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ORIGINAL ARTICLE

Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications

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Abstract This study aimed to evaluate the evolution of iron overload, assessed by serum ferritin (SF), in transfusion-dependent lower risk patients with myelodysplastic syndrome (MDS), as well as to describe the occurrence of organ complications, and to analyze its relationship with iron chelation therapy. This observational retrospective study was conducted from March 2010 to March 2011 in 47 Spanish hospitals. A total of 263 patients with lower risk MDS (International Prognostic Scoring System [IPSS] low/intermediate-1 risk or Spanish Prognostic Index [SPI] 0–1 risk), transfusion-dependent, and who had received ≥10 packed red blood cells (PRBC) were included. At MDS diagnosis, patients received a mean of 2.8±3.9 PRBC/month, and 8.7 % of patients showed SF ≥1000 μg/L. Over the course of the disease, patients received a mean of 83.4±83.3 PRBC, and 36.1 % of patients presented SF ≥2500 μg/L. Cardiac, hepatic, endocrine, or arthropathy complications appeared/worsened in 20.2, 11.4, 9.9, and 3.8 % of patients, respectively. According to investigator, iron overload was a main cause of hepatic (70.0 %) and endocrine (26.9 %) complications. A total of 96 (36.5 %) patients received iron chelation therapy for ≥6 months, being deferasirox the most frequent first chelation treatment (71.9 %). Chelation-treated patients showed longer overall survival ($p<0.001$), leukemia-free survival ($p=0.007$), and cardiac event-free survival ($p=0.017$) than non-chelated patients. In multivariable analyses, age ($p=0.011$), IPSS ($p<0.001$), and chelation treatment ($p=0.015$) were predictors for overall survival; IPSS ($p=0.014$) and transfusion frequency ($p=0.001$) for leukemia-free survival; and chelation treatment ($p=0.040$) and Sorror comorbidity index ($p=0.039$) for

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cardiac event-free survival. In conclusion, these results confirm the potential survival benefit of iron chelation therapy and provide additional evidence on the deleterious effect of iron overload in lower risk MDS patients.

Keywords Myelodysplastic syndrome · Iron overload · Iron chelation therapy · Cardiac · hepatic · Serum ferritin

Introduction

The myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by ineffective hematopoiesis and by a significant risk of progression to acute myeloid leukemia. Anemia is the most frequent peripheral cytopenia described in MDS patients, with up to 85 % of patients manifesting anemia at diagnosis [1], and most MDS patients develop transfusion dependence.

Because of transfusion dependence, MDS patients are at high risk of transfusional iron overload evidenced by high serum ferritin (SF) levels, which has been associated with inferior overall survival (OS) and leukemia-free survival (LFS) in multiple retrospective studies in lower risk MDS [2–7]. Iron chelation has emerged as a therapeutic option to prevent the potential complications associated with regularly transfused MDS patients. Multiple analyses suggest that an appropriate iron chelation therapy is associated with improved OS and LFS in this group of patients [8–12].

Additionally, there is increasing evidence relating iron overload with cardiac and hepatic dysfunction in MDS patients [13–18]. In this regard, multiple retrospective analyses suggest that mortality is higher in MDS iron overloaded patients, with cardiac dysfunction being the primary cause of nonleukemic death [2, 4, 19]. The impact of iron overload on patients with thalassemia and the consequent benefits of iron chelation therapy have been widely validated. Nevertheless, the benefits of iron chelation therapy on organ damage, OS, and LFS in MDS patients are still a clinical debate [15]. Thus, specific studies are needed in order to provide sound evidence to support treatment guidelines in MDS patients.

The goals of this study were to evaluate the evolution of iron overload, assessed by SF, in transfusion-dependent lower risk MDS patients, as well as to describe the occurrence of clinical complications, and to analyze its relationship with chelation therapy.

Patients and methods

Study design

This was an observational, retrospective, and multicenter study conducted over 12 months (March 2010 to March 2011) in 47 Hematology Departments in Spanish hospitals. This study was conducted in accordance with the Guidelines for Ethical Review of Epidemiological Studies, Spanish Society of Epidemiology, the principles of the Helsinki Declaration, and its subsequent amendments. The study was approved by the Ethics Committee from Hospital Clínico Universitario San Carlos (Madrid, Spain). Written informed consent was obtained from patients prior to their inclusion in the study.

Patient population and study procedures

Inclusion criteria comprised patients aged over 18 years; with MDS according to the French-American-British cooperative group and the World Health Organization criteria, and an International Prognostic Scoring System (IPSS) low/intermediate-1 risk or Spanish Prognostic Index (SPI) 0–1 risk [5, 20, 21]; and red blood cell transfusion-dependent patients who had received ≥10 concentrates of packed red blood cells (PRBC) during at least 12 months previous to study inclusion.

The following variables were collected from all patients: (1) demographics (age and gender), (2) clinical data at MDS diagnosis (date of diagnosis, symptoms, comorbidities, and concomitant diseases), (3) hematological parameters at diagnosis (hemoglobin level, absolute neutrophil and platelet counts, and proportion of blast cells in bone marrow), (4) cytogenetics (conventional karyotype and fluorescence in situ hybridization [FISH], if available), (5) morphological classification (by IPSS and SPI), (6) treatment received for MDS (lenalidomide, azacitidine, and others), (7) data about PRBC transfusion requirements (date of first PRBC transfusion, and number of PRBC units administered from diagnosis and during the last 12 months), (8) SF levels (at diagnosis, at the start of iron chelation therapy, and at last assessment), (9) Sorror comorbidity index [22], (10) data about iron chelation therapy (date of first and last administration of an iron chelating agent, drug/s, dose/s, duration of chelation with every drug used, and reason for discontinuation or change in prescription), and (11) organ complications during the course of the disease (cardiac, hepatic, endocrine, and arthropathy). For cardiac complications, a patient was considered to experience a cardiac complication if he/she has suffered a complication related to cardiac insufficiency, arrhythmia, or both. The cause of complications was assessed as per investigator's criteria. The investigator obtained retrospective patients' information and survival status from medical charts and recorded them in case report forms.

