Original Article

Azacitidine for the Treatment of Lower Risk Myelodysplastic Syndromes

A Retrospective Study of 74 Patients Enrolled in an Italian Named Patient Program

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BACKGROUND: Azacitidine induces responses and prolongs overall survival compared with conventional care regimens in patients who have high-risk myelodysplastic syndromes (MDS). However, limited data are available concerning the efficacy and safety of azacitidine in patients who have lower risk MDS. **METHODS:** The authors retrospectively evaluated 74 patients with International Prognostic Scoring System low-risk or intermediate 1-risk MDS, who received azacitidine on a national named patient program. At baseline, 84% of patients were transfusion-dependent, 57% had received erythropoietin, and 51% were aged >70 years. Azacitidine was administered subcutaneously for 5 days (n = 29 patients), 7 days (n = 43 patients), or 10 days (n = 2 patients) every month at a dose of 75 mg/m^2 daily (n = 45 patients) or at a fixed dose of 100 mg daily (n = 29 patients) and for a median of 7 cycles (range, 1-30 cycles). **RESULTS:** According to the 2006 International Working Group criteria, overall response rate (ORR) was 45.9%, including complete responses (10.8%), partial responses (9.5%), hematologic improvements (20.3%), and bone marrow complete responses (5.4%). The ORR was 51.6% in 64 patients who completed ≥4 cycles of treatment. The median duration of response was 6 months (range, 1-30 months). After a median follow-up of 15 months, 71% of patients remained alive. A survival benefit was observed in responders versus nonresponders (94% vs 54% of patients projected to be alive at 2.5 years, respectively; $P < .0014$). The most common grade 3 or 4 adverse events were myelosuppression (21.6%) and infection (6.8%). **CONCLUSIONS:** The current results indicated that azacitidine may be a feasible and effective treatment for patients with lower risk MDS. ***Cancer* 2010;116:1485–94.** © *2010 American Cancer Society.*

KEYWORDS: azacitidine, hypomethylating agents, myelodysplastic syndromes, prognosis, International Prognostic Scoring System, transfusion.

Myelodysplastic syndromes (MDS) are a diverse group of clonal hematopoietic stem cell disorders associated with gradually worsening cytopenias and anemia requiring frequent blood transfusions, and they also have the potential to

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transform to acute myeloid leukemia (AML).[1,2] Because of the heterogeneous nature of these neoplastic disorders, several different systems have been proposed to identify MDS subtypes. The most widely used are the French-American-British (FAB)[3] classification and the World Health Organization (WHO)[4,5] classification, both of which are based mainly on morphologic criteria assessing dysplastic features, blast cells, and ring sideroblasts, and both also have contributed to recognizing some specific clinical entities.

Although the FAB classification and the WHO classification may provide relevant prognostic information, the International Prognostic Scoring System (IPSS) is the most commonly applied tool used to predict the long-term outcome of patients who are diagnosed with MDS.[1] By using the IPSS classification, patients are categorized as low risk, intermediate risk (Int-1 or Int-2), or high risk based on cytogenetic subgroups, the percentage of bone marrow blasts, and the number of cytopenias. For patients with MDS, the IPSS provides an estimated evaluation of life expectancy and transformation to AML that can vary from a few months to several years, according to the level of risk.[1]

Among the current therapeutic options available for patients with lower risk MDS, it has been established that erythropoiesis-stimulating agents (ESAs),[6-12] immunomodulatory drugs like thalidomide and lenalidomide,[13-19] and immunosuppressive therapies[20,21] can at least partially restore hematopoiesis and induce transfusion independence in selected patients. However, with the possible exception of younger patients who are candidates for allogeneic stem cell transplantation,[21-23] transfusions and chelating therapy remain widely used treatment options for a large number patients.[9,23-25]

Recently, the use of hypomethylating agents, such as azacitidine or decitabine, has emerged as a possible new treatment option for patients with MDS.[26] These drugs induce the re-expression of previously silenced genes that are relevant for cell growth, differentiation, and apoptotic processes, thus providing a rationale for an epigenetic therapy in MDS.[27-30]

