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Effectiveness and safety of different azacitidine dosage regimens in patients with myelodysplastic syndromes or acute myeloid leukemia☆

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ABSTRACT

We investigated the effectiveness and tolerability of azacitidine in patients with World Health Organization-defined myelodysplastic syndromes, or acute myeloid leukemia with 20–30% bone marrow blasts. Patients were treated with azacitidine, with one of three dosage regimens: for 5 days (AZA 5); 7 days including a 2-day break (AZA 5-2-2); or 7 days (AZA 7); all 28-day cycles. Overall response rates were 39.4%, 67.9%, and 51.3%, respectively, and median overall survival (OS) durations were 13.2, 19.1, and 14.9 months. Neutropenia was the most common grade 3–4 adverse event. These results suggest better effectiveness–tolerability profiles for 7-day schedules.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal stem cell disorders characterized by ineffective hematopoiesis leading to gradually worsening cytopenias, and a high risk of progression to acute myeloid leukemia (AML). Prognosis varies widely – patients with International Prognostic Scoring System (IPSS)-defined Low- or Intermediate (Int)-1-risk MDS have a median survival of 5.7 and 3.5 years, respectively. In contrast, patients with IPSS-defined Int-2- or High-risk MDS have a shorter median survival (1.2 and 0.4 years, respectively) and a higher risk of progression to AML [1].

Azacitidine (Vidaza®; Celgene Corporation, Summit, NJ, USA) significantly reduces red blood cell (RBC)-transfusion dependence, decreases risk of transformation to AML, improves quality of life, and increases overall survival (OS) compared with supportive care

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in patients with MDS across all French–American–British (FAB) subtypes [2,3]. In a large phase III trial, azacitidine resulted in significantly increased hematologic response rates in higher-risk MDS patients. It also significantly extended OS and time to AML progression in higher-risk MDS patients, and in elderly patients with World Health Organization (WHO)-defined AML with 20–30% bone marrow blasts, when compared with conventional care regimens (best supportive care, low-dose cytarabine, or intensive chemotherapy) [4–6].

Azacitidine is approved in the USA for the treatment of all 5 FAB subtypes of MDS [7], and is also approved in Europe for treating adult patients ineligible for hematopoietic stem cell transplantation who have IPSS-defined Int-2- or High-risk MDS, chronic myelomonocytic leukemia with 10–29% bone marrow blasts without myeloproliferative disorders, or AML with 20–30% bone marrow blasts and multilineage dysplasia according to the WHO criteria [8]. The approved starting dose of azacitidine is 75 mg/m^2/day administered subcutaneously (USA and Europe) or intravenously (USA only), on days 1–7 of each 28-day cycle for at least 4–6 cycles (USA) or 6 cycles (Europe), until disease progression or unacceptable adverse events (AEs) ensue [7,8]. However, AVIDA, a prospective, longitudinal, multicenter patient registry in the USA, found that the majority of patients receiving azacitidine in a community-based setting do not receive the approved schedule of 7 consecutive treatment days [9].

Before receiving marketing authorization in May 2009, azacitidine was available in Spain through clinical trials or compassionate use. This retrospective, multicenter study analyzed a Spanish compassionate use registry to investigate the effectiveness and tolerability of various azacitidine dosing schedules used in daily clinical practice in patients with MDS or WHO-defined AML with 20–30% bone marrow blasts.

2. Patients and methods

This retrospective analysis of clinical data from a multicenter Spanish compassionate use registry included patients who initiated azacitidine treatment between February 6, 2006, and May 5, 2009. The protocol was approved by an independent ethics committee in April 2009.

2.1. Patients and treatment

Patients aged ≥18 years with either a confirmed diagnosis of WHO-defined MDS, or a confirmed diagnosis of de novo (primary) or secondary AML according to WHO criteria with 20–30% bone marrow blasts were included [10]. All patients were required to have received ≥1 cycle of azacitidine at a starting dose of 75 mg/m^2/day under compassionate use conditions, with a documented dosage regimen as follows (all 28-day cycles): days 1–5 (AZA 5); days 1–5, weekend (2 days) without treatment, followed by 2 days of treatment (AZA 5-2-2); or days 1–7 (AZA 7). Azacitidine dosing schedule and administration route (subcutaneous or intravenous) were chosen at the physician's discretion based on the patient's Eastern Cooperative Oncology Group (ECOG) performance status score and the feasibility of weekend drug administration.

