Original Article

Overall Survival of Myelodysplastic Syndrome Patients After Azacitidine Discontinuation and Applicability of the North American MDS Consortium Scoring System in Clinical Practice

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BACKGROUND: Azacitidine (AZA) is the standard treatment for myelodysplastic syndromes (MDS); however, many patients prematurely stop therapy and have a dismal outcome. **METHODS:** The authors analyzed outcomes after AZA treatment for 402 MDS patients consecutively enrolled in the Italian MDS Registry of the Fondazione Italiana Sindromi Mielodisplastiche, and they evaluated the North American MDS Consortium scoring system in a clinical practice setting. **RESULTS:** At treatment discontinuation, 20.3% of the patients were still responding to AZA, 35.4% of the cases had primary resistance, and 44.3% developed adaptive resistance. Overall survival (OS) was better for patients who discontinued treatment while in response because of planned allogeneic hematopoietic stem cell transplantation (HSCT; median OS, not reached) in comparison with patients with primary resistance (median OS, 4 months) or adaptive resistance (median OS, 5 months) or patients responsive but noncompliant/intolerant to AZA (median OS, 4 months; $P = .004$). After AZA discontinuation, 309 patients (77%) received best supportive care (BSC), 60 (15%) received active treatments, and 33 (8%) received HSCT. HSCT was associated with a significant survival advantage, regardless of the response to AZA. The North American MDS Consortium scoring system was evaluable in 278 of the 402 cases: patients at high risk had worse OS than patients at low risk (3 and 7 months, respectively; $P < .001$). The score was predictive of survival both in patients receiving BSC (median OS, 2 months for high-risk patients vs 5 months for low-risk patients) and in patients being actively treated (median OS, 8 months for high-risk patients vs 16 months for low-risk patients; $P < .001$), including transplant patients. **CONCLUSIONS:** Real-life data confirm that this prognostic scoring system for MDS patients failing a hypomethylating agent seems to be a useful tool for optimal prognostic stratification and for choosing a second-line treatment after AZA discontinuation. ***Cancer* 2021;127:2015-2024**. *© 2021 American Cancer Society*.

KEYWORDS: azacitidine, myelodysplastic syndromes (MDS), prognostic scoring system.

INTRODUCTION

The hypomethylating agent (HMA) azacitidine (AZA) induces hematological and cytogenetic responses in a good proportion of patients with myelodysplastic syndromes (MDS) and prolongs survival in comparison with conventional

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33472, **Received:** October 20, 2020; **Revised:** December 7, 2020; **Accepted:** December 16, 2020, **Published online** March 19, 2021 in Wiley Online Library (wileyonlinelibrary.com)

care.[1] Currently, AZA represents the standard of care for higher risk MDS, especially in Europe. However, discontinuation of HMA therapy is invariably followed by a loss of response, disease progression, and short survival.[2-7] New experimental agents may be proposed for patients who have failed an HMA, and it is crucial to select those patients who may benefit from second-line treatments.

Recently, a predictive model for evaluating survival after AZA failure was developed; it considers several variables, including age, marrow blasts, Eastern Cooperative Oncology Group (ECOG) score, cytogenetics, transfusion dependence, and platelet counts at the time of AZA discontinuation.[8] The score was validated later by the same group in a phase 3 randomized controlled trial[9] and retrospectively by the Groupe Francophone des Myelodysplasies[10] and by the Hellenic Myelodysplastic Syndrome Study Group[11] in a population of HMA-resistant or -intolerant patients.

Here we present the results of a retrospective study of nonselected MDS patients enrolled in the Italian MDS Registry of the Fondazione Italiana Sindromi Mielodisplastiche, which has been approved by each Center institutional review committee. We evaluate the rates of AZA therapy and the reasons for its interruption as well as subsequent therapeutic choices, and we provide an analysis of prognostic factors and outcomes after drug discontinuation. In particular, we validate the North American MDS Consortium scoring system in a clinical practice setting.

MATERIALS AND METHODS

Data were entered prospectively into the Italian MDS Registry of the Fondazione Italiana Sindromi Mielodisplastiche, which has been approved by each Center istitutional review committee. We selected on purpose MDS cases treated with AZA in a period in which clinical studies with experimental drugs were not easily available to evaluate standard treatments, as in real-life practice, outside clinical trials. The data lock for analysis was established to be December 2018. Patients treated with at least 1 course of AZA were included in this analysis. The considered schedules of AZA therapy were 75 mg/m^2/d subcutaneously for 7 consecutive days on a 28-day cycle and 75 mg/m^2/d (5-2-2) on a 28-day cycle. Informed consent was obtained from all patients at the moment of enrollment into the registry and before AZA therapy.