Azacitidine (Vidaza; Celgene, Summit, NJ) is a DNA-hypomethylating agent with antineoplastic activity[26] that is licensed in the United States for the treatment of all MDS subtypes as defined by FAB criteria, in Europe for Int-2–risk and high-risk MDS defined by the IPSS classification, and in Europe for AML defined by the WHO classification. In patients with higher risk MDS, azacitidine reduces transfusion dependence, delays transformation to AML, and improves quality of life.[31-35] Recent data also have demonstrated that azacitidine is the first agent to induce a significant survival advantage compared with conventional care regimens in patients with higher risk MDS.[36] Most previous studies of azacitidine in patients with MDS, however, included only a very small proportion of those with lower risk disease, and a specific analysis of response rates and survival based on IPSS criteria was never performed exclusively on this population of patients. To evaluate the real-world clinical benefits of azacitidine in patients with lower risk MDS, we conducted a retrospective analysis of patients who received this drug in an Italian named patient program.

MATERIALS AND METHODS

Patients

For the purposes of this retrospective analysis, patients with IPSS low-risk or Int-1–risk MDS who received azacitidine through a compassionate-use, named patient program were identified in an institutional database from 22 medical centers in Italy between June 2005 and September 2007. Initially, 66 patients with MDS were classified as IPSS low-risk (n = 13 patients; 19.7%) or Int-1–risk (n = 53 patients; 80.3%) on initial assessment. An additional 8 patients who were missing karyotype data also were included because they had IPSS scores of 0 with regard to cytopenias and bone marrow blast counts; therefore, even a hypothetical high-risk karyotype score would not modify their risk class as greater than Int-1. Therefore, in total, 74 patients were evaluated for efficacy and safety. Assessment of IPSS scores and reviews of bone marrow cytology initially were completed by local investigators and subsequently were centrally reviewed (by P.M., L.M., and V.S). There was no change in IPSS grading after the central review, and only 2 patients (2.7%; 1 with unclassifiable MDS and 1 with refractory anemia) were reclassified (both as refractory anemia with multilineage dysplasia).

All patients (or the relatives of patients who died) provided written informed consent to allow the collection of personal data in accordance with the Declaration of Helsinki and Italian privacy laws. To facilitate the systematic collection of patient data, a standard prepared form was used. No specific blood or bone marrow samples were obtained, and no specific instrumental or laboratory examinations were undertaken in addition to the normal investigations and follow-up controls that the different centers regularly applied in these patients.

Procedures and Treatment

An azacitidine dose and administration schedule was determined at the discretion of the prescribing clinician. All transfusion-dependent patients received supportive therapy with packed erythrocyte or platelet transfusions and iron chelation according to a single-center policy. Transfusion dependence was defined as the need for at least 1 packed erythrocyte or platelet transfusion every 2 months. In all study centers, a hemoglobin level of <8 g/dL and the occurrence of bleeding and/or a platelet count $<10{,}000/\mu L$ represented indications for transfusion.

Assessment of Efficacy and Safety

The primary efficacy endpoint of this retrospective analysis was overall response rate (ORR), which was assessed according to modified International Working Group criteria[37] and was defined as the combined rates of complete response (CR), partial response (PR), hematologic improvement (HI), and bone marrow CR. Patients were considered to be responders if they had a response duration ≥ 8 weeks. The evaluation of response, as provided initially by local investigators, was reassessed independently by a restricted panel of reviewers (P.M., L.M., and V.S.) and was confirmed in 72 of 74 patients (97.3%) before final analysis of the data.

Secondary outcomes were response duration, transfusion independence, AML transformation, overall survival (OS), and safety. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0; National Cancer Institute, Bethesda, Md) and were assessed at each patient visit.