2.2. Outcome measures

The primary endpoint was clinical response. Hematologic response (defined as complete response [CR], partial response [PR], marrow CR [mCR], or hematologic improvement [HI]), stable disease (SD), and progressive disease (PD) were assessed according to the International Working Group 2003 and 2006 criteria for AML and MDS, respectively [11,12]. Overall response rate (ORR) was defined as CR + PR + mCR + HI. Secondary endpoints included OS according to dosing schedule, cytogenetic risk groups at baseline, best response achieved, and clinical response at four and six cycles of azacitidine treatment, as well as safety of azacitidine treatment. OS was defined as time from azacitidine initiation to death from any cause, and the median duration of follow-up was 1.4 years. Cytogenetics were classified according to IPSS criteria [1]. AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

2.3. Statistical methods

Baseline characteristics between azacitidine dosing groups were compared using chi-square, Fisher's exact, or LR chi-square tests for qualitative variables where appropriate; and analysis of variance, Mann–Whitney–Wilcoxon, or Kruskal–Wallis tests for quantitative variables as appropriate. Comparison of response to azacitidine across dosing groups was tested for homogeneity of distributions using chi-square test.

A multivariate logistic regression identified potential risk factors for best overall response. Variables included: bone marrow blast percentage; platelet count; time since diagnosis; sex; age; ECOG performance status score; IPSS risk; azacitidine administration route and dosing schedule; cytogenetics; WHO classification; disease status; and transfusion dependence. Continuous variables were: age; time since diagnosis; platelet count; and bone marrow blast percentage. The categorical variables were: sex; disease status; WHO classification; IPSS risk; cytogenetics; ECOG performance status score; transfusion dependence; azacitidine administration route; and dosing schedule.

OS was described with median survival values, 95% confidence intervals (CIs), as well as using the Kaplan–Meier method. To compare OS between the dosing groups, a Cox proportional hazards regression model was used. In a separate multivariate Cox model, sex, age, disease status, time since diagnosis, WHO classification, IPSS risk, cytogenetics, ECOG performance status score, and azacitidine administration route and dosing schedule were included as prognostic factors for OS. To simplify the multivariate model, a backward selection method was applied, using $p \geq 0.05$ as a criterion for variable exclusion.

The relationship between response to azacitidine and OS was analyzed using a Cox proportional hazards model. To prospectively explore this relationship, responses to azacitidine treatment at cycles 4 and 6 were used as dependent variables to explain and predict the OS of those patients alive and not censored after 4 or 6 months of treatment, respectively.

Statistical analyses were performed by the statistics department of the Autonomous University of Barcelona, Spain, using SAS® software version 9.2 (SAS Institute Inc., Cary, NC, USA). The nominal significance level was 5% ($p < 0.05$) for all statistical tests performed. No corrections for multiplicity of statistical tests were applied due to the exploratory nature of the study. Data were included up to a cutoff date of June 30, 2010.

3. Results

3.1. Patient demographics

Of 240 patients treated with azacitidine-based regimens in the Spanish compassionate use registry, 200 met the inclusion criteria: 66 (33.0%) received AZA 5; 56 (28.0%) received AZA 5-2-2; and 78 (39.0%) received AZA 7. Baseline characteristics were similar across the 3 dosing groups (Table 1). The majority of patients (67.0%) were male and 83.0% had primary MDS. The median age was 69 years (range 28–86 years). There were fewer patients without excess blasts in the AZA 5 and

Table 1
Patient baseline characteristics and details of azacitidine administration according to azacitidine dosing schedule.