Responses to AZA and to salvage treatments were defined according to the 2006 International Working Group criteria for MDS.[12] The disease status at the end of AZA was categorized as a response in the case of a complete response (CR), a partial response (PR), or stable disease (SD) with hematological improvement (HI) after a minimum of 4 cycles of AZA; as primary resistance in the case of an absence of response after at least 6 cycles of AZA or progressive disease (PD) before the achievement of any response; and as secondary resistance or adaptive resistance in the case of a loss of response or progression during treatment after the achievement of a response.

Patients were defined according to the North American MDS Consortium scoring system[8] as high-risk if a minimum score of 2.25 was reached and as low-risk if the score was less than 2.25; the worst case scenario was considered if information was partially missing.

Statistical Analysis

Dichotomous variables were compared with the χ^2 test or the Fisher exact test when necessary. Continuous variables were compared with the Student *t* test or, if a normal distribution could not be confirmed, with the Wilcoxon rank test.

Overall survival (OS) was calculated from the time of discontinuation to death by any cause or last follow-up. The survival analysis was performed with the Kaplan-Meier method, and any statistical difference between curves was assessed with log-rank tests. A Cox proportional hazards model, including only the variables that respected a proportional risk assumption, was built for each multivariate survival analysis.

The cumulative incidence of AZA discontinuation and leukemic evolution at various time points was calculated in a competing risk analysis considering death without discontinuation as a competing event.

Competing risk analyses were performed with the Fine and Gray subdistribution relative hazard method, and comparisons were made with the Gray test and R statistical software.

All 2-tailed *P* values $< .05$ were considered statistically significant.

RESULTS

Patients

From January 2009 to June 2014, 1799 MDS patients were enrolled in the registry, and 414 of them received AZA: 283 received it as a first-line treatment (68%), and 131 received it as second-line or further therapy, mainly after the failure of an erythropoiesis-stimulating agent treatment and progression to higher risk (28%). Patients receiving first-line chemotherapy or decitabine (off-label use in Europe) were excluded from the analysis.

The median age of the patients treated with AZA was 73 years (range, 18-91 years), and 256 patients (62%)

TABLE 1. Patient Characteristics at the Start of AZA

Variable	No. (% of Evaluable Patients)
MDS patients treated with AZA	414
Age, median (range), y	73 (18-91)
Male/female	256 (62)/158 (38)
Diagnosis according to WHO 2008	
RA/RARS	20 (5)
RCMD (± RS)	47 (11)
RAEB-1	106 (26)
RAEB-2	232 (56)
Other	9 (2)
ECOG score	
0	144 (46)
1	113 (36)
2	47 (15)
3	5 (2)
4	4 (1)
Not reported	101
IPSS score	
Low	20 (6)
Intermediate-1	100 (24)
Intermediate-2	233 (56)
High	51 (12)
Not available	10 (2)
RBC transfusion dependence	
Yes	243 (59)
No	166 (41)

Abbreviations: AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts; RBC, red blood cell; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts; WHO, World Health Organization.

were male. The diagnosis according to the 2008 World Health Organization classification[13] was refractory anemia or refractory anemia with ring sideroblasts in 20 patients (5%), refractory cytopenia with multilineage dysplasia with or without ring sideroblasts in 47 patients (11%), refractory anemia with excess blasts type 1 in 106 patients (26%), refractory anemia with excess blasts type 2 in 232 patients (56%), and other subtypes in 9 patients (2%; Table 1).

When AZA therapy was initiated, the International Prognostic Scoring System (IPSS) score[14] was low for 20 patients (6%), intermediate-1 for 100 patients (24%), intermediate-2 for 233 patients (56%), high for 51 patients (12%), and not evaluable for 10 patients (2%). Two hundred forty-three patients (59%) had transfusion-dependent anemia. Patients with low/intermediate-1 IPSS scores were mainly treated for a high transfusion burden or other life-threatening cytopenia.[15] Table 1 summarizes patients' characteristics before the inception of AZA therapy.

Response to AZA and Outcome

A response to AZA was evaluable according to the International Working Group in 373 of the 414 patients (90%) who completed at least 4 cycles of treatment. Two hundred one (54%) responded to treatment after a median of 6 courses (range, 4-11 courses), with 48 of the 373 patients achieving a CR (13%), 84 achieving a PR (23%), 69 achieving HI (18%), and 56 achieving SD. One hundred seventy-two patients (46%) did not achieve a response at any time during treatment; 56 of these patients had SD without HI, and 116 had PD.

OS after AZA discontinuation was significantly longer for patients who achieved a CR, regardless of their disease status at AZA discontinuation, with a median survival of 8 months and with 25% of the patients still alive at 2 years, in comparison with patients with a response less than a CR (median OS, 5.5, 4, and 3.9 months for PR, SD, and PD, respectively; 2-year survival rate, 15%, 10%, and 7% for PR, SD, and PD, respectively). This difference was observed even with the censoring of transplant patients at the time of allogeneic hematopoietic stem cell transplantation (HSCT; $P = .014$).

On the contrary, the IPSS score at the start of AZA, the treatment duration, and the response duration did not affect outcomes after discontinuation.

