation is defined by heritable (through mitosis) modulation of gene expression related to DNA complex modifications without alteration of the coding sequence. Two complementary mechanisms support this regulation: methylation of DNA CpG islands by DNA methyl transferase enzymes (DNMTs), which prevents transcriptional factor binding in promoting/regulating regions and thus leads to silencing of the gene expression[4,5]; and the histone tails modifications, which change the accessibility of the reading frame to RNA polymerases.[6] In addition to the fundamental role of epigenetic regulation in physiological settings (eg, chromosome X inactivation), it appears that these mechanisms are involved in cancer pathogenesis and progression in multiple models.[7] In the hematology field, the DNMT inhibitors azacitidine (AZA) and 2-deoxy-5-azacytidine (decitabine) have demonstrated clinical activity with cytologic and cytogenetic responses in patients with

MDS,[8-10] and they are now the current standard of care for patients with high-risk MDS, (ie, MDS with intermediate 2 or high risk according to the International Prognostic Scoring System [IPSS]). Moreover, results of the recent AZA001 study[11] showed that treatment was associated with an improved survival when compared with conventional care. Although these results represent an important advance for patients with MDS, 40% to 50% of patients did not respond to therapy (ie, primary treatment failures), and most responders experienced disease progression within 2 years of response (ie, secondary treatment failures).[11]

The M.D. Anderson Cancer Center group recently reported a median OS of 4.3 months in 87 patients with MDS or AML in whom decitabine treatment failed,[12] and outcome was correlated with the MDS prognostic model developed by the same team.[13] The outcome after AZA failure also is generally considered poor; however, to date, there are no published data supporting this assumption. In addition, there is currently no standard salvage treatment, and the absence of data on the outcome after AZA failure limits the development and interpretation of clinical trials in this setting. Therefore, we analyzed the outcome of 435 patients with high-risk MDS who experienced AZA treatment failure, as collected from four independent data sets.

PATIENTS AND METHODS

Patient Selection

All patients included on this study had received treatment with AZA for an initial diagnosis of high-risk MDS (ie, IPSS intermediate 2 and high risks) or AML with 20% to 30% blasts (former refractory anemia with excess blasts in transformation [RAEB-T] according to French-American-British classification) according to WHO classification.[14] Morphologic diagnoses and marrow responses were confirmed by centralized pathologic review in the J9950, J0443, and AZA001 studies but not in the French compassionate program. All patients received AZA for at least one cycle. All patients gave signed informed consent for the use of their clinical and biologic data.

A total of 435 patients treated between 2000 and 2009 who fulfilled criteria were included on this study. Patients in the AZA001 study received AZA single agent 75 mg/m^2/d for 7 days, whereas combination therapies were used for patients in J9950 study (with phenylbutyrate) and the J0443 study (with entinostat) and for some patients in the French compassionate program. More details about the AZA regimens have been described in the related publications.[11,15-17] Because the doses and schedules were not homogeneous, AZA courses are described with the total dose per cycle, and we defined 500 mg/m^2/cycle (corresponding to 95% of the registered 75 mg/m^2/d for 7 days schedule) as the reference dose. The bone marrow blast count was determined at the initiation of AZA therapy. Cytogenetic risk was assessed on the basis of IPSS.[18]

Definition of AZA Failure

Response to initial AZA treatment had been assessed with International Working Group 2000 criteria.[19] A minimum of four cycles of AZA was planned for J9950 and J0443 studies, whereas six cycles minimum were planned for the other data sets. Response evaluations, including bone marrow aspirates, were scheduled each 8 weeks in the J9950, J0443, and AZA001 trials and each 12 weeks in the French compassionate program. Patients with signs of progressive disease were evaluated before the scheduled evaluation. Responding patients in all studies continued AZA until progression occurred. Date of AZA failure was defined by the date of the evaluation of response after the last cycle of AZA. Disease status at the end of AZA was categorized as stable disease in the absence of any response to AZA and no signs of progression; as progressive disease, if patients had lost their responses to AZA or had experienced progression during treatment; and as AZA intolerance if patients had stopped AZA because of adverse events, regardless of clinical response. Patients who stopped AZA for other reasons, including patients who underwent allogeneic transplantation while responding to AZA, were excluded from the analysis. Of note, response to salvage therapy was assessed according to International Working Group 2000 criteria for MDS and according to criteria by Cheson et al[20] for AML.