Characteristic	Azacitidine dosing schedule[a]			Total (n = 200)	p-Value
	AZA 5 (n = 66)	AZA 5-2-2 (n = 56)	AZA 7 (n = 78)		
Median age, years (range)[b]	70 (28–86)	69 (29–82)	70 (33–82)	69 (28–86)	0.6685
Male, n (%)	46 (69.7)	36 (64.3)	52 (66.7)	134 (67.0)	0.5863
Disease status, n (%)					0.3694
Primary MDS	55 (83.3)	50 (89.3)	61 (78.2)	166 (83.0)	
Secondary MDS	5 (7.6)	2 (3.6)	8 (10.3)	15 (7.5)	
Primary/secondary MDS unknown	1 (1.5)	0	0	1 (0.5)	
AML	1 (1.5)	2 (3.6)	6 (7.7)	9 (4.5)	
Refractory AML	4 (6.1)	2 (3.6)	3 (3.8)	9 (4.5)	
Median time from diagnosis to AZA therapy, months (range)[c]	7.4 (0–174.0)	7.5 (0–83.4)	6.6 (0–202.0)	7.4 (0–202.0)	0.8423
WHO classification, n (%)[d]					0.0883
RA	3 (4.9)	2 (3.8)	5 (7.2)	10 (5.5)	
RCMD	10 (16.4)	14 (26.9)	17 (24.6)	41 (22.5)	
RARS	5 (8.2)	2 (3.8)	12 (17.4)	19 (10.4)	
RCMD-RS	3 (4.9)	0	2 (2.9)	5 (2.7)	
RAEB-1	19 (31.1)	10 (19.2)	11 (15.9)	40 (22.0)	
RAEB-2	11 (18.0)	14 (26.9)	13 (18.8)	38 (20.9)	
MDS-U	3 (4.9)	3 (5.8)	6 (8.7)	12 (6.6)	
MDS del(5q)	1 (1.6)	3 (5.8)	0	4 (2.2)	
Unknown	6 (9.8)	4 (7.7)	3 (4.3)	13 (7.1)	
IPSS risk group, n (%)[e]					0.8443
Low	13 (19.7)	10 (17.9)	16 (20.5)	39 (19.5)	
Int-1	28 (42.4)	23 (41.1)	27 (34.6)	78 (39.0)	
Int-2	15 (22.7)	12 (21.4)	15 (19.2)	42 (21.0)	
High	3 (4.5)	6 (10.7)	10 (12.8)	19 (9.5)	
Unknown	7 (10.6)	5 (8.9)	10 (12.8)	22 (11.0)	
Cytogenetic risk, n (%)					0.7241
Poor	7 (10.6)	5 (8.9)	8 (10.3)	20 (10.0)	
Intermediate	45 (68.2)	37 (66.1)	41 (52.6)	123 (61.5)	
Good	1 (1.5)	1 (1.8)	2 (2.6)	4 (2.0)	
Unknown[f]	13 (19.7)	13 (23.2)	27 (34.6)	53 (26.5)	
ECOG status by grade, n (%)					0.1767
0	17 (25.8)	8 (14.3)	14 (17.9)	39 (19.5)	
1	27 (40.9)	36 (64.3)	32 (41.0)	95 (47.5)	
2	12 (18.2)	5 (8.9)	18 (23.1)	35 (17.5)	
3	3 (4.5)	3 (5.4)	5 (6.4)	11 (5.5)	
Unknown	7 (10.6)	4 (7.1)	9 (11.5)	20 (10.0)	
Median number of AZA cycles[g] (range)	6 (1–26)	8 (1–29)	8 (1–34)	8 (1–34)	0.8677
Subcutaneous AZA administration, n (%)	52 (78.8)	51 (91.1)	66 (84.6)	169 (84.5)	0.1745

AML, acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; Int, Intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; MDS-U, MDS unclassified; RA, refractory anemia; RAEB, RA with excess blasts; RARS, RA with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, RCMD with ringed sideroblasts; WHO, World Health Organization.