Statistical Analysis

The correlations between different groups and treatment response were estimated by using 2-sided chi-square tests and Wilcoxon tests for categorical and continuous covariates, respectively. OS was calculated from the date therapy started to the date of either death from any cause or last follow-up. The Kaplan-Meier method was used to estimate OS. ORR and OS were also assessed according to age (aged <70 years vs ≥ 70 years), transfusion dependence at baseline (no vs yes), azacitidine dose schedule (75 mg/m^2 daily vs 100 mg as a daily fixed dose), total median azacitidine dose per cycle (≤ 700 mg vs >700 mg), and prior therapy (no vs yes). Patients also were analyzed according to IPSS subgroups (low risk or Int-1 risk) and according to the more recent WHO-based prognostic scoring system (WPSS)[38] and The University of Texas M. D. Anderson Cancer Center (MDACC) model,[39] which is specific to lower risk MDS. Both the WPSS and the MDACC models include parameters that are not present in the IPSS, such as transfusion requirement and WHO classification[38] or age and degree of thrombocytopenia,[39] respectively.

For comparison of survival between 2 groups, the log-rank test was applied. A P value $\leq .05$ was considered significant in all analyses.

RESULTS

Baseline Characteristics

The main patient characteristics are presented in Table 1. The median patient age was 70 years, and most patients were men (52.7%) and were transfusion-dependent (83.8%).

The majority of patients (73%) had previously received at least 1 line of therapy before initiating azacitidine, including ESA in 58.1% of patients and low-dose cytosine arabinoside or AML-like chemotherapy (followed by autologous stem cell transplantation in 1 patient) in 8.1% of patients.

Treatment Administration

Azacitidine was administered as inpatient treatment subcutaneously either at a dose of 75 mg/m^2 daily (60.8%) or at a fixed dose of 100 mg daily (39.2%) (Table 1). The most common treatment regimens that were used for azacitidine administration were a monthly schedule of 7 consecutive days or a 5 + 2 + 2 day schedule (azacitidine given Monday through Friday, with no weekend dosing, and Monday and Tuesday on treatment; received by 58.1% of patients) and a monthly schedule of 5 consecutive days (received by 39.2% of patients). A few patients (2.7%) received azacitidine for 10 consecutive days or 5 + 2 + 5 days (weekend off treatment) of each month (Table 1). Patients received a median of 7 treatment cycles (range, 1-30 cycles) (Fig. 1), and the median total dose per cycle was 700 mg (range, 425-1105 mg per cycle). Most patients received azacitidine as single-agent therapy (74.3%), and the remaining patients received concomitant therapy with ESA (13.5%), ESA plus granulocyte–colony-stimulating factor (G-CSF) (2.7%), valproic acid with or without all-trans retinoic acid (4.1%), or other drugs (5.4%) (Table 1).

Efficacy Outcomes

Overall, 34 of 74 patients achieved a response (ORR, 45.9%), which included 8 CRs (10.8%), 7 PRs (9.5%),

Table 1. Patient Characteristics and Study Treatment Received for All Patients With International Prognostic Scoring System Low-Risk or Intermediate-1–Risk Myelodysplastic Syndrome Treated With Azacitidine (n=74)

Characteristic	No.	%
Sex		
Men	39	52.7
Women	35	47.3
Age, y		
Median	70	
Range	34-84	
<70	36	48.6
≥70	38	51.4
Time since diagnosis, mo		
Median	21.5	
Range	1-132	
WHO classification[a]		
Refractory anemia	18	24.3
Refractory anemia with ringed sideroblasts	4	5.4
MDS with isolated del(5q)	5	6.8
Refractory cytopenias with multilineage dysplasia[b]	24	32.4
Refractory anemia with excess of blasts-1	23	31.1
Karyotype[c]		
Good	51	68.9
Intermediate	11	14.9
Poor	4	5.4
Missing	8	10.8
IPSS classification[d]		
Low-risk	13	19.7
Intermediate-1 risk	53	80.3
Transfusion dependence at baseline		
No	12	16.2
Yes	62	83.8
Erythrocytes	50	67.8
Platelets	3	4.1
Erythrocytes and platelets	9	12.1
Prior therapies		
None	20	27
Yes	54	73
1 Line	38	51.4
2 Lines	16	21.6
Low-dose chemotherapy	3	4.1
High-dose chemotherapy	3	4.1
ESA	42	56.8
ESA plus granulocyte-colony-stimulating factors	1	1.4
Other	5	6.8
Study treatment received		
Azacitidine (n=74)		
Azacitidine dose		
75 mg/m^2/d	45	60.8
100 mg/d fixed dose	29	39.2
Dose schedule		
5 Consecutive d	29	39.2
7 Consecutive d or 5+2+2 d	43	58.1
10 Consecutive d or 5+2+5 d	2	2.7
Median total azacitidine dose per cycle, mg		
≤700	53	71.6
>700	21	28.4
Concomitant medication		
None	55	74.3
ESA	10	13.5
ESA plus granulocyte-colony-stimulating factors	2	2.7
Valproic acid with or without all-*trans* retinoic acid	3	4.1
Other	4	5.4

