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ORIGINAL ARTICLE

Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry

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The benefit of azacitidine treatment in survival of high-risk myelodysplastic syndromes (MDS) patients compared with conventional care treatment (CCT) has not been established outside clinical trials. To assess its effectiveness, we compared overall survival (OS) between azacitidine and conventional treatment (CCT) in high-risk MDS patients, excluding those undergoing stem cell transplantation, submitted to the Spanish MDS registry from 2000 to 2013. Several Cox regression and competing risk models, considering azacitidine as a time-dependent covariate, were used to assess survival and acute myeloblastic leukemia (AML) progression. Among 821 patients included, 251 received azacitidine. Median survival was 13.4 (11.8–16) months for azacitidine-treated patients and 12.2 (11–14.1) for patients under CCT ($P = 0.41$). In a multivariate model, age, International prognostic scoring system and lactate dehydrogenase were predictors of OS whereas azacitidine was not (adjusted odds ratio 1.08, 95% confidence interval 0.86–1.35, $P = 0.49$). However, in patients with chromosome 7 abnormalities, a trend toward a better survival was observed in azacitidine-treated patients (median survival 13.3 (11–18) months) compared with CCT (median survival 8.6 (5–10.4) months, $P = 0.08$). In conclusion, our data show that, in spite of a widespread use of azacitidine, there is a lack of improvement in survival over the years. Identification of predicting factors of response and survival is mandatory.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of clonal hematological disorders affecting mainly elderly people and characterized by cytopenias, ineffective hematopoiesis and increased risk of evolution to acute myeloblastic leukemia (AML).[1] The prognosis of individuals with MDS is very heterogeneous and accurately estimated by universally accepted prognostic scoring indexes such as the International prognostic scoring system (IPSS, R-IPSS WPSS), which are able to segregate different risk groups in terms of overall survival (OS) and risk of AML evolution.[2–4] Currently, allogeneic hematopoietic cell transplantation is the only potential curative treatment for MDS but is applicable only in a minority of the patients, those younger fitted patients with a suitable donor. Recently, a randomized clinical trial undertaken in higher-risk MDS patients who were not eligible for transplantation has shown that the hypomethylating agent azacitidine is superior to conventional care treatment, including best supportive care, in terms of improving OS and delaying evolution to AML.[5,6] However, information regarding the performance of azacitidine on daily clinical practice is scarce. Further, the survival advantage of azacitidine over other treatment alternatives for higher-risk MDS patients outside the scope of clinical trials remains unknown.

The main aim of this study was to analyze the potential effect of different treatment alternatives on OS in a large series of higher-risk (intermediate-2 and high risk by the IPSS) MDS patients reported during the last decade to the registry of the Spanish cooperative group on Myelodysplastic Syndromes (GESMD). For that purpose we compared the outcome of these patients after treatment with azacitidine, best supportive care and AML-type intensive chemotherapy.

PATIENTS AND METHODS

Patients

The primary objective of the study was to compare OS between patients who received azacitidine as front line therapy and patients who received conventional treatment, including best supportive care and intensive AML chemotherapy, in patients with higher-risk MDS. Secondary end points were to examine risk of AML evolution after the different alternatives and to recognize predictive factors for OS and risk of AML progression. For these purposes, this retrospective study included all consecutive higher-risk MDS patients (defined by FAB and WHO morphological criteria and having an IPSS risk score of 1.5 or more—intermediate-2 and high-risk groups) with sufficient follow-up data reported to the registry of the GESMD between 2000 and 2013. Reporting criteria did not change with time. Patients with therapy-related MDS were included in the analysis whereas patients receiving an allogeneic hematopoietic cell

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transplantation were excluded. Patient and disease characteristics recorded included demographic data, such as date of birth and sex, data at diagnosis, including date of MDS diagnosis, hemoglobin level, white blood cell leukocytes, neutrophil, and platelet counts, percentage of blasts in peripheral blood and bone marrow, cytogenetic abnormalities (classified as good, intermediate or poor according to the IPSS classification), serum level of lactate dehydrogenase (LDH), FAB and WHO[7] morphologic classifications, IPSS risk score, type and date of starting treatment, date of AML progression, date of death and date of last follow-up. All data were double-checked for data inconsistency. No central morphology review was attempted. The cytogenetic reports of all cases were centrally reviewed (Enric Solé and Elisa Luño) to ensure they followed the ISCN 2009 guidelines.[8] In keeping with the guidelines of the Declaration of Helsinki Principles, the study was conducted with the approval of the internal review board of the GESMD. All patients provided informed consent.