Causes of AZA Discontinuation, Disease Response, and Outcome

The median follow-up from the first AZA cycle was 84.5 months (range, 79.5-89.5 months). At the time of the data lock (2018), 402 of the 414 patients had discontinued AZA after a median of 8 cycles (range, 1-72 cycles); 33% (n = 135) had discontinued AZA before completing 6 cycles. The cumulative incidence of AZA discontinuation was 64.3%, 84.3%, and 92.7% at 12, 24, and 36 months, respectively, and the median time to drug discontinuation was 8.3 months.

At the moment of AZA discontinuation, the median age was 75 years, and 27% of the patients had an ECOG score > 2. The main clinical and hematological parameters at AZA discontinuation are summarized in Table 2.

The median OS after AZA discontinuation was 4 months, with 12% of the patients alive at 2 years.

Forty-three patients discontinued AZA before completing 4 cycles because of early death (n = 9), intolerance (n = 4), severe toxicity (n = 17; mostly infective episodes), or progression (n = 13).

The main reason for treatment discontinuation reported by the clinicians was defined as failure, which occurred in 70.4% of the patients (n = 283). Other reported reasons for discontinuation were adverse events in 20.9% of cases (n = 84; after a median of 5 cycles), including infections, solid neoplasia, and extrahematological toxicities

TABLE 2. Patient Characteristics at AZA Discontinuation

Variable	No. (% of Evaluable Patients)
Patients who discontinued AZA	402 (97)
Age, median (range), y	75 (19-93)
ECOG score	
0	12 (3)
1	62 (17)
2	197 (53)
3	97 (26)
4	4 (1)
Not reported	30
RBC transfusion dependence	
Yes	303 (81)
No	73 (19)
Not reported	26
Platelets < 30000/μl	
Yes	192 (51)
No	184 (49)
Not reported	26
BM blasts	
<5%	76 (20)
5%-20%	163 (44)
>20%	136 (36)
Not reported	27
Complex karyotype	
Yes	29 (34)
No	57 (66)
Not reported	316

Abbreviations: AZA, azacitidine; BM, bone marrow; ECOG, Eastern Cooperative Oncology Group; RBC, red blood cell.

related or unrelated to AZA. A lack of compliance was reported in 3.5% of the cases (n = 14; after a median of 6 cycles), and planned HSCT was reported for 5.2% of the patients (n = 21; after a median of 5 cycles; only 20 of the 21 patients underwent transplantation).

When we considered the response status at AZA discontinuation, which was evaluable in 359 patients, 127 patients had PD or SD without HI (35.4%), and 66 of these patients (52%) had progressed to acute myeloid leukemia (AML; after a median of 5 cycles); 159 patients (44.3%) relapsed or progressed (n = 75) after they had achieved a response and had completed a median of 12 cycles (Fig. 1).

Fifty-nine percent of the resistant patients (75 of 127) did not complete 6 cycles (range, 4-5 cycles): 43 because of AML progression, 2 because of early death, and 30 because of severe toxicity in the absence of a response.

Seventy-three patients stopped AZA while still responding after having received a median of 10 cycles (Fig. 1).

The median OS after discontinuation for patients with primary and adaptive resistance was 4 and 5 months, respectively. Long-term survival was significantly better for patients who discontinued treatment while in response in comparison with patients with primary or adaptive resistance ($P = .004$). However, the outcomes of patients who stopped AZA while in response were quite heterogeneous. In fact, 75% of the patients who discontinued treatment because of an adverse event (n = 45 [including 7 early deaths not related to MDS]) or noncompliance (n = 10) had a poor outcome with a median survival of 4 months (similar to the OS of resistant patients), whereas 18 patients who discontinued AZA to undergo planned HSCT had the best outcome with the median survival not reached and a 5-year survival rate of 56% ($P < .001$; Fig. 2).

Notably, the median age of the patients who discontinued AZA while in response because of intolerance or adverse events was 77 years, whereas the median age was 58 years for patients who stopped treatment because of planned HSCT and 73 years for patients experiencing failure ($P < .001$). The main characteristics of the patients according to their responses at AZA discontinuation are described in Supporting Table 1.

OS After AZA Discontinuation According to the North American MDS Consortium Scoring System

We could calculate the scoring system proposed by Nazha et al[8] for 278 of the 402 patients.

Patients at high risk according to the score had a median OS of 3 months versus 7 months for patients at low risk ($P < .001$; Fig. 3A).

The North American score could identify high-risk patients among those who stopped treatment in the absence of a response (median OS, 3 months for high-risk patients vs 7 months for low-risk patients; $P < .001$), but this did not reach significance in the group of patients who discontinued treatment while in response ($P = .165$).

Moreover, the score was predictive of survival not only in patients receiving best supportive care (BSC; median OS, 2 and 5 months for high- and low-risk patients, respectively; $P < .001$; Fig. 3B) but also in patients who received active treatment (median OS, 8 and 16 months for high- and low-risk patents, respectively; $P = .001$; Fig. 3C), including transplant patients (Fig. 3D).