WHO indicates World Health Organization; MDS, myelodysplastic syndromes; IPSS, International Prognostic Scoring System; ESA, erythropoiesis-stimulating agents (recombinant erythropoietin or darbepoetin).
[a]See Vardiman 2002[4] and Swerdlow 2008.[5]
[b]Including 2 patients who had ringed sideroblasts.
[c]According to the IPSS.
[d]Eight patients did not have an evaluable karyotype, and a precise IPSS score could not be assessed in those patients (see Greenberg et al 1997[1]).

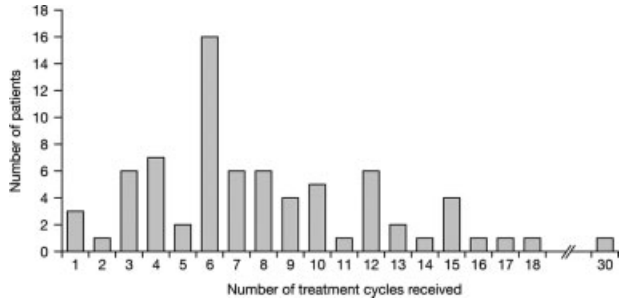

Figure 1. This bar chart illustrates the number of cycles of azacitidine received by patients who had lower risk myelodysplastic syndromes (n = 74).

15 HIs (20.3%), and 4 bone marrow CRs (5.4%) (Table 2). Among the 64 patients who received at least 4 cycles of azacitidine therapy, the ORR was 51.6% (Table 2).

In total, 77% of responses occurred within the first 6 cycles, and most patients (59%) achieved their best response between the fourth and sixth cycles of azacitidine treatment. The remaining responses (23%) were observed after the sixth cycle of treatment. Of the 25 patients who had stable disease (SD), 8 patients continued to receive azacitidine for 7 to 10 cycles without significant modifications in their disease condition.

Response to azacitidine was defined further according to patient subgroups (Table 3). There were no significant differences in ORR when patients were analyzed according to age, transfusion dependence, azacitidine dose, total median azacitidine dose per cycle, or prior therapy (Table 3). The median time from diagnosis was

Table 2. Best Response Using Modified International Working Group Criteria for All Patients with International Prognostic Scoring System Low- or Intermediate-1-Risk Myelodysplastic Syndromes Receiving Azacitidine and for Patients Who Received ≥4 Cycles of Azacitidine

	All Patients		Patients Receiving ≥4 Cycles	
Response According to Modified IWG Criteria[a]	No.	%	No.	%
Total no. of patients	74		64	
Overall response[b]	34	45.9	33	51.5
Complete response	8	10.8	7	10.9
Partial response	7	9.5	7	10.9
Hematologic improvement[c]	15	20.3	15	23.4
Bone marrow complete response	4	5.4	4	6.3
Stable disease	25	33.8	21	32.8
Progressive disease	10	13.5	7	10.9
Failure	5	6.8	3	4.7

IWG indicates International Working Group.
[a]See Cheson 2006[37].
[b]Transfusion independence was achieved in 24 of 27 transfusion-dependent patients who responded.
[c]Comprised 11 erythroid improvements, 1 platelet improvement, 1 neutrophil improvement, and 2 erythroid/platelet improvements.

similar between responders (21 months; range, 1-132 months) and nonresponders (22 months; range, 1-120 months). Five of 12 patients (41.6%) who received azacitidine in combination with recombinant erythropoietin (with G-CSF in 2 patients) experienced a response that was not observed previously with these drugs without azacitidine.