Statistical analysis

Data are shown as median (interquartile range) or count (percentage) for descriptive statistics. Comparisons of ranks and proportions were done using Mann–Whitney *U*-test, χ^2-test or Fisher's exact test as appropriate. OS was defined as the time from diagnosis to last follow-up or death from any cause and analyzed using the Kaplan–Meier estimator. Patients who remained alive were censored at the time of last follow-up. Survival curves of patients treated with azacitidine or other therapies were compared using the method proposed by Simon and Makuch,[9] with azacitidine therapy treated as a time-dependent covariate. In order to analyze differences in OS between treatment groups, a multivariate Cox regression model was developed. Treatment with azacitidine was included in the model as a time-dependent covariate. Possible confounders were also included in the model. Using this model, hazard ratios with their 95% confidence interval (CI) were computed. In order to minimize the potential effect of unmeasured or unknown confounders, an instrumental variable was also used.[10] In particular, and similarly to other authors,[11] the percentage of azacitidine prescription by region was used as the instrumental variable. This variable was included as a predictor in the assessment of the mortality risk by Cox proportional hazard analysis. The same analysis was repeated in specific subgroups such as in patients with chronic myelomonocytic leukemia (CMML) and in those with 7/del (7q) chromosomal abnormalities. We also performed a matched paired comparison of the outcomes of patients receiving azacitidine and intensive AML chemotherapy. For this subanalysis, patients who received azacitidine were matched with patients treated with intensive AML-type chemotherapy according to a propensity score-based approach that estimates the probability for a particular patient of being treated with chemotherapy. This propensity to receive chemotherapy was computed after adjustment to a general linear model that included age, cytogenetics and percentage of blasts in bone marrow. Seventy-two matched pairs of patients were identified using this method and compared.

Evolution to AML was measured from diagnosis to the date of AML (presence of more than 19% of blasts in bone marrow or peripheral blood). Patients dying before leukemic evolution were considered as censored at the time of death. For the analysis of AML transformation, we exclude cases that progressed into leukemia within 3 months from diagnosis, as those patients should be considered closer to AML than to MDS. A similar scheme to the one previously reported for OS was used for analyzing the subdistribution from diagnosis to AML evolution. Due to the presence of competing risks, risk of progression to AML was analyzed by cumulative incidence methodology; thus, for multivariate analysis of this end point, the Fine and Gray proportional hazards regression method[12] was used.

Two sided *P*-values < 0.05 were considered as statistically significant in all analyses. All the statistical studies and graphs were done using R software (version 3.0.1) with the packages 'Survival', 'cmprsk' and 'ggplot2' (R Foundation for Statistical Computing, Vienna, Austria, available at http://www.R-project.org/). R code is available on request.

RESULTS

Characteristics of the patients and therapeutic strategies used

A total of 821 patients with higher-risk MDS were included in the analysis. There were 512 males and 309 females, with a median age at diagnosis of 75 years (range, 67–80; Table 1). Median follow-up time was 9 months (range, 3.7–17.7) for the overall population and 9.4 months (range, 3.1–19.6) for patients alive at last follow-up. Median OS for the whole cohort of patients was 12.3 (95% CI, 11.4–14.1) months. The corresponding Kaplan–Meier survival plot is shown in Figure 1a. OS did not improve over time (Figure 1b), as the slope of the regression line of median OS versus year of diagnosis was not significantly different from 0 ($P = 0.16$).