Table 1. Patients Demographic and Clinical Characteristics According to the Initial Cohorts

Characteristic	Total Population (N = 435) No.	%	Cohort JHU (n = 27) No.	%	AZA001 (n = 138) No.	%	French ATU (n = 270) No.	%
Median age, years	69		64		68		70	
Sex								
Ratio	1.9		2.8		2.6		1.7	
M	283		20		100		183	
F	152		7		38		109	
BM blasts before AZA, %								
< 10	83	16	5	14	11	8	67	25
10-19	219	51	16	47	89	64	114	42
≥ 20	133	33	6	39	38	28	89	33
Cytogenetics								
Favorable	146	35	5	22	60	43	81	30
Intermediate	104	25	14	47	35	25	55	20
High risk	185	40	8	31	43	31	134	50
First-line AZA treatment	351	81	9	57	131	95	211	78
AZA-based combination*	89	20	27	100	0		62	23
Cycle 1 dose of AZA > 500 mg/m^2	326	75	11	45	138	100	177	66
Median duration of AZA cycle, days	29		32		29		28	
Best response to AZA								
Hematologic improvement	127	30	8	30	49	36	70	26
Partial response	12	2	0		4	3	8	3
Complete response	34	7	0		2	1	32	11
Duration of AZA, No. of cycles								
≤ 6	251	60	21	67	65	47	165	61
7 to 12	123	27	4	22	42	30	77	29
> 12	61	13	2	10	31	22	28	10

NOTE. Cycle 1 dose of AZA indicates the total dose of AZA delivered during the cycle.

*The use of growth factors prior to AZA was not considered a significant treatment (n = 102).

Abbreviations: JHU, Johns Hopkins University trials (J9950 and J0443); AZA001, AZA001 trial; French ATU, French AZA compassionate program; BM, bone marrow; AZA, azacitidine.

Statistical Analysis

Data were summarized by frequency and percentage for categoric variables. For continuous variables, the median and range were computed. All results are presented with their 95% CIs. Statistical tests were two sided at the 5% level of significance. To investigate the association between continuous variables and categoric variables, univariate statistical analyses were performed by using the nonparametric Wilcoxon rank sum test, χ^2 test, or Fisher's exact test as appropriate. Survival rates were estimated by the Kaplan-Meier method. OS was measured from the date of AZA failure until death as a result of any cause, and observation ended at the date of last contact for patients last known to be alive. Patients without events were censored at the date of last follow-up. Multivariate analyses were performed by using a Cox proportional hazards method. All variables with

$P < .15$ in univariate analysis, with the exception of IPSS (which integrates several other analyzed variables) and number of cycle of AZA (which mostly overlaps with AZA response) were included in the Cox model with a stepwise procedure selection. Statistical analysis was performed with the R.2.3.0. software (R Development Core Team, Vienna, Austria).

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 1. Of the 435 study patients, 74% (n = 302) were treated for MDS, and 26% (n = 133) were treated for RAEB-T. Eighty-one percents of the patients (n = 351) had been treated with AZA as first-line therapy. This group included 102 patients who received growth factors (ie, erythropoietin with or without granulocyte colony-stimulating factor) before AZA. The remaining 19% patients had received prior therapy that consisted of chemotherapy (low-dose cytarabine, n = 28; AML-like induction chemotherapy, n = 42), steroids (n = 2), thalidomide derivatives (n = 4), allogeneic stem-cell transplantation (SCT, n = 5), and investigational agents (arsenic trioxide, sodium valproate and/or all-*trans* retinoic acid, n = 6). The median number of previous treatments before AZA was 1.[1-3] Table 2 lists the distribution of patients according to the type of treatment failure.