[a] Patients were not pretreated.
[b] Data were available for 63 patients in the AZA 5 group, 51 patients in the AZA 5-2-2 group, and 77 patients in the AZA 7 group.
[c] Data were available for 61 patients in the AZA 5 group, 47 patients in the AZA 5-2-2 group, and 73 patients in the AZA 7 group.
[d] Comprises only those 182 patients with MDS according to WHO classification (primary and secondary MDS), including 61 patients in the AZA 5 group, 52 patients in the AZA 5-2-2 group, and 69 patients in the AZA 7 group.
[e] At start of treatment.
[f] Due to insufficient bone marrow sample.
[g] Data were available for 66 patients in the AZA 5 group, 55 patients in the AZA 5-2-2 group, and 78 patients in the AZA 7 group.

AZA 5-2-2 groups (p = 0.09). Most MDS patients had IPSS-defined Low- or Int-1-risk disease; 62.1%, 59.0%, and 55.1% in the AZA 5, AZA 5-2-2, and AZA 7 groups, respectively. The median time from diagnosis in the overall population was 7.4 months (95% CI 16.1–26.4 months). Patients in the AZA 5-2-2 and AZA 7 groups received a median of 8 cycles of azacitidine, whereas patients in the AZA 5 group received a median of 6 cycles. Azacitidine was administered subcutaneously in 78.8%, 91.1%, and 84.6% of patients in the AZA 5, AZA 5-2-2, and AZA 7 groups, respectively. Only 18 patients with AML and 20–30% blasts were included in the study: 5 patients (28%) received AZA 5, 4 patients (22%) received AZA 5-2-2, and 9 patients (50%) received AZA 7.

3.2. Clinical response

Of the 199 patients for whom data were available, 104 (52%) achieved any response (CR, PR, mCR, or HI). The ORRs varied across the 3 groups: 39.4% for AZA 5; 67.9% for AZA 5-2-2; and 51.3% for AZA 7 (overall, p = 0.0094; AZA 5 vs. AZA 5-2-2, p = 0.0021; AZA 5 vs. AZA 7, p = 0.1530; AZA 5-2-2 vs. AZA 7, p = 0.0489) (Table 2). In the Cox multivariate model, increased platelet count (p = 0.0247) and azacitidine dose (AZA 5-2-2 vs. AZA 5; p = 0.0365) were predictive of response.

Among patients with available time-to-response data in the AZA 5 (n = 36), AZA 5-2-2 (n = 37), and AZA 7 (n = 46) groups, best response was achieved after a median of 4 azacitidine cycles (range 1–22 cycles).

3.3. Overall survival

The median duration of follow-up was 1.4 years (range 0.1–3.4 years). Median OS duration in the overall study population was 16.5 months (95% CI 12.4–19.1 months).

Reported 1-year OS rates were 52.2%, 69.0%, and 57.6% for the AZA 5, AZA 5-2-2, and AZA 7 groups, respectively (p = 0.2952). The respective median OS durations were 13.2 months (95% CI 9.3–17.5 months), 19.1 months (95% CI 13.1–26.0 months), and 14.9 months (95% CI 9.6–21.4 months) (p = 0.3305) (Fig. 1). Median OS according

Table 2
Clinical response rates according to azacitidine dosing schedule.

Characteristic, *n* (%)	Azacitidine dosing schedule			Total (*n* = 200)
	AZA 5 (*n* = 66)	AZA 5-2-2 (*n* = 56)	AZA 7 (*n* = 78)	
CR	8 (12.1)	11 (19.6)	13 (16.7)	32 (16.0)
mCR	7 (10.6)	13 (23.2)	8 (10.3)	28 (14.0)
PR	6 (9.1)	6 (10.7)	13 (16.7)	25 (12.5)
HI	5 (7.6)	8 (14.3)	6 (7.7)	19 (9.5)
SD	18 (27.3)	7 (12.5)	11 (14.1)	36 (18.0)
PD	22 (33.3)	10 (17.9)	27 (34.6)	59 (29.5)
Missing	0	1 (1.8)	0	1 (0.5)
ORR (CR + mCR + PR + HI), %	39.4	67.9	51.3	52.0

AZA, azacitidine; CR, complete response; HI, hematologic improvement; mCR, marrow CR; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