From March 2004 to September 2013, 251 patients (31%) received azacitidine as first-line therapy. The number of cases treated with azacitidine per year and the percentage of treated patients according to the year of diagnosis are shown in Figure 2a and b, respectively. The median delay between diagnosis and onset of azacitidine was 35 days (range, 18–111). Beyond 2009, 66% of the patients receiving azacitidine as first-line therapy were treated within the first 2 months after diagnosis (Figure 2c). Dosing schedule was available in 179 patients (71%). Seventy-six patients received a standard 7-day dosing, and the remaining 103 were treated with less intensive regimens. There were no differences in survival between these two dosing schedules ($P = 0.12$, Supplementary Figure S1). Data regarding the number of cycles received was available in 102 patients (41%). Median number of cycles given was 6 (interquartile range, 3–9). The remaining 570 patients (69%) received conventional care treatment (CCT), including best supportive care in 468 patients (57%), high-dose chemotherapy in 81 patients (16%) and other therapies in 21 patients (4%; lenalidomide in 18, cyclosporine in 2, and antithymocyte globulin in 1). The main characteristics of the patients according to the treatment received (azacitidine or CCT) are shown in Table 1. Age, platelets, absolute neutrophil count and serum LDH level were significantly higher in patients treated with CCT. All other demographic and biological characteristics, and IPSS risk score were similar in both treatment groups.

Effect of treatment on OS in the whole series

Median OS was 12.2 months (95% CI, 11–14.1) in the CCT group compared with 13.4 months (95% CI, 11.8–16) in the azacitidine group (Figure 3a, $P = 0.41$). The corresponding actuarial probabilities of OS at 2 years were 22% for patients in the azacitidine group and 29% in the CCT group. In an attempt to avoid potential biases inherent to the retrospective nature of the study and reflected in the presence of significant differences in some characteristics of the patients between both treatment groups, we developed a time-dependent Cox regression model to adjust for confounding covariates. The results of this model are shown in Table 2. Treatment with azacitidine was not associated with a statistically significant improvement in OS in this model (hazard ratio, 1.08; 95% CI, 0.86–1.35; $P = 0.49$; Figure 3b). Variables showing a significant independent effect on OS in multivariable models were age, IPSS risk category and LDH, although the impact of the latter was marginal. Inclusion of other covariates in the model such as year of diagnosis, sex, bone marrow blasts, cytogenetics or adding and interaction between azacitidine treatment and IPSS risk score did not modify the results. Again, the results were similar when patients with CMML or MDS/myeloproliferative neoplasm or patients who died within 3 months from diagnosis were excluded from the analysis. Likewise, when the instrumental variable was added to the model, overall results were almost identical.

Effect of treatment on OS in different subpopulations of patients

As shown in Figure 3c, OS in the two risk groups defined by the IPSS did not clearly differ between those who received azacitidine or CCT ($P = 0.853$ and $P = 0.364$, respectively, for patients belonging to the intermediate-2 and high-risk groups). In the subgroup of patients with CMML, the median OS of patients treated with azacitidine was 20.8 months (95% CI, 10–not reached), whereas it was 15.3 months (95% CI, 7.5–26.2) in those treated with CCT ($P = 0.9$).

Abnormalities in chromosome 7 were present in 145 patients (17% of the whole cohort), with 66% harboring a complex