Of note, there were significantly fewer patients with AML after MDS and more previously untreated patients in the AZA001 cohort (Table 1). All patients from Johns Hopkins University, 23% in the French AZA compassionate use program cohort, and no patients in the AZA001 cohort received combination therapy. Most of the combination treatments were histone deacetylase (HDAC) inhibitors (n = 71, including valproic acid, phenylbutyrate, or entinostat). Other combination agents included chemotherapy (anthracyclines, hydroxyurea, gemtuzumab ozogamycin) or lenalidomide. Despite differences in patient characteristics, there was no difference in OS between the cohorts (Fig 1A).

OS After AZA Failure for Patients With High-Risk MDS

Median follow-up of the whole population was 15 months. Of the 435 patients who had high-risk MDS or RAEB-T (corresponding to US Food and Drug Administration and European Medicine Agency label of AZA; Table 3), 306 had died, and 129 were alive at last follow-up. Median OS was 5.6 months (95% CI, 5 to 7.2) and the probabilities of 1-year and 2-year survival were 28.9% (95% CI, 24.6% to 34.1%) and 15.3% (95% CI, 11.4% to 20.7%), respectively, as shown in Figure 1B. Prognostic factors of OS in univariate analysis included age at relapse (continuous variable, $P = .002$), male sex (median OS, 5.5 months for male patients *v* 8 months for women; $P = .04$), bone marrow blast count before AZA (median OS, 7.9 months and 5.2 months for patients with < 10% *v* 10% to 29%; $P = .04$), IPSS cytogenetic risk stratification (median OS, 8 months, 7.3 months, and 4.6 months for patients with favorable-risk *v* intermediate-risk *v* high-risk cytogenetics, respectively; $P = .002$) and