For 197 of the 402 patients, 1 or more variables were missing (cytogenetics at AZA discontinuation in 99% of the cases); nevertheless, as mentioned previously, scoring was still possible.

The median OS of the 124 patients for whom the score was not evaluable was similar to that of the high-risk patients (4 months; Supporting Fig. 1). This was probably due to the fact that this group of patients shared with the high-risk group some poor prognostic features that

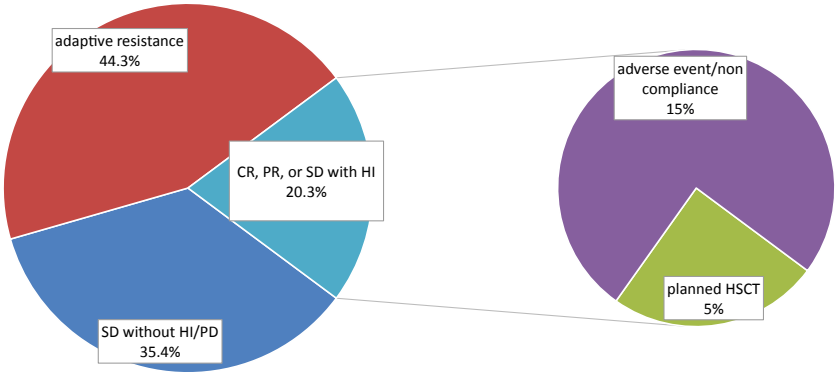

Figure 1. Response to azacitidine at treatment discontinuation. CR indicates complete response; HI, hematological improvement; HSCT, allogeneic hematopoietic stem cell transplantation; PD, progressive disease; PR, partial response; SD, stable disease.

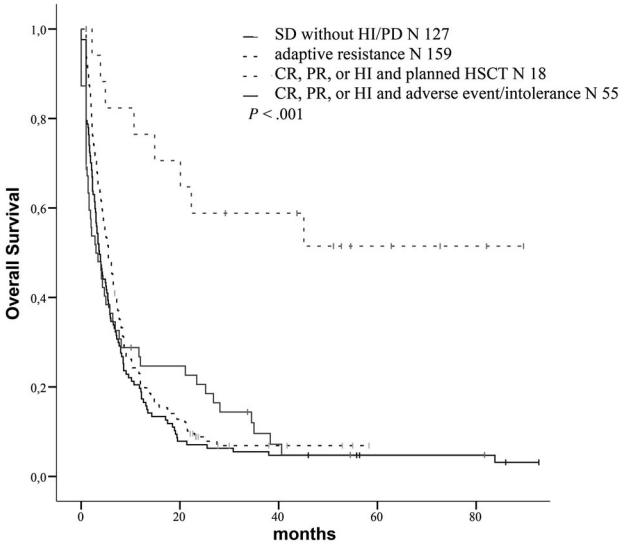

Figure 2. Overall survival after azacitidine discontinuation according to the response at discontinuation. Patients who discontinued azacitidine while in response are further classified according to the causes for discontinuation. CR indicates complete response; HI, hematological improvement; HSCT, allogeneic hematopoietic stem cell transplantation; PD, progressive disease; PR, partial response; SD, stable disease.

strongly affected the score calculation. In fact, 88% of them had an ECOG score ≥ 2, 50% were older than 75 years, and 45% progressed to AML.

OS After AZA Discontinuation According to Subsequent Salvage Therapy

After AZA discontinuation, the majority of the patients (309 [77%]) received BSC, 29 (7%) received low-dose chemotherapy (LDC; hydroxyurea [n = 20], low-dose cytarabine [n = 7], or lenalidomide [n = 2]), 14 (3%) were treated with AML-like intensive chemotherapy (IC), 15 (4%) received other treatments, and 35 (9%) underwent HSCT (characteristics of the patients in the different treatment groups are described in Table 3).

A higher proportion of patients was actively treated if AZA was interrupted in the absence of a response (77% of the patients received BSC, 9% received LDC, 6% received HSCT, 4% received IC, and 4% received other therapies) in comparison with the group of patients responsive to AZA who discontinued treatment because of intolerance of adverse events (92% received BSC, 2% received IC, 2% received LDC, and 4% received other therapies; $P < .001$).

Overall, 35 patients underwent HSCT: 28 as part of the frontline planned management and 7 as salvage treatment upfront or after second-line IC (Supporting Fig. 2). Initially, AZA was planned as a bridge to HSCT for 30 patients, but 2 died before getting to transplantation (1 of AML and 1 of bladder cancer); however, the median OS in this group in an intention-to-treat analysis was 21 months with a 5-year survival rate of 36%.