Table 1. General characteristics of the population

	First line azacitidine (N = *251*)	*Conventional therapy* (N = *570*)	P-*value*
Gender			0.36
Male	166 (66)	346 (61)	
Female	90 (34)	219 (39)	
Age (years)	74 (68–78)	75 (67–81)	0.04
Hemoglobin at diagnosis (g/dl)	9.1 (8–10.4)	9.2 (8–10.5)	0.80
Platelet count at diagnosis ($\times 10^9$/l)	70 (37–114)	75 (43–145)	0.03
WBC ($\times 10^9$/l)	2.95 (1.97–4.99)	3.27 (2.18–5.90)	0.09
ANC ($\times 10^9$/l)	1.06 (0.56–2.04)	1.20 (0.67–2.78)	0.04
Bone marrow blasts (%)	13 (9–16)	13 (8–16)	0.56
LDH (U/l)	338 (233–470)	379 (270–516)	0.01
Secondary MDS			0.36
No	215 (86)	503 (88)	
Yes	36 (14)	67 (12)	
FAB			0.20
Not classified	7 (3)	8 (2)	
RA	12 (5)	48 (8)	
RAEB	162 (64)	350 (61)	
RAEB-T	40 (16)	82 (14)	
RAS	7 (3)	14 (3)	
CMML	19 (8)	64 (11)	
Other	4 (1)	4 (1)	
WHO			0.23
Not classified	19 (8)	24 (4)	
RA	0	5 (1)	
RAEB-1	43 (17)	99 (17)	
RAEB-2	128 (51)	271 (48)	
RAS	1 (0.3)	1 (0)	
RCMD	9 (3.3)	34 (6)	
RCMD-SA	6 (2)	15 (3)	
AML (>20% bl)	23 (9)	51 (9)	
5q-	1 (0.3)	4 (1)	
Unclassificable	0	2 (0)	
MDS/MPN (CMML)	19 (8)	57 (10)	
MDS/MPN (no CMML)	2 (1)	7 (1)	
Cytogenetics			0.99
Good	99 (39.5)	221 (39)	
Intermediate	48 (19)	109 (19)	
Poor	103 (41)	233 (41)	
Not available	1 (0.5)	7 (1)	
IPSS			0.55
1.5	75 (30)	212 (37)	
2	94 (37)	192 (34)	
2.5	37 (15)	71 (13)	
3	40 (16)	81 (14)	
3.5	5 (2)	14 (2)	

Abbrevaitions: AML, acute myeloblastic leukemia; ANC, absolute neutrophil count; CMML, chronic myelomonocytic leukemia; FAB, French-American-British; IPSS, International prognostic score system; LDH, lactate dehydrogenase; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasms; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; RAEB-t, refractory anemia with excess of blasts in transformation; RAS, refractory anemia with ring sideroblasts; RCMD, refractory anemia with multilineage dysplasia; RCMD-SA, refractory anemia with multilineage dysplasia and ring sideroblasts; WBC, white blood cell leukocytes; WHO, World Health Organization.

karyotype. Of those, 49 were treated with azacitidine and 96 with CCT. OS observed in the azacitidine-treated patients was 13.3 months (95% CI, 11–18) and 8.57 months (95% CI, 5–10.4) in the CCT group (log-rank $P = 0.11$, Figure 3d). In the time-dependent Cox model including FAB classification, IPSS, instrumental variable and LDH, treatment with azacitidine showed a trend for better OS compared with CCT (hazard ratio 0.57; 95% CI, 0.30–1.07; $P = 0.08$).

Then we performed, as described in Patients and methods, a matched pair comparison between 72 patients treated with chemotherapy and 72 patients treated with azacitidine. General characteristics of matched patients and their corresponding survival curves are shown in Supplementary Table S1 and Supplementary Figures S2A and B. There were no clear differences in OS between groups ($P = 0.81$ and $P = 0.63$, respectively). A multivariable regression analysis of this subset of patients also failed to detect any significant effect of treatment with azacitidine in OS (Supplementary Table S2). In another analysis, excluding patients who received chemotherapy, median OS was 13.4 months (11.8–16) for azacitidine-treated patients and 12 months (10.6–14.8) for patients receiving only supportive care ($P = 0.55$, Supplementary Figure S3).

Effect of treatment on AML transformation in the overall series

Cumulative incidence of AML transformation is shown in Figure 4. Twenty-three percent of the CCT-treated patients progressed into