Overall, the response rate did not differ significantly among the different prognostic subgroups (Table 4). A response was observed in 2 of 3 patients who had chromosome 7 abnormalities and in 3 of 6 patients who had abnormal karyotypes, including del(5q).

Among the 34 patients who responded to azacitidine, the median duration of response was 6 months (range, 1-30 months). Thirteen patients (38.2%) developed recurrent disease, including 3 of 8 patients who had a CR, 2 of 7 patients who had a PR, 7 of 15 patients who had an HI, and 1 of 4 patients who had a bone marrow CR. Three patients who were still on therapy developed recurrent disease after 4 to 12 cycles of treatment, and 10 patients developed recurrent disease out of therapy (after 6-9 cycles had been received). In 2 of the latter patients (1 patient who had refractory cytopenia with multilineage

Table 3. Overall Response Rate to Azacitidine and Survival According to Patient Age, Transfusion-Dependence Status, Dose, and Prior Therapy at Baseline[a]

		No. of Patients (%)		
Characteristic	Total No.	ORR	No Response	OS at a Median Follow-Up of 15 Months, %
All patients	74	34 (45.9)	40 (54.1)	71
Age, y				
<70	36	14 (38.9)	22 (61.1)	78.6
≥70	38	20 (52.6)	18 (47.4)	62.5
Transfusion-dependence				
No	12	5 (41.7)	7 (58.3)	100
Yes	62	29 (46.8)	33 (53.2)	66.1[b]
Azacitidine dose schedule				
75 mg/m^2/d	45	23 (51.1)	22 (48.9)	73
100 mg/d Fixed dose	29	11 (37.9)	18 (62.1)	67.4
Median total azacitidine dose per cycle, mg				
≤700	53	24 (45.3)	29 (54.7)	67.5
>700	21	10 (47.6)	11 (52.4)	78.3
Prior therapies				
No	20	10 (50)	10 (50)	52.7
Yes	54	24 (44.4)	30 (55.6)	76.1

ORR indicates overall response rate; OS, overall survival.
P values were not significant in all comparisons.
P=.058 versus no transfusion dependence at baseline.

Table 4. Response Rates and Survival in 66 Patients With Lower Risk Myelodysplastic Syndromes Who Had All Required Parameters Available Calculated According to Different Prognostic Scoring Systems: The International Prognostic Scoring System, the World Health Organization-Based Prognostic Scoring System, and The M. D. Anderson Cancer Center Model

Scoring System	Total No.	No. of Patients (%)[a] ORR	No Response	OS at a Median Follow-Up of 15 Months, %[b]
IPSS risk group[c]				
Low	13	7 (53.8)	6 (46.2)	92.3
Intermediate-1	53	23 (43.4)	30 (56.6)	66.1
WPSS risk group[d]				
Very low	4	2 (50)	2 (50)	75
Low	24	11 (45.8)	13 (54.2)	90
Intermediate	15	8 (53.3)	7 (46.7)	62.5
High	20	8 (40)	12 (60)	57.1
Very high	3	1 (33.3)	2 (66.7)	0
MDACC model[e]				
Category 1 (low)	14	6 (42.9)	8 (57.1)	100
Category 2 (intermediate)	34	18 (52.9)	16 (47.1)	69.6
Category 3 (high)	18	6 (33.3)	12 (66.7)	48.7

ORR indicates overall response rate; OS, overall survival; IPSS indicates International Prognostic Scoring System; WPSS, World Health Organization-based Prognostic Scoring System; MDACC, The University of Texas M. D. Anderson Cancer Center Prognostic Model.

[a] *P* values were not significant for all comparisons.

[b] IPSS: *P* values were not significant between IPSS subgroups; WPSS: $P = .024$ between WPSS subgroups; MDACC: 1 vs 2, $P = .048$; 1 vs 3, $P = .022$.

[c] See Greenberg 1997.[1]

[d] See Malcovati 2007.[38]

[e] See Garcia-Manero 2008.[39]

dysplasia plus del 20 who had achieved a CR combined with a cytogenetic response and 1 patient with a 5q− syndrome who had a previous HI), a durable second response was achieved when azacitidine was restarted.