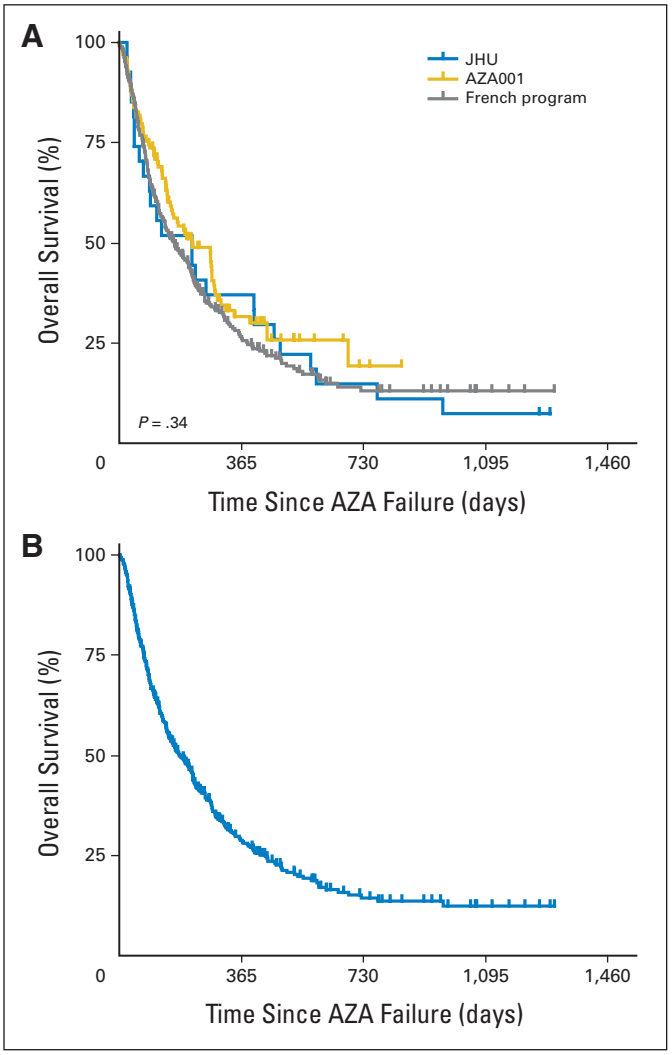


Fig 1. Kaplan-Meier estimates of the overall survival (OS) after azacitidine (AZA) failure. (A) Survival estimates for the different data sets. (B) Survival estimates for the myelodysplastic syndrome (MDS) population. The curves represent the survival estimates for the MDS and AML cohorts of patients and of the three independent data sets. Each tick mark represent a censored patient. There were no significant differences of survival among the Johns Hopkins University (JHU) study, the AZA001 study, and the French AZA compassionate use program (ie, French ATU); median OS times were 6.9 months, 7.1 months, and 5.6 months, respectively ($P = .34$ by log-rank test).

Table 2. Distribution of Patients According to the Type of Failure

Disease Status	Patients	
	No.	%
Primary failure*	229	55
Stable disease	91	24
Progressive disease	138	31
Secondary failure†	164	36
Failure after CR	32	7
Failure after PR	12	2
Failure after HI	120	27
AZA intolerance	42	9
Without ongoing response	29	6
During response to AZA	13	3

Abbreviations: CR, complete response; PR, partial response; HI, hematologic improvement, as defined by International Working Group 2000 criteria; AZA, azacitidine.
*Nonresponders.
†Prior response.

Table 3. Demographic and Clinical Characteristics of the Patients With High-Risk MDS

Characteristic	Patients With High-Risk MDS (n = 435)* No.	%	Survival After Failure (months)	P
Median age, years	69		—	.002
Sex				
Ratio	1.9			.03
M	283		5.5	
F	152		8	
Therapy-related MDS†				.16
Yes	67	18	4.6	
No			6.5	
MDS duration before AZA, years				.19
< 1	283	65	5.3	
1 to 2	58	13	7.1	
> 2	94	22	8.9	
Cytopenias‡				.8
0 or 1	72	20	7.5	
2 or 3	271	80	6.1	
BM blasts before AZA, %				.01
< 10	104	24	7.9	
10 to 29	331	76	5.2	
Cytogenetics§				.003
Favorable	146	34	8	
Intermediate	104	24	7.3	
High risk	185	42	4.6	
IPSS				.03
Intermediate 2	223	51	7	
High risk	212	49	4.6	
First-line AZA treatment				.94
Yes	351	81	6.5	
No			5.8	
AZA-based combination				.56
Yes	89	20	6.3	
No			5.9	
Cycle1 dose of AZA > 500 mg/m^2				.67
Yes	326	75	6.1	
No			5.3	
Median duration of AZA cycle, days				.19
Median	29			
≥ 29			6.1	
< 29			7.2	
Duration of AZA, cycles				.008
≤ 6	251	58	4.8	
7 to 12	123	28	8.4	
> 12	61	14	7.2	

Abbreviations: MDS, myelodysplastic syndrome; AZA, azacitidine; BM, bone marrow; IPSS, International Prognostic Scoring System.
*On the basis of US Food and Drug Administration approval of AZA, patients with former refractory anemia with excess blasts in transformation were included in the cohort of patients with high-risk MDS.
†Total, N = 379; unknown, n = 56.
‡Unknown, n = 82.
§Cytogenetic risk according to IPSS stratification.

Table 4. Analysis of Prognostic Factors of Survival After AZA Failure for Patients Treated for High-Risk MDS and Former RAEB-T

Variable	Univariate Analysis Median OS (months)	95% CI	P	Multivariate Analysis HR	95% CI	P
Age as continuous variable			.002	1.02 per year	1.01 to 1.03	.02
Sex						
Female	8	5.2 to 10.3	.04	1		.005
Male	5.5	4.7 to 6.8		1.42	1.12 to 1.82	
Cytogenetic risk						
Favorable	8	6.5 to 9.7	.003	1		
Intermediate	7.3	4.9 to 9.4		1.18	0.85 to 1.62	.32
High risk	4.6	3.7 to 5.8		1.96	1.48 to 2.59	< .001
BM blasts before AZA, %						
< 10	7.9	5.6 to 10.3	.01	1		.004
10-29	5.2	4.8 to 7.3		1.5	1.14 to 1.99	
Response to AZA						
No	4.6	3.9 to 6.3	.007	1		< .001
Yes	7.4	6.5 to 9.3		0.67	0.53 to 0.85	