Eighteen of the 28 patients who were treated with AZA as a bridge to HSCT had achieved a clinical response with AZA, but only 14 of them were in response at the time of transplantation (4 with a CR, 5 with a PR, and 5 with HI). Ten patients failed to respond to pre-HSCT AZA treatment but nonetheless underwent HSCT: 6 directly and 4 after a further chemotherapy course. Among the 7 transplant-eligible patients for whom HSCT was not planned at the start of AZA (because of a lack of a donor or the patient's decision) but for whom it was the salvage therapy after HMA failure,

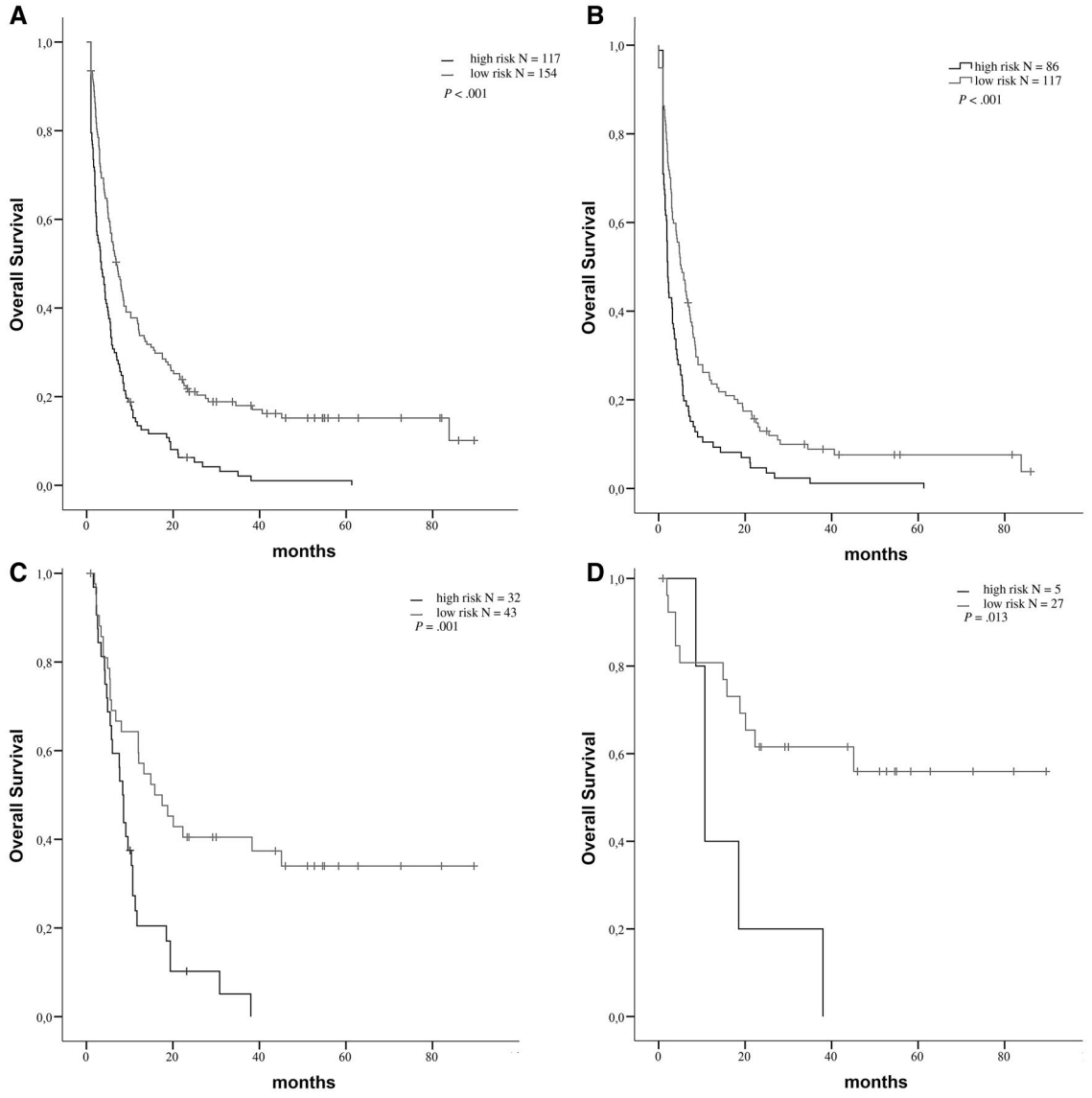

Figure 3. Overall survival after azacitidine discontinuation according to the Nazha scoring system (high risk vs low risk): (A) whole study population, (B) patients receiving best supportive care, (C) all treated patients, and (D) patients who underwent allogeneic hematopoietic stem cell transplantation.

only 5 were treated with chemotherapy and achieved a response before transplantation (1 with a CR, 2 with a PR, and 2 with HI).