At a median follow-up of 15 months (range, 4-30 months), the projected OS rate at 30 months was 70.8% (Fig. 2, Top), and it was projected that more responders compared with nonresponders would remain alive (93.9% vs 53.8%, respectively; $P < .0014$) (Fig. 2, Bottom). A trend toward improved OS was observed favoring patients who were not transfusion-dependent at baseline (Table 3). OS was not influenced by age, azacitidine dose, total median azacitidine dose per cycle, or prior therapy. Likewise, no clear difference in OS was observed according to the different types of responses achieved (data not shown).

Overall, the 1-year OS rate was 74.9%. OS remained significantly lower in the higher risk categories of WPSS and MDACC prognostic scores (Table 4). During the evaluated period (June 2005 to December 2008), 4 patients (5.4%) developed AML: None of those patients had exhibited any response to azacitidine therapy after 1 cycle, 4 cycles, 5 cycles, and 14 cycles, respectively. Thus, as of December 15, 2008, 32 treated patients (43.2%) still were receiving azacitidine treatment (including 24 responders and 8 patients with SD), 19 patients (25.7%) were receiving alternative therapies, 21 patients (28.4%) had died, and 2 patients (2.7%) were lost to follow-up.

Safety Outcomes

The most common grade 3 or 4 adverse events observed were myelosuppression (21.6%), including thrombocytopenia plus neutropenia (n = 6 patients), neutropenia alone (n = 4 patients), anemia plus neutropenia (n = 2 patients), thrombocytopenia alone (n = 3 patients), and pancytopenia (n = 1 patient). Infections were observed in 6.8% of patients (Table 5). Two patients required azacitidine dose reductions because of grade 3 thrombocytopenia plus neutropenia, and 3 patients discontinued treatment after 1 to 5 cycles because of grade 4 adverse events (atrial fibrillation, thrombocytopenia plus neutropenia, and pancytopenia, respectively; severe infection [pneumonia] also occurred in the latter 2 patients). No deaths attributable to azacitidine therapy were reported.