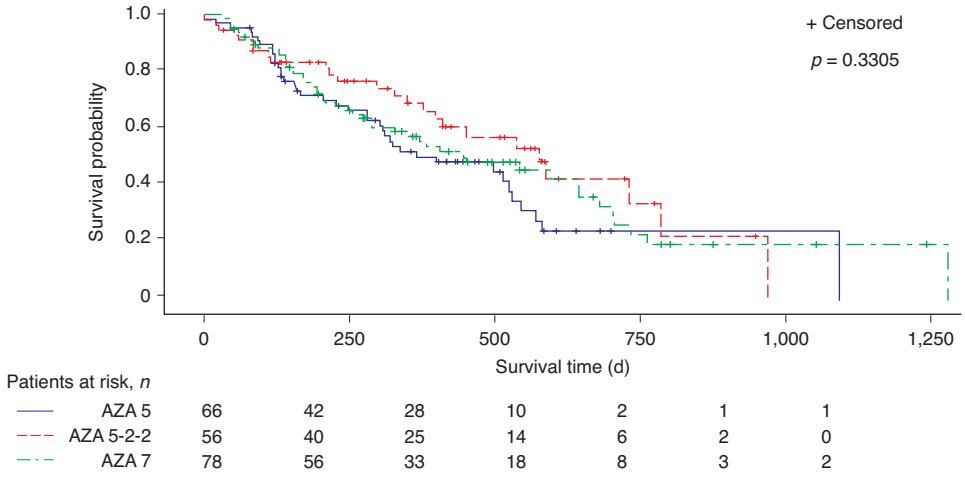

Fig. 1. Overall survival according to azacitidine dosing schedule received (*n* = 200). *Note*: The 3 azacitidine dosing groups were not balanced at baseline due to the nature of the study.

to IPSS was 24.4 months for Low-risk, 16.5 months for Int-1-risk, 14.9 months for Int-2-risk, and 10.4 months for High-risk patients. The characteristics of patients with Low- and Int-1-risk MDS were further analyzed according to the scoring system described by Garcia-Manero et al. [13] (Table 3). OS was similar across cytogenetic risk groups ($p = 0.4852$).

In the Cox multivariate model there were no variables or interactions with predictive value (data not shown).

Median OS duration in the overall study population was significantly longer in patients who achieved any response (CR, PR, mCR, or HI) compared with non-responders (SD and PD) (23.3 months [95% CI 19.4–36.1 months] vs. 7.4 months [95% CI 5.2–10.5 months], respectively; $p < 0.0001$). Median OS according to best ORR was 26.0 months for CR (95% CI 22.5—not reached [NR]), 23.3 months for PR (95% CI 14.8—NR), 21.4 months for mCR (95% CI 9.8–21.4 months), 19.7 months for HI (95% CI 13.2–42.2 months), 10.7 months for SD (95% CI 6.5–17.4 months), and 4.5 months for PD (95% CI 3.1–6.2 months). There were differences in OS according to best response achieved at azacitidine cycles 4 and 6 (all $p < 0.0001$; Fig. 2).

Overall, SD or achievement of any response (CR, PR, mCR, or HI) to azacitidine was associated with significantly reduced risk of death relative to PD (all $p \leq 0.001$). OS was significantly improved in patients with CR or PR at azacitidine cycles 4 and 6 compared with patients with SD as the best response (all $p < 0.05$). In addition, patients with HI at cycle 6 (with no other response achieved previously) had significantly better OS compared with those with SD ($p = 0.0118$).

3.4. Safety

The most common grade 3 and 4 hematologic AE in the AZA 5 (*n* = 66), AZA 5-2-2 (*n* = 56), and AZA 7 (*n* = 78) groups was neutropenia in 39.4%, 19.6%, and 24.4% of patients, respectively. The rates of grade 3 and 4 thrombocytopenia were 15.2%, 8.9%, and 10.3%, respectively, and rates of grade 3 and 4 anemia were 10.6%,

Table 3
Assigned scores in lower-risk patients based on the prognostic score described by Garcia-Manero et al. [13] (*n* = 117).