When we analyzed the outcomes according to subsequent therapy after AZA discontinuation, HSCT was associated with a significant survival advantage both in patients who discontinued treatment because of a lack/loss of response (median OS, 19 months for HSCT vs 6 months for IC, 7 months for LDC, and 4 months for BSC; $P < .001$) and in patients who stopped AZA because of planned HSCT or reasons other than AZA failure, such as toxicity or poor compliance (median OS, not reached for HSCT vs 3 months for BSC [not available for other treatments because of small numbers]; $P = .001$; Fig. 4).

Notably, patients who underwent HSCT were younger (median age, 61 years vs 70 years for the IC group and 75 years for the other treatment groups; $P < .001$) and had an ECOG score < 2; moreover, 52% of these patients had responded to AZA, and 84% were at low risk according to the North American MDS Consortium scoring system (Table 3).

On the other hand, IC was the salvage treatment for patients who had already progressed to AML in 86% of

TABLE 3. Clinical Characteristics at AZA Discontinuation According to the Treatment Received After AZA Discontinuation

Variable	Treatment Received After AZA Discontinuation, No. (%)					
	BSC (n = 309)	HSCT (n = 35)	LDC (n = 29)	IC (n = 14)	Other Therapy (n = 15)	*P*
Age, median, y	75	61	75	70	75	<.001
Disease status						<.001
Failure	220 (81)	16 (47)	26 (96)	12 (92)	12 (86)	
Any response	51 (19)	18 (53)	1 (4)	1 (8)	2 (14)	
NA	38	1	2	1	1	
ECOG score						<.001
0	2 (1)	9 (27)	0	1 (7)	0	
1	43 (15)	12 (36)	6 (21)	0	1 (7)	
2	155 (55)	12 (36)	13 (45)	8 (57)	9 (64)	
3	80 (28)	0	10 (34)	5 (36)	3 (21)	
4	3 (1)	0	0	0	1 (7)	
NA	26	2	0	0	1	
BM blasts						.032
<5%	60 (20)	8 (23.5)	2 (7)	0	6 (40)	
5%-20%	127 (43)	16 (47)	12 (41)	2 (14)	6 (40)	
>20%	106 (36)	10 (29.5)	15 (52)	12 (86)	3 (20)	
NA	16	1	0	0	0	
Transfusion dependence						<.001
Yes	234 (82)	18 (53)	24 (83)	14 (100)	14 (93)	
No	51 (18)	16 (47)	5 (17)	0	1 (7)	
NA	24	1	0	0	0	
North American MDS Consortium scoring system						<.001
High	86 (42)	5 (16)	15 (65)	8 (80)	4 (40)	
Low	117 (58)	27 (84)	8 (35)	2 (20)	6 (60)	
NA	106	3	6	4	5	

Abbreviations: AZA, azacitidine; BM, bone marrow; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; HSCT, allogeneic hematopoietic stem cell transplantation; IC, intensive chemotherapy; LDC, low-dose chemotherapy; NA, not available.

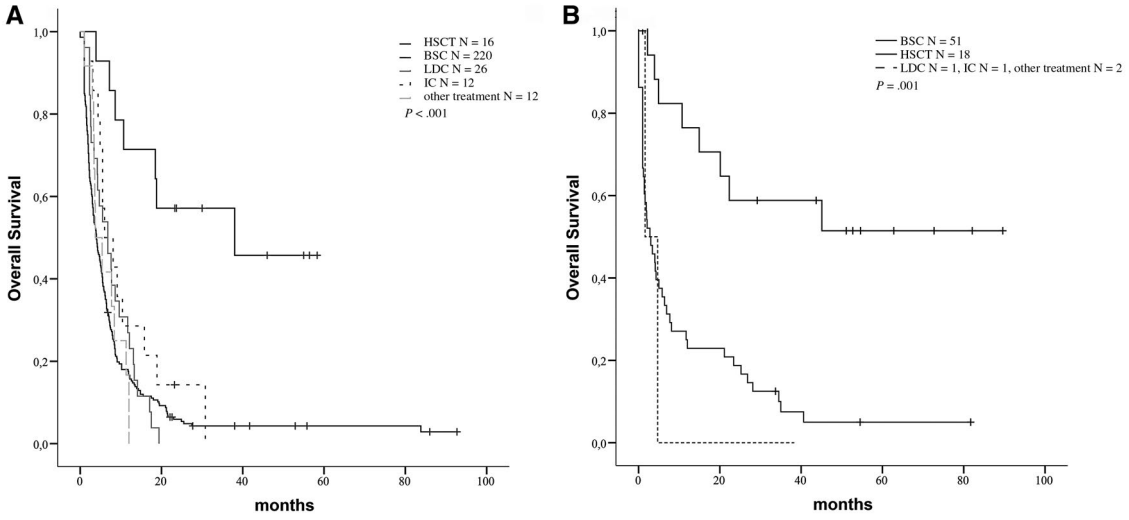

Figure 4. Overall survival after azacitidine discontinuation according to subsequent treatment: (A) patients who discontinued azacitidine after treatment failure and (B) patients who discontinued azacitidine while in response. BSC indicates best supportive care; HSCT, allogeneic hematopoietic stem cell transplantation; IC, intensive chemotherapy; LDC, low-dose chemotherapy.