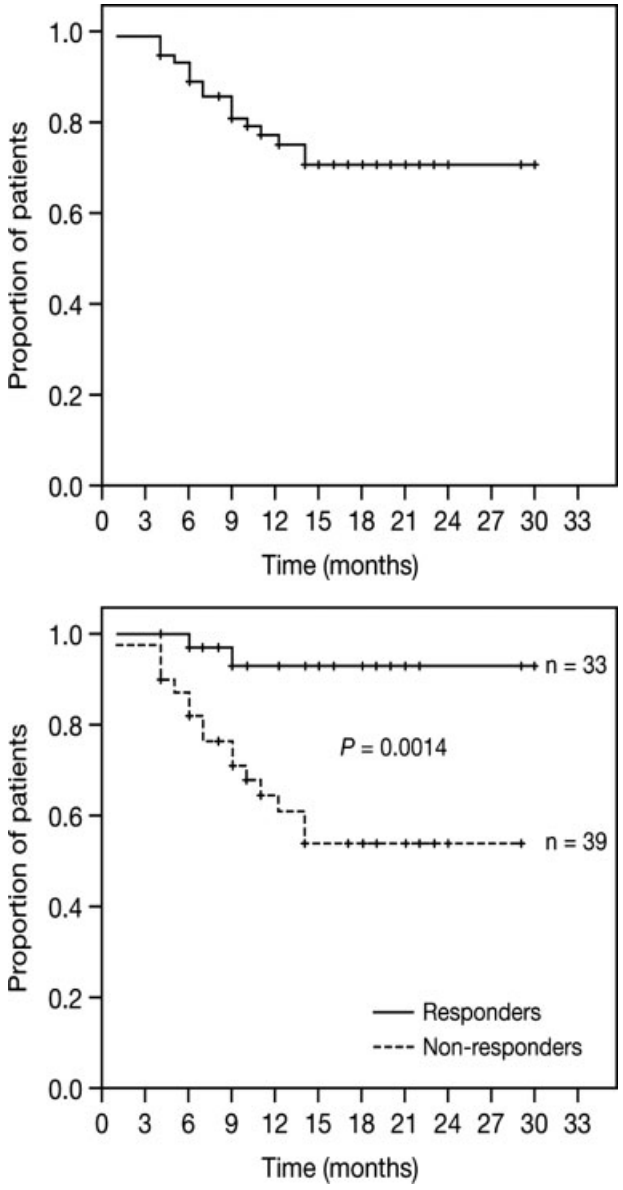

Figure 2. These graphs illustrate Kaplan-Meier estimates of overall survival for patients with low-risk or intermediate-1 risk myelodysplastic syndrome patients who received azacitidine (n = 72; 2 patients were lost to follow-up) in (*Top*) the overall study population and (*Bottom*) according to response to azacitidine therapy.

Table 5. Adverse Events Reported in 74 Patients With International Prognostic Scoring System Low-Risk or Intermediate-1–Risk Myelodysplastic Syndromes Who Received Treatment With Azacitidine According to Grade

	No. of Patients (%)	
Adverse Event	Grade 1-2	Grade 3-4
Myelosuppression	9 (12.2)	16 (21.6)
Local erythema	17 (23)	0 (0)
Gastrointestinal	12 (16.2)	1 (1.4)
Infections	2 (2.7)	5 (6.8)
Rash or joint pain	4 (5.4)	0 (0)
Atrial fibrillation	0 (0)	1 (1.4)

DISCUSSION

In this multicenter retrospective analysis, 74 patients with IPSS-defined low-risk or Int-1–risk MDS received azacitidine for a median of 7 cycles. Over half of the patients who received at least 4 cycles of therapy achieved a response, and the median response duration was 6 months. It is noteworthy that approximately 50% of the study population was aged ≥70 years, and 57% had recurrent or resistant disease after previous ESA treatment and had few alternative treatment options.

In total, 77% of responses occurred within the first 6 cycles of azacitidine treatment. However, a minority of patients with MDS responded after >6 cycles of therapy. Furthermore, 10 of 13 observed recurrences developed after interruption of the treatment; in 2 of these patients, a second response was achieved when azacitidine was given again. These data are consistent with the benefit of continued azacitidine treatment observed in patients with higher risk MDS.[40] Altogether, these observations highlight the possible benefit of maintaining patients with MDS on azacitidine therapy in the absence of undue toxicity or signs of progressive disease.

In the current study, responses included improvement in hemoglobin levels and in neutrophil and platelet counts, as reported previously in patients with higher risk MDS, although to a lesser extent. Furthermore, responses were observed in patients with chromosome 7 abnormalities, consistent with recently reported results.[41,42] The response to azacitidine was not influenced by age, prior therapy, transfusion dependence at baseline, azacitidine dose, or the total median azacitidine dose per cycle. The ORR also was similar among the different prognostic subgroups when patients were reclassified according to the WPSS and the MDACC lower risk-oriented prognostic models. In addition, transfusion independence was obtained in the majority of responders.

With a median time since diagnosis at baseline of 21.5 months, 71% of patients remained alive after a median follow-up duration of 15 months (range, 4-30 months) after the initiation of azacitidine treatment. The projected OS was not influenced by patient age, prior therapy, or azacitidine dose. However, a favorable trend

was observed in patients who were transfusion independent at baseline.

In our cohort of patients with lower risk MDS, similar to what was observed in Cancer and Leukemia Group B (CALGB) Trial 9221,[34,35] which used FAB classification, the survival of patients in higher risk categories, as defined by the MDACC score, and, perhaps more noteworthy, the survival of patients in the "very-high-risk" category (according to the dynamic WPSS score, which permits evaluation and allows reassessment of prognosis for patients with MDS during the course of the disease) remained poorer than the survival reported in the other MDS subsets despite treatment with azacitidine. Indeed, because this was a nonrandomized, retrospective study without a control arm, we hesitate to draw conclusions about the impact of azacitidine on the OS of any single subgroup.