Score	Frequency	Percentage	Cumulative frequency	Cumulative percentage
0	1	0.85	1	0.85
1	2	1.71	3	2.56
2	11	9.40	14	11.97
3	17	14.53	31	26.50
4	32	27.35	63	53.85
5	39	33.33	102	87.18
6	14	11.97	116	99.15
7	1	0.85	117	100.00

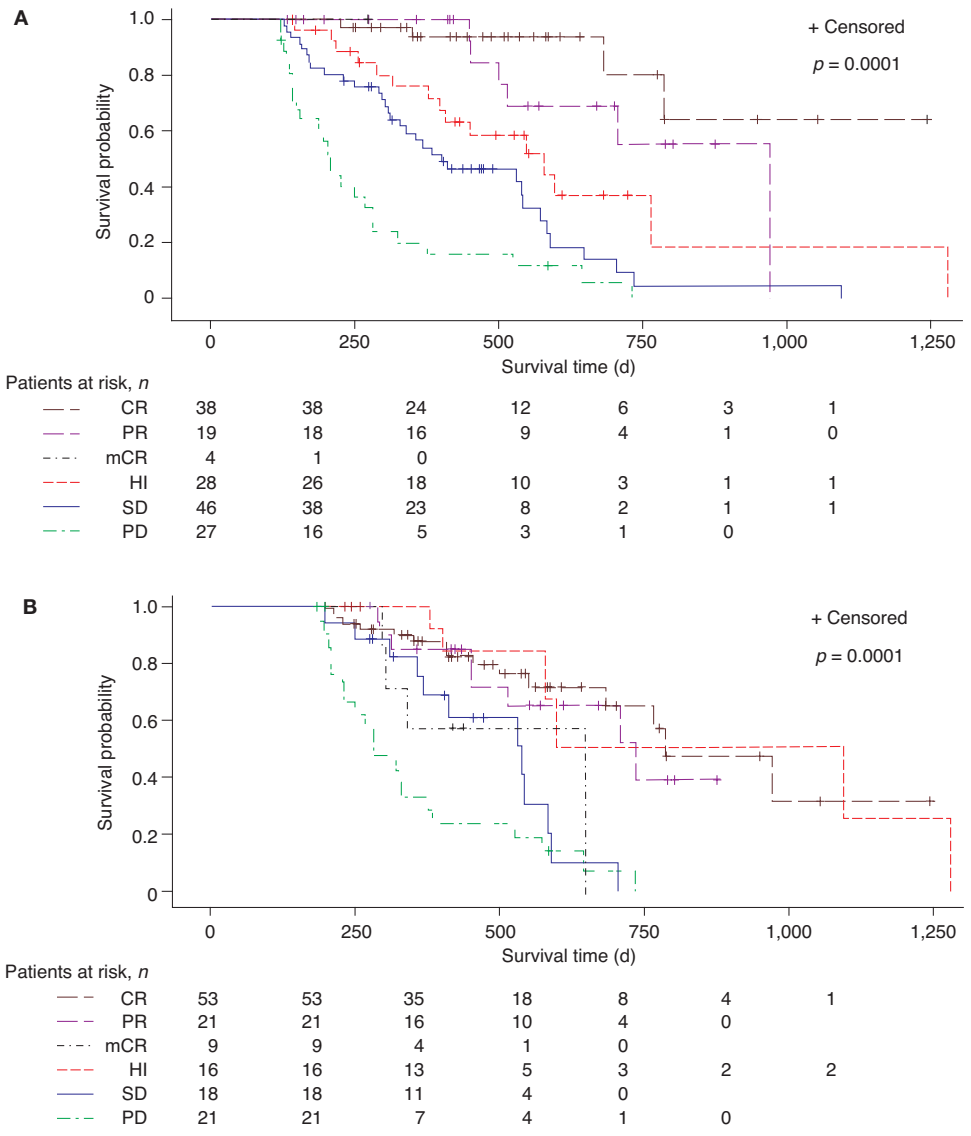

Fig. 2. Overall survival according to best response to azacitidine therapy after cycle 4 (A) and cycle 6 (B) in those patients who were alive and not censored at 4 months ($n = 162$) and 6 months ($n = 138$) of azacitidine treatment, respectively.