NOTE. The International Prognostic Scoring System score and the number of cycles of AZA were not included in this analysis.
Abbreviations: AZA, azacitidine; MDS, myelodysplastic syndrome; RAEB-T, refractory anemia with excess blasts in transformation; OS, overall survival; HR, hazard ratio; BM, bone marrow.

response to AZA (median OS, 4.6 months for nonresponders *v* 7.4 months for patients with prior response; $P = .007$). There was no effect of MDS duration, prior treatment exposure, or initial schedule of AZA (eg, cycle dose or association with other drugs). In the Cox model (Table 4), older age at relapse, male sex, bone marrow blast count greater than 10% before AZA, high-risk cytogenetics, and initial response to AZA remained significantly associated with shorter OS.

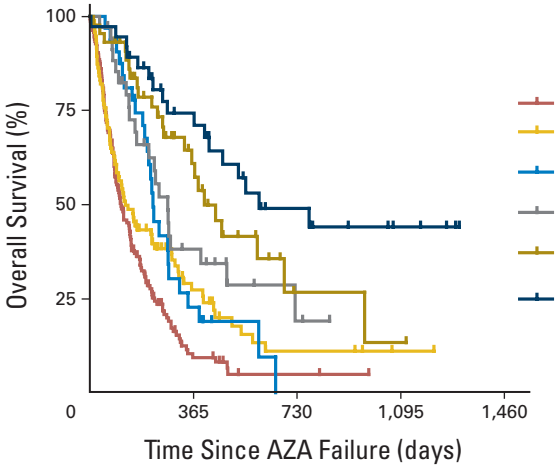
Among initial responders to AZA, older age ($P = .08$), high-risk cytogenetics ($P = .03$), and a low number of administered cycles of AZA ($P = .13$) were associated with a poorer outcome after treatment failure. The initial percentage of marrow blasts, male sex, or the type of response (complete or partial response *v* HI) had no impact on survival after progression (data not shown).

Management of AZA Failure

Information on treatment given after failure of AZA was available in 270 patients (Fig 2). Patient characteristics differed between treatment groups (eg, younger patients and less advanced diseases received the more aggressive approaches; data not shown).

Patients with unknown salvage or best supportive care (BSC) had the worst prognoses (median OS, 4 months). Poor outcome also was seen in those who received low-dose chemotherapy (n = 32, including hydroxyurea, mercaptopurine, low-dose cytarabine, low-dose melphalan), with a response rate of 0% (0 of 18 patients) and a median survival of 7.3 months. Patients treated with intensive AML-like chemotherapy (n = 35) also had a poor outcome, with 14% (three of 22 patients) as the overall response and 8.9 months as the median survival. There was no significant difference of survival between these two groups ($P = .21$), and only patients treated with intensive chemotherapy had a better outcome than those who received BSC ($P = .38$ for low-dose chemotherapy and $P = .04$ for intensive chemotherapy).

Forty-four patients received investigational therapies (ITs), including epigenetic agents (ie, DNMT inhibitor alone or in combination with HDAC inhibitor [n = 17] or HDAC inhibitors–based regimen [n = 14]), thalidomide derivatives (ie, lenalidomide



Type of salvage	N	ORR	Median OS (months)
Unknown	165	NA	3.6
Best supportive care	122	NA	4.1
Low-dose chemotherapy	32	0/18	7.3
Intensive chemotherapy	35	3/22	8.9*
Investigational therapy	44	4/36	13.2*†
Allogeneic transplantation	37	13/19	19.5*†