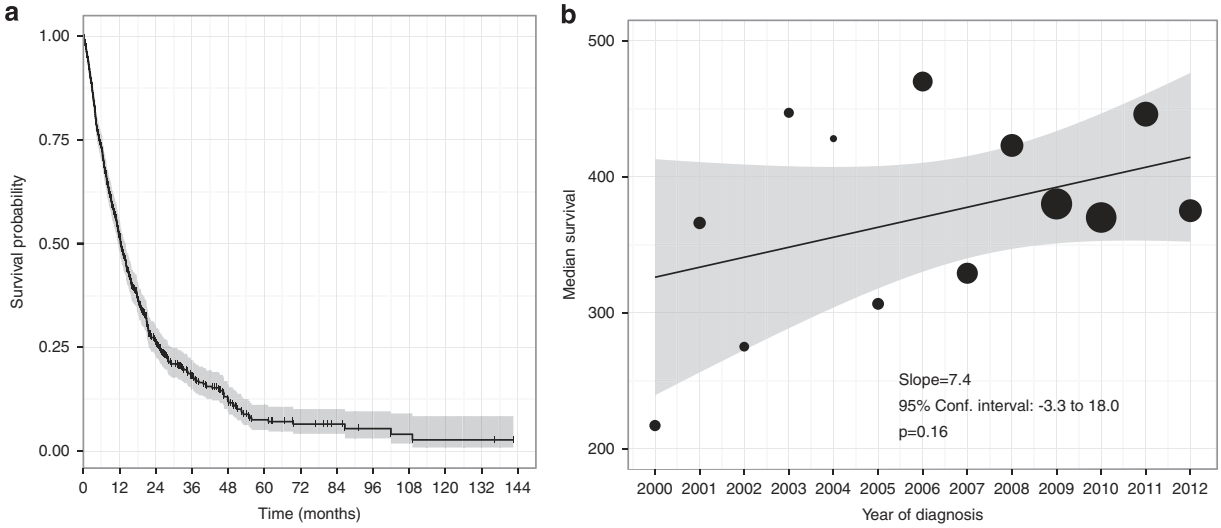

Figure 1. Overall survival. (**a**) Survival curve of the whole cohort. (**b**) Median survival according to the year of diagnosis. Size of each data point is proportional to the number of cases. A regression line with their 95% confidence interval (shaded area) is presented.