7.2%, and 10.2%, respectively. Grade 5 neutropenia occurred in 9.1%, 25.0%, and 7.7% of patients in the AZA 5, AZA 5-2-2, and AZA 7 groups, respectively. Grade 5 thrombocytopenia occurred in 21.2%, 19.6%, and 16.7% of patients; and grade 5 anemia occurred in 22.7%, 14.3, and 15.4% of patients in the 3 dosing groups. Details on other hematologic and non-hematologic AEs were incompletely reported and, therefore, not statistically analyzed. Dose modifications due to AEs were required in 13.6% of patients in the AZA 5 group, 28.6% in the AZA 5-2-2 group, and 14.1% in the AZA 7 group. Treatment interruptions were reported in 15.2%, 8.9%, and 15.4% of patients in the 3 dosing groups.

4. Discussion

Data obtained from retrospective analysis of compassionate use registries should be cautiously analyzed in order to avoid as much as possible any bias in the observation, analysis, or interpretation of the results. This retrospective analysis of clinical data from a multicenter Spanish azacitidine compassionate use registry shows that azacitidine was effective and generally well tolerated in patients with MDS or WHO-defined AML with 20–30% bone marrow blasts treated in a community-based practice setting.

The approved azacitidine dosing schedule is 75 mg/m^2/day on days 1–7 of each 28-day treatment cycle (AZA 7). However, it has been shown that the majority of patients treated in community-based hematology clinics do not receive the approved schedule of treatment [9]. Most patients with lower-risk MDS receive <7 days of azacitidine (consecutive or non-consecutive) treatment, whereas most patients with higher-risk MDS receive ≥7 days of azacitidine (consecutive or non-consecutive) treatment per 28-day cycle. A prospective, community-based phase II study compared the efficacy and safety of alternative azacitidine schedules without weekend dosing: AZA 5, AZA 5-2-2, and azacitidine for 5 days followed by a 2-day weekend break and then an additional 5 days of treatment (AZA 5-2-5) in a predominantly lower-risk MDS patient population [14]. The rates of HI and RBC-transfusion independence together with safety evaluations reported appeared consistent with those seen using the approved dosing regimen; however, a direct comparison of the alternative azacitidine dosing regimens with the currently approved schedule was not included.

In the present study, which included 58.5% of patients with IPSS Low- or Int-1-risk MDS, the 3 dosing schedules were distributed approximately equally across the total study population. ORRs (CR + PR + mCR + HI) appeared higher with the AZA 5-2-2 dosing schedule (67.9%) compared with AZA 7 (51.3%) and AZA 5 (39.4%). The ORR for the entire patient cohort was 52.0%. In a prospective, phase III study in 179 patients with higher-risk MDS or AML with 20–30% bone marrow blasts treated with azacitidine, the rates of overall response (defined as CR + PR) and HI were 29% and 49%, respectively [4]. Retrospective analyses in patients with lower-risk MDS or AML with 21–38% bone marrow blasts treated with azacitidine reported ORRs of 45.6% (defined as CR + PR + mCR + HI) and 60% (defined as CR + PR + HI), respectively [15,16].

OS is an important treatment goal, particularly in patients with higher-risk MDS or AML. A prospective, phase III study reported significantly higher median OS with azacitidine versus conventional care regimens in patients with higher-risk MDS (24.5 months [95% CI 9.9—NR] vs. 15.0 months [95% CI 5.6–24.1]); and in elderly AML patients with 20–30% bone marrow blasts (24.5 months [95% CI 14.6—NR] vs. 16.0 months [95% CI 11.5–17.5]) [4,6]. In the current study, median OS was 13.2, 19.1, and 14.9 months in the AZA 5, AZA 5-2-2, and AZA 7 groups, respectively. A retrospective analysis of 74 patients with lower-risk MDS treated with azacitidine in an Italian named patient program showed that 71% remained alive at a median follow-up of 15 months [15].