Fig 2. Survival analysis according to the salvage treatment regimens. Overall response rate for each treatment group is presented with the number of patients evaluable for response in each cohort. (*) Univariate analysis (log-rank test) showed significant differences between palliative care and intensive chemotherapy (CT; $P = .04$), investigational therapy (IT; $P < .001$), or allogeneic stem-cell transplantation (ASCT; $P < .001$). (†)There was also a significant difference between intensive CT and IT ($P = .05$) and intensive CT and ASCT ($P = .008$). The difference between IT and ASCT reached borderline significance ($P = .09$). AZA, azacitidine; NA, not applicable; ORR, overall response rate; OS, overall survival.

or thalidomide, n = 5), treatments for patients on clinical trials evaluating nonregistered drugs (n = 8, including immunotherapy, bryostatin,[21] triapine,[22] farnesyl transferase inhibitors,[23] and mammalian target of rapamycine inhibitors). The median OS of this group was13 months, which was better than the OS of patients who received low-dose chemotherapy ($P = .05$), intensive chemotherapy ($P = .05$), or palliative care ($P < .001$). Interestingly, among the 17 patients re-treated with DNMT inhibitors (including 16 of 17 received decitabine), none of 10 evaluable patients achieved complete or partial response, and the median OS was 11.8 months.

Finally, 37 patients (14%) were treated with allogeneic SCT after a median of 5 months (range, 1 to 26 months) after AZA failure. Twenty-eight patients underwent transplantation up front (including 14 with progressive disease), and nine underwent transplantation after one or more salvage treatments (including AML-like chemotherapy in seven patients and/or investigational agents in four patients). Their median survival was 19 months and was significantly superior to that of other treatments. Five patients were alive greater than 3 years after transplantation. The median OS of the 14 patients who underwent transplantation with progressive disease after AZA was 17 months and was not reached in the 14 patients who underwent transplantation with stable disease after AZA ($P = .08$).

DISCUSSION

This report is the first to present the outcome of a large series of patients with MDS patients who were treated with AZA and whose disease failed to respond or progressed after an initial clinical response. This work is based on the compilation of four data sets, including three clinical trials and the French AZA compassionate use program. The median OS of 5.6 months for high-risk MDS confirmed the poor outcome of these patients. The results of our multivariate model showed that simple clinical and biologic characteristics, including age, sex, cytogenetics, initial bone marrow blast count before AZA, and initial response to AZA, can predict the outcome after failure of AZA treatment. Conventional treatment, such as BSC or cytotoxic drugs, appeared to be of little benefit for such patients.

Our survival analysis results resemble those of Jabbour et al[12] after failure of decitabine, in which a median OS and 1-year probability of survival were reported. The M.D. Anderson MDS scoring system[13] predicted survival in that cohort. This score includes age, bone marrow blast count, and cytogenetics, which also had prognostic value in our series. The initial response to AZA also had an impact on survival after failure. This raises interesting issues regarding possible effects of AZA, including, as suggested by others, a possible modification of the MDS natural history.[11,24]

A variety of salvage regimens were administered to patients in the current cohort, although information regarding salvage treatment was missing for many of them. Outcome after any type of treatment appeared better than supportive care, though, which possibly reflected patient selection. Allogeneic transplantation remained the option with the best outcome, with long-term survival in a substantial proportion of patients even if some patients underwent transplantation with progressive disease. Of note, we were not able to analyze the choice of conditioning regimen, which plays an important role for patients with MDS and AML.[25] Likewise, the improved outcome with investigational treatments (ITs) may in part reflect patient selection and closer monitoring associated with enrollment on clinical trials. These findings are also in line with the results from the M.D. Anderson experience after decitabine failure[12,26] that showed response rates of 20% to 30% with IT, which was comparable with results of intensive chemotherapy. Dedicated studies for each type of treatment will be necessary to refine the response rates and prognosis factors associated with each group of patient. This will also include studies for patients with low-risk MDS and de novo AML, two indications for which AZA is currently increasingly used.[27-30]

Finally, this study is also important in the perspective of designing future clinical trials in this population. We suggest that the survival of patients treated with palliative care (median OS, 4.1 months; 1-year probability of OS, 17%; 95% CI, 14.3% to 26.1%) should be considered as the most relevant reference, because no standard treatment is currently available.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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