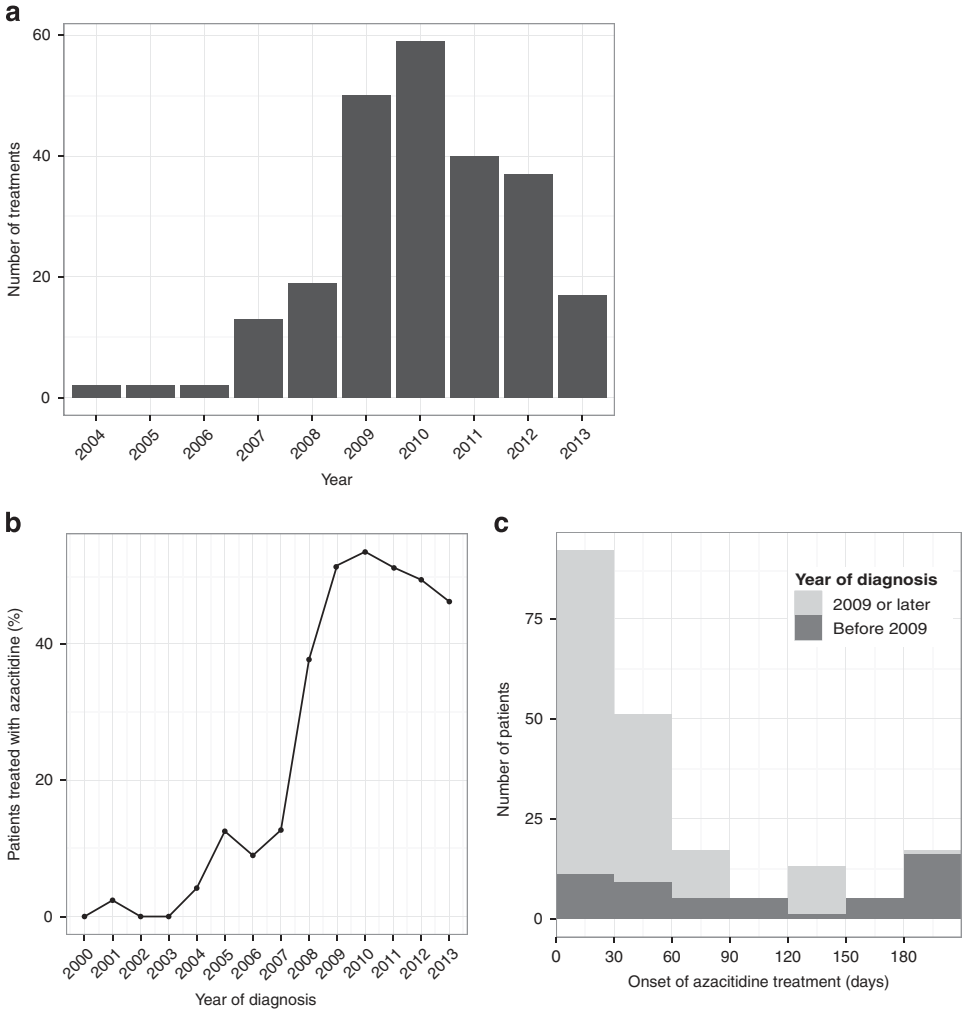

Figure 2. Treatment with azacitidine. (**a**) Number of treatments per year. (**b**) Percentage of patients who are treated with azacitidine as first-line therapy according to the year of diagnosis. (**c**) Delay between diagnosis of high-risk myelodysplastic syndrome and the onset of azacitidine treatment. Sample was split according to the year of diagnosis (before or after 2009).

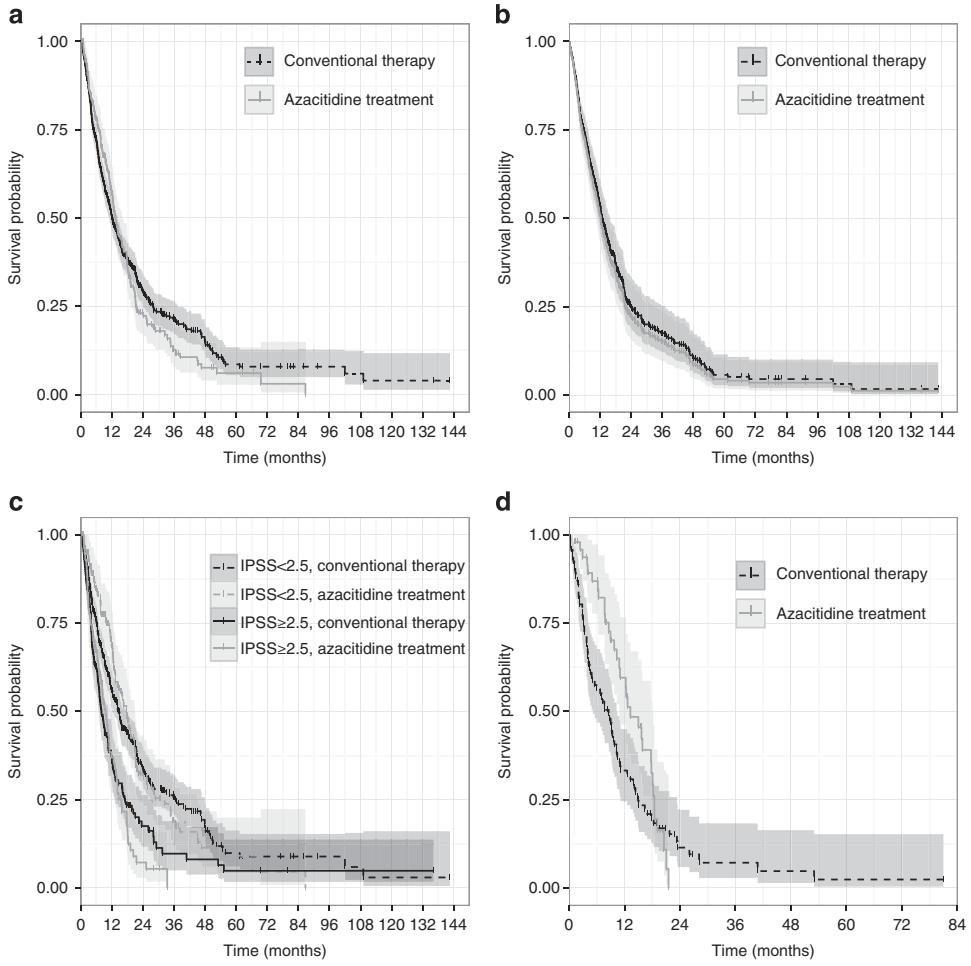

Figure 3. Impact of azacitidine on survival. (**a**) Survival curves in patients treated with conventional therapy or azacitidine (as first-line therapy). (**b**) Estimated survival curves according to the Cox regression model, after adjustment by age, IPSS, LDH levels at diagnosis, FAB classification and leukocyte count at diagnosis. There were no significant differences between azacitidine and conventional treatment. (**c**) Survival curves according to the treatment and the IPSS. (**d**) Impact of azacitidine on survival in the subgroup of patients with chromosome 7 abnormalities.