As the OS of lower-risk patients was lower than expected [1], these patients were analyzed using the recently defined prognostic tool for lower-risk patients, which includes variables such as age, hemoglobin levels, platelets, cytogenetics, and bone marrow blast count [13]. A majority of lower-risk patients were classified with elevated scores and estimated median survival times of between 14 and 22 months. It is possible that their worse prognosis determined their treatment with azacitidine within the compassionate use program.

In the present heterogeneous study population, OS differed across azacitidine dosing groups but the differences observed were not statistically significant, most likely as a result of the small patient numbers in each dosing group; these results need to be confirmed in a prospective randomized study. Interestingly, the quality of response to treatment had a significant impact on OS in the overall patient cohort. Furthermore, in line with a previous prospective study [17,18], this survival advantage was not necessarily dependent on achieving CR and PR; however, best response achieved with azacitidine at cycles 4 and 6 was predictive for OS.

The median number of azacitidine cycles received was 6, 8, and 8 in the AZA 5, AZA 5-2-2, and AZA 7 groups, respectively. This could help explain the lower response rates observed in the AZA 5 group, as additional cycles of azacitidine therapy have been shown to improve the quality of response in patients with higher-risk MDS [19]. Also, a median of 9 cycles of azacitidine was previously demonstrated to be associated with prolonged OS versus conventional care [4].

The most common hematologic AEs reported with azacitidine were neutropenia, thrombocytopenia, and anemia, whereas non-hematologic events include injection site reactions, fatigue, and gastrointestinal events, such as nausea and vomiting [2,4,14,15,20]. In line with these studies, the most common grade 3 and 4 hematologic AEs reported here were neutropenia, thrombocytopenia, and anemia with rates of 20–39%, 9–15%, and 7–11%, respectively. The dosing group with the most hematologic toxicities experienced the fewest dose modifications, possibly because the treatment was stopped.

The data presented here are based on a retrospective analysis and are thereby subject to any limitations normally imposed on such analyses, such as potential selection bias resulting from ad hoc assessment of the data set. Among evaluable patients, data were often incomplete for individual patients. Furthermore, there was a lack of stratification across the 3 dosing groups. This study included patients across all IPSS subgroups; therefore, the authors caution the application of these results to specific IPSS subgroups of MDS. The limited sample size may have prevented demonstration of statistical differences across the azacitidine dosing groups. Despite these limitations, the study reports daily clinical practice data in a wide range of patients, providing valuable information on the effectiveness and safety profile of various azacitidine dosing schedules.

In conclusion, these retrospective findings in mainly lower-risk MDS and WHO-defined AML patients with 20–30% bone marrow blasts, registered in a community-based Spanish azacitidine compassionate use registry, show differences in overall clinical response and OS across 3 different azacitidine dosing schedules used in daily clinical practice. The effectiveness–tolerability profile appears to be superior for the 7-day azacitidine schedules (AZA 5-2-2 and AZA 7) compared with the 5-day schedule (AZA 5). Quality of response achieved during azacitidine treatment was associated with prolonged survival.

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Conflict of interest statement

RGD and JB have received research funding from Celgene Corporation. D de M has participated in speakers bureaus for Celgene Corporation. FR has been a consultant, a member of an entity's board of directors or advisory committee(s), participated in speakers bureaus, and received research funding and honoraria from Celgene Corporation. GS has participated in advisory committees and received honoraria from Celgene Corporation, Amgen, and Novartis; and participated in an advisory committee for Boehringer Ingelheim Pharma GmbH. All other authors have no conflict of interest to disclose.

Contributors

RGD developed the concept and design of the study, and collected data; D de M, AB, JRG, JB, JFF, RA, FR, MT, SB, AF, JC, AM, AFJ, and GS collected data; LB analyzed the data; and all authors provided final approval of the version to be submitted.

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Appendix A.

The following Spain-based hematologists also contributed to this study manuscript by providing their patients' data: **Rafael F. Duarte**, Institut Català d'Oncologia, Barcelona; **MarÍa José Jiménez Lorenzo**, Hospital Germans Trias i Pujol, Barcelona; **Benet Nomdedeu**, Hospital Clínic, Barcelona; **Manuel Almagro**, Hospital Virgen de las Nieves, Granada; **Maria Elena Amutio Diez**, Hospital

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