TABLE 4. Univariate and Multivariate Analyses of Variables Affecting Survival After AZA Discontinuation

Variable	Univariate	HR (95% CI)	Multivariate	HR2 (95% CI)
Age (continuous variable)	**<.001**	**1.036 (1.023-1.048)**	**.001**	**1.023 (1.018-1.039)**
Female sex	.775	1.032 (0.834-1.276)	—	—
Low to INT-1 IPSS at start of AZA	.918	1.011 (0.816-1.254)	—	—
Response to AZA (CR)	**<.001**	1.192 (1.091-1.302)	.383	1.038 (0.927-1.099)
BM blasts < 5% at AZA discontinuation	.001	1.290 (1.114-1.494)	.659	1.062 (0.897-1.232)
Transfusion dependence at AZA discontinuation	**<.001**	**2.225 (1.660-2.983)**	**.006**	**1.579 (1.201-2.197)**
Platelets < 30,000/mm^3 at AZA discontinuation	**<.001**	1.460 (1.182-1.805)	.389	1.136 (0.899-1.402)
ECOG score at suspension > 0	**<.001**	**1.863 (1.607-2.160)**	**<.001**	**1.603 (1.398-1.973)**
Duration of response (continuous variable)	.840	0.998 (0.983-1.014)	—	—
No. of AZA cycles (continuous variable)	.074	0.990 (0.980-1.001)	—	—

Abbreviations: AZA, azacitidine; BM, bone marrow; CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HR2, hazard ratio 2; INT-1, intermediate-1; IPSS, International Prognostic Scoring System.
In bold statistically significant variables.

the cases and were at high risk according to Nazha et al[8] in 80% of the cases.

Prognostic Factors Affecting OS in a Multivariate Analysis

In a multivariate analysis, older age (HR for every year of age, 1.023; $P < .001$), transfusion dependence (HR, 1.579; $P < .01$), and a higher ECOG score (HR, 1.603; $P < .001$) at the time of AZA discontinuation were correlated with shorter survival, whereas the blast count and a response to AZA or treatment duration were not. Univariate and multivariate analyses of factors affecting survival after AZA discontinuation are reported in Table 4.

Progression-Free Survival and AML Evolution

Leukemic evolution was reported in 196 of the 402 patients (49%). The cumulative risk of leukemic evolution was 20.8% at 12 months for the whole cohort. The risk of leukemic evolution was significantly lower in patients receiving scheduled HSCT (12-month cumulative incidence of leukemic evolution, 5.9% for patients receiving frontline HSCT vs 28% for patients not receiving frontline HSCT; $P < .001$).

DISCUSSION

The management of long-term AZA treatment is a major clinical challenge. This registry study reflects nationwide clinical practice in Italy and confirms an extremely dismal outcome for MDS patients after AZA discontinuation.[3-8] It has been recently reported that OS after AZA discontinuation does not differ according to the causes of discontinuation considering resistance or intolerance.[11] In contrast to other reports, we have evaluated the impact of the presence of a response at the moment of AZA discontinuation on patient outcomes.

In fact, in our study, 44.3% of the patients for whom a response was evaluable stopped treatment because of adaptive resistance, and 35.4% stopped treatment because of primary resistance; unexpectedly, 20.3% stopped treatment while in clinical response. Interestingly, patients who discontinued treatment for intolerance or adverse events despite being in response had the same dismal outcome as patients with primary or adaptive resistance.

Overall, severe myelotoxicity, infectious complications (21%), or poor compliance (3%) led to premature discontinuation of AZA, as reported in other patient series.[3,5,16] The infection rate may have been related to nonuniform use of antibacterial and antifungal prophylaxis,[17] which is important for preventing infective episodes and keeping patients on treatment.

Because the totality of MDS patients treated with AZA will eventually lose their response, predicting their survival after AZA interruption may help to plan an optimal rescue. In this study, we validated the North American MDS Consortium scoring system in a cohort of unselected MDS patients who discontinued AZA for different reasons and evaluated its applicability in a clinical practice setting, in which some of the required variables are frequently missing.

We could calculate the score for 69% of the patients, even if there was missing information for 70% of the cases. The absence of cytogenetic data, which was extremely frequent in our cohort, reflected the clinical practice of avoiding marrow aspiration procedures in elderly patients when concrete treatment options are lacking. On the other hand, the residual data needed to calculate the score (age, ECOG score, transfusion dependence, and platelet count) are easy to collect, and this makes the score easy to apply in routine clinical practice.

We confirmed the efficacy of the Nazha scoring system in predicting survival in patients who failed HMA but quite importantly not in patients who discontinued AZA with an ongoing response.