AML compared with 26% of the azacitidine-treated patients ($P = 0.42$). In the multivariable model with competitive risks, AML transformation was not significantly associated with the type of treatment received (hazard ratio, 1.14; 95% CI, 0.85–1.56; $P = 0.38$). The low number of events precluded to analyze the impact of treatment on AML progression in specific subsets of patients.

DISCUSSION

In this work we studied the changes in the therapies and outcomes over a 14-year period in a series of 821 patients with higher-risk MDS included in the registry of the GESMD. As expected, our data show that the use of azacitidine as first-line therapy in higher-risk MDS has experienced a fourfold increase in recent years, largely due to the publication of the results of two large randomized clinical trials[5,6] showing azacitidine to be more effective than conventional treatment and demonstrating in one of them a clear survival benefit in patients with higher-risk MDS (AZA-MDS-001 trial).[5] However, in sharp contrast with the results of these randomized multicenter trials comparing azacitidine to conventional CCT in patients with higher-risk MDS, we were unable to show in an unselected population of patients a significant advantage for azacitidine-treated patients in terms of both OS and AML-free survival. Noteworthy, OS in CCT-treated patients (median OS, 12.3 months) was similar to the one observed in the AZA-MDS-001 clinical trial (median OS, 15 months) whereas OS in azacitidine-treated patients was markedly shorter than in that study (median OS, 13.1 and 24.5 months, respectively). Further, OS for azacitidine-treated patients in the current series was closely similar to the one reported by Itzykson *et al.*[13] (median OS, 13.5 months) in 282 higher-risk MDS patients receiving azacitidine in a patient-named compassionate program (ATU program). This lack of significant benefit for azacitidine-treated patients remained in multivariable analysis and after excluding patients with CMML. Additionally, by using a propensity score technique, a matched pair comparison between azacitidine- and AML-type chemotherapy-treated patients also failed to reveal clear differences in their outcomes. Finally, in line with the lack of survival advantage observed for azacitidine-treated patients, there were no significant changes in the OS of patients with higher-risk MDS throughout the 2000–2013 period analyzed.

Several factors could potentially explain the apparent discrepancies between the results of this retrospective comparative study and the AZA-MDS-001 clinical trial. First, the incidence of poor-risk cytogenetics according to IPSS was higher in this report than in AZA-MDS-001 trial (40% vs 28%, respectively). Further, most of the chromosome 7 abnormalities were found in the context of a complex karyotype. Whereas it has been shown that the beneficial effect of azacitidine is more pronounced in MDS with chromosome 7 abnormalities,[5] its advantage in patients with

Table 2. Results of the Cox regression model

	HR	*95% Confidence interval*	P-*value*
Age at diagnosis (per year)	1.01	1.00–1.02	< 0.01
Instrumental variable	1.00	0.99–1.01	0.54
First line azacitidine	1.08	0.86–1.35	0.49
LDH (per U/l)	1.01	1.00–1.01	< 0.01
FAB			
Not classified	1	0.65–3.84	0.32
RA	1.57	0.55–2.83	0.59
RAEB	1.25	0.46–2.54	0.85
RAEB-T	1.08	0.46–3.87	0.60
RAS	1.33	0.61–3.48	0.39
CMML	1.46	0.25–3.64	0.95
Other	0.96		
IPSS			
1.5	1	1.19–2.00	< 0.01
2	1.54	1.29–2.5	< 0.01
2.5	1.80	2.01–3.75	< 0.01
3	2.75	1.99–6.85	< 0.01
3.5	3.69		
WBC (per 10^9/l)	1.00	0.99–1.01	0.38

Abbreviations: CMML, chronic myelomonocytic leukemia; FAB, French-American-British; HR, hazard ratio; IPSS, International prognostic score system; LDH, lactate dehydrogenase; RA, refractory anemia; RAEB, refractory anemia with excess of blasts; RAEB-t, refractory anemia with excess of blasts in transformation; RAS, refractory anemia with ring sideroblasts; WBC, white blood cell leukocytes.