To date, few data are available on the specific use of azacitidine in patients with lower risk MDS. In the randomized azacitidine versus supportive care CALGB Trial 9221, only 44 patients with low-risk MDS were included.[34] The ORR in patients who received azacitidine (n = 23) was 59% (9% CRs, 18% PRs, and 32% HIs), as assessed using the CALGB response criteria, and OS was longer in azacitidine-treated patients than in controls (44 months vs 27 months, respectively). No specific information on the outcomes of 11 patients who had refractory anemia or refractory anemia with ringed sideroblasts from another CALGB study (the 8921 protocol) were given.[32] A reanalysis of these trials did not produce further detailed data on patients with lower risk MDS.[35]

More recently, in a US community-based, multicenter patient registry study (AVIDA; currently only published in abstract form), 52 MDS patients with IPSS classified as low risk or Int-1 risk received a median of 3 cycles of azacitidine.[43] In total, 24 patients (46%) achieved erythrocyte transfusion independence.[43] In addition, 8 of 13 patients (62%) who received platelet transfusions at baseline achieved platelet transfusion independence.[43] Most of these responses were obtained during the first 2 cycles.[43] The most common adverse events were anemia (20%), thrombocytopenia (13%), nausea (11%), constipation (10%), fatigue (10%), and neutropenia (10%).[43]

Finally, using International Working Group 2000 criteria, Lyons and coworkers[44] reported an HI in 44% to 56% of 151 patients with MDS (63% had lower risk MDS according to FAB criteria) who received 3 alternative dosing schedules of azacitidine. The proportion of transfusion-dependent patients with lower FAB risk who achieved transfusion independence ranged from 50% to 61% in the 3 arms of the study.[44] However, patients with MDS were not classified according to the IPSS because of the lack of cytogenetic data.[44] Furthermore, no data on survival were reported by those authors.[44]

Our findings demonstrated that azacitidine generally is tolerated well in a population of patients with lower risk MDS, including elderly patients (median age, 70 years). The most frequent grade 3 or 4 adverse event, as expected, was myelosuppression, but only a few patients required azacitidine dose reduction or interruption, and none of the patients died from infections or hemorrhagic complications.

The use of azacitidine recently was associated with improved survival in patients with high-risk MDS.[36] It is noteworthy that, in the current study of patients with lower risk MDS, a significant OS benefit was observed in responders to azacitidine compared with nonresponders. An improvement in survival was reported recently in patients with MDS who received ESA with or without G-CSF compared with untreated patients.[11,12] Taken together, these observations suggest that different effective treatments possibly may modify the natural history of lower risk MDS (and, consequently, the paradigm of the desired therapeutic objectives in these patients), not necessarily by inducing a CR but simply by improving cytopenias and eliminating their negative impact on survival (ie, by reducing heart failure-related deaths from anemia, reducing the negative effects of iron overload because of transfusions, or decreasing the rate of infections or hemorrhages in patients with severe neutropenia or thrombocytopenia). Other mechanisms also might play a role, for example, the potential activity of azacitidine in delaying progression to AML, as demonstrated in high-risk MDS[34-36]; however, the limited number of patients who experienced leukemic evolution in the current study did not allow us to draw any conclusions regarding this issue.

In conclusion, in this retrospective study, we have demonstrated that azacitidine may be a good therapeutic option for patients with lower risk MDS. Adverse events were minor, and clinicians generally continued administering treatment for several cycles without interrupting therapy before benefit or clear inefficacy was evident. These observations represent real-world data, because patients were treated outside of the setting of a clinical trial, in which strict inclusion and exclusion criteria may have limited the generalizability of the findings. Although we are conscious that our analysis may suffer from relevant

bias derived from the multicenter and retrospective nature of the study, we believe it clearly indicates that azacitidine should be considered within the therapeutic armamentarium of IPSS-classified low-risk or Int-1–risk MDS, including elderly and transfusion-dependent patients who are refractory to or unsuited for treatment with growth factors and for whom limited treatment options remain.

Prospective studies are warranted to confirm the impact of azacitidine on survival in patients with lower risk MDS who have anemia or other symptomatic cytopenias. The effect of different dosing schedules, doses, duration of therapy, route of administration,[44-46] and combinations of azacitidine with other agents[47] also should be investigated further in this important subset of patients with MDS.

CONFLICT OF INTEREST DISCLOSURES

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