We showed that the score was predictive of survival not only in patients receiving BSC but also in patients who received a second-line treatment, including HSCT. Therefore, it should be used to direct treatment allocation and risk stratification in clinical trials after AZA failure.

As for post-AZA treatment, the great majority of these patients (74%) were offered supportive care only, probably because of age (50% were older than 75 years), complications, and/or a poor clinical status (27% of the patients had an ECOG score > 2). The survival of patients treated with BSC was only slightly worse than that of patients receiving active treatment (either AML-like IC or LDC). Only a select group of younger patients (median age, 61 years) underwent HSCT, and their good outcomes were consistent with what had been previously observed,[3,5] even when it was used as salvage therapy. Twenty-eight of the 30 patients for whom AZA was the planned bridge to HSCT eventually underwent transplantation with an acceptable 5-year survival rate of 36%, even though 30% experienced AML progression. Our data suggest that eligible MDS patients should always be offered HSCT before or early after the start of AZA.[18,19]

Finally, our study showed that 70% of the patients who received BSC after AZA failure had an ECOG score ≤ 2, which may have allowed their inclusion in nonintensive therapeutic programs. It is important to stress the relevance of the complete re-evaluation of the patient at relapse, including careful screening for somatic mutations[20] that may be actionable.[21-24]

In conclusion, the approach to patients who have discontinued AZA for any reason should be complete and include a reassessment of patients' fitness and disease characteristics, including somatic mutations, in order to offer the optimal subsequent treatment. Younger patients may benefit from HSCT, whereas unfit patients may possibly be treated with target therapies or experimental studies. The proposed new prognostic scoring system for MDS patients who stop AZA because of failure may be the best way to proceed for optimal prognostic stratification, for guiding the choice of a second-line treatment, including HSCT, or for more rational allocation and risk stratification of patients in clinical trials.

FUNDING SUPPORT

FISiM received support by Celgene Corporation to carry on the analysis.

CONFLICT OF INTEREST DISCLOSURES

Carlo Finelli reports grants and personal fees from Celgene/BMS and personal fees from Novartis outside the submitted work. Monica Crugnola reports honoraria from and membership in speakers' bureaus for Novartis and Incyte. Esther N. Oliva reports personal fees from BMS, Alexion, Apellis, AbbVie, Amgen, and Novartis outside the submitted work. Emanuele Angelucci reports personal fees from Novartis, Celgene, Vertex Pharmaceuticals, CRISPR Therapeutics, Bluebird Bio, and Menarini outside the submitted work. Valeria Santini reports grants and personal fees from Celgene/BMS and personal fees from Takeda, Menarini, Novartis, Janssen, and Geron outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Marino Clavio: Data analysis, writing of the manuscript, study design, data collection, and review and approval of the manuscript. **Elena Crisà:** Data analysis, writing of the manuscript, statistical analysis, data collection, and review and approval of the manuscript. **Maurizio Miglino:** Data collection and review and approval of the manuscript. **Fabio Guolo:** Statistical analysis, data collection, and review and approval of the manuscript. **Manuela Ceccarelli:** Statistical analysis, data collection, and review and approval of the manuscript. **Flavia Salvi:** Data collection and review and approval of the manuscript. **Bernardino Allione:** Data collection and review and approval of the manuscript. **Dario Ferrero:** Data collection and review and approval of the manuscript. **Enrico Balleari:** Data collection and review and approval of the manuscript. **Carlo Finelli:** Data collection and review and approval of the manuscript. **Antonella Poloni:** Data collection and review and approval of the manuscript. **Carmine Selleri:** Data collection and review and approval of the manuscript. **Paolo Danise:** Data collection and review and approval of the manuscript. **Daniela Cilloni:** Data collection and review and approval of the manuscript. **Anna Angela Di Tucci:** Data collection and review and approval of the manuscript. **Gianni Cametti:** Data collection and review and approval of the manuscript. **Roberto Freilone:** Data collection and review and approval of the manuscript. **Renato Fanin:** Data collection and review and approval of the manuscript. **Catia Bigazzi:** Data collection and review and approval of the manuscript. **Renato Zambello:** Data collection and review and approval of the manuscript. **Monica Crugnola:** Data collection and review and approval of the manuscript. **Esther N. Oliva:** Data collection and review and approval of the manuscript. **Riccardo Centurioni:** Data collection and review and approval of the manuscript. **Francesco Alesiani:** Data collection and review and approval of the manuscript. **Massimo Catarini:** Data collection and review and approval of the manuscript. **Andrea Castelli:** Data collection and review and approval of the manuscript. **Antonio Abbadessa:** Data collection and review and approval of the manuscript. **Silvana F. Capalbo:** Data collection and review and approval of the manuscript. **Pellegrino Musto:** Data collection and review and approval of the manuscript. **Emanuele Angelucci:** Data collection and review and approval of the manuscript. **Valeria Santini:** Data analysis, writing of the manuscript, study design, data collection, and review and approval of the manuscript.

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