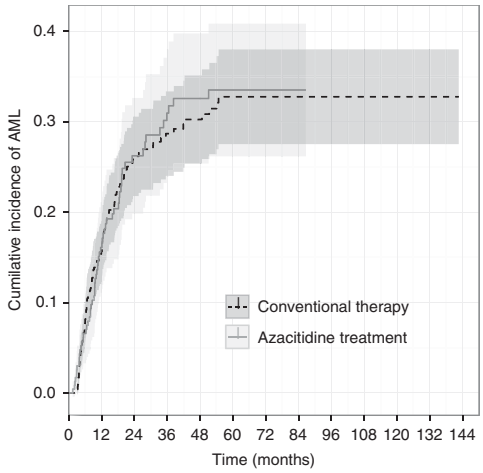

Figure 4. Cumulative incidence of AML transformation in patients treated with conventional therapy or azacitidine.

complex karyotype is less clear.[13] Yet, azacitidine-treated patients harboring a -7/del(7q) cytogenetic abnormality showed in our study a trend to a better OS compared with those in the CCT group. Another factor that could have affected influenced the results is the inclusion in this report, as in the ATU program,[13] of patients with therapy-related MDS (14% in the current series). This subset of patients has a grim outcome[14] and also responds poorly to azacitidine.[15] Third, the median number of cycles of azacitidine administered in this report (information available in 41% of the patients) was inferior to the one reported in the randomized AZA-MDS-001[5] clinical trial (6 vs 9), but similar to that reported in the AZA-AML-001 trial[16] and in the ATU program. Whether the lower than expected number of cycles of azacitidine administered in the current series in comparison with AZA-MDS-001 clinical trial was due to more advanced age (median, 74 vs 69 years), presence of comorbidities or differences in clinical practice is difficult to ascertain. In spite of these uncertainties, the lack of significance of the instrumental variable allows us to discard a clear influence of these or other hidden variables in our the results.

The main strength of this study is the use of a nationwide, unselected population of higher-risk MDS patients and reflecting clinical daily practice. In fact, our MDS population seems to be quite representative of these disorders. Their main characteristics were similar to those observed in other large epidemiological studies recently published[17–20] and the prognostic factors of outcome isolated in multivariable models, such as age,[21] IPSS score[2] and LDH,[22] were those expected in MDS patients. Additionally, the robustness of our findings is also supported by the fact that we could not find a beneficial effect of azacitidine when patients treated with chemotherapy or specific subgroups (CMML, MDS/myeloproliferative neoplasm and early deaths) were excluded from the analysis.

In conclusion, our data show that the outcome of patients with higher-risk MDS has not improved in recent years. Moreover, the use of azacitidine in this unselected population did not translate into better outcomes. The reasons for our findings are unclear and we cannot exclude that treatment with azacitidine was beneficial in specific subgroups of patients. Obviously, the results of this study require confirmation by other studies, especially coming from registries in larger populations of patients. Furthermore, these results illustrate the urgent need of both identifying the clinical and biological variables related to response to azacitidine and also addressing the management, efficacy and toxicity of new agents after regulatory approval and outside clinical trials.

CONFLICT OF INTEREST

TB has served as advisory board member and consultant for Celgene. DV is part of the speaker bureau of Celgene, Amgen, GSK, Novartis, MSD and astellas, and member of advisory boards for Celgene, Amgen, GSK and Pfizer. GS has received honoraria and research funding from Celgene, Novartis and Amgen, and is on the advisory committee for Amgen, Böehringer-Ingelheim, Celgene, Merck-Sharp and Dohme and Novartis. The Spanish Group on Myelodysplastic Syndromes is sponsored by Celgene and Novartis. The remaining authors declare no conflict of interest.

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