Statistical analysis

Data were summarized using descriptive statistics. Continuous variables were described using central tendency and dispersion measurements (mean±1 standard deviation) and were

compared using *t* tests or nonparametric methods (Mann-Whitney *U* tests or Kolmogorov-Smirnov Z tests, as appropriate). Frequency distributions of discrete variables were compared using chi-squared tests or Fisher's exact tests, as appropriate. OS, LFS, and event-free survival were calculated by the Kaplan-Meier method; results were presented as survival curves and median survival times with 95 % confidence intervals. Patients receiving iron chelation therapy for ≥6 months were considered as chelated for survival analyses. Cardiac event-free survival was analyzed taking into account the first cardiac event per patient. The log-rank or Breslow test was used to compare survival curves, as appropriate. Multivariable proportional hazard regression models were used to evaluate prognostic factors for OS, LFS, and cardiac event-free survival. Independent variables (covariates) included for possible selection were age at diagnosis, gender, IPSS score at diagnosis, frequency of transfusions, iron overload (SF ≥2500 μg/L, as all patients were transfusion-dependent and had received ≥10 PRBC), chelation treatment, lenalidomide/azacitidine treatment, and Sorror comorbidity index. A forward stepwise variable selection procedure was used to determine the final multivariable model, which finally included the following covariates: age, gender, chelation treatment, iron overload, lenalidomide/azacitidine treatment, IPSS score, frequency of transfusions, and Sorror comorbidity index.

Missing data were not considered in the analyses, and a two-sided significance level of 0.05 was considered as statistically significant. Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc, Chicago, USA).

Results

Patients' characteristics

A total of 263 patients were evaluated in this study. Patient characteristics at diagnosis are described in Table 1. The median observation time (interquartile range) of patients included in the study analysis was 41 (19–80) months.

Overall iron metabolism

Data on iron metabolism is shown in Table 2. Patients had a mean transferrin saturation index (TSI) of 57.4±25.0, with 100 (38.0 %) patients reporting TSI ≥50 %. In addition, SF levels at diagnosis were 515.6±470.8 μg/L; 23 (8.7 %) patients had SF levels ≥1000 μg/L. Over the course of the disease, all patients received a mean of 83.4±83.3 PRBC, and a total of 95 (36.1 %) patients showed SF levels ≥2500 μg/L.

Iron metabolism according to chelation therapy

A total of 146 (55.5 %) patients received iron chelation therapy during the course of the disease. Fifty (19.0 %) patients discontinued it within 6 months of starting treatment, while 96 (36.5 %) patients received it for ≥6 months (PRBC transfusions at starting treatment, 31.7±28.5; SF levels at starting treament, 1865.5±1040.8 μg/L). Chelated patients were younger at MDS diagnosis than nonchelated patients (67.2±11.5 vs 74.6± 9.0 years; $p<0.001$) and showed lower Sorror comorbidity index (0.9±1.2 vs 1.7±1.9; $p=0.002$); there were no significant differences with regard to patients' gender.

Among patients under chelation therapy, most patients received deferasirox as the first iron chelation therapy (69 subjects, 71.9 %), followed by deferoxamine (21 subjects, 21.9 %), and deferiprone (4 subjects, 4.2 %).

As deferasirox was the agent most frequently used in our study population, detailed analyses of changes in iron balance throughout the course of the disease and causes for treatment discontinuation were performed in patients receiving deferasirox. Specifically, data were evaluated according to whether a decrease or an increase in SF levels was observed when deferasirox was used as a first iron chelation agent (Table 3). Patients with increased SF levels showed slightly lower deferasirox doses (16.8±5.6 vs 18.3±3.6 mg/kg/day), higher transfusion frequencies (2.7±2.2 vs 2.2±1.0 PRBC/months), and shorter treatment durations (20.8±10.7 vs 24.6±11.3 months).

Twenty-one (30.4 %) patients discontinued deferasirox. The main causes for deferasirox discontinuation were adverse events (eight patients), reaching normal SF levels (four patients), and lack of efficacy (two patients).

Overall survival

OS was longer for patients receiving chelation treatment (not reached vs 153 [78.0–228.0] months; $p<0.001$) (Fig. 1a). When data were analyzed in patients who presented SF levels lower than 2500 μg/L, OS was also longer for chelated patients than nonchelated patients (median survival was not reached in both groups; $p=0.008$). In patients who maintained SF levels ≥2500 μg/L, OS was also longer for chelated patients (177.0 [139.6–214.4] vs 98.0 [70.1–125.9] months; $p=0.011$).

In a multivariable analysis, the independent variables predicting OS were age ($p=0.011$), IPSS ($p<0.001$), and chelation treatment ($p=0.015$) (Table 4).

Leukemia-free survival

Only a small proportion of the study patients developed acute myeloid leukemia (18 subjects, 6.8 %), the majority of whom (14 subjects, 77.8 %) were from the nonchelated patient group. Patients receiving iron chelation therapy had longer

Table 1 Baseline patient characteristics (N=263)

Patient characteristics	Value
Age, mean±SD, years[a]	71.9±10.5
Gender, *n* (%)[b]	
Male	150 (57.0)
Female	107 (40.7)
French–American–British classification, *n* (%):[c]	
RA	122 (46.4)
RARS	122 (46.4)
RAEB	8 (3.0)
CMML	9 (3.4)
World Health Organization classification, *n* (%):[c]	
RA	39 (14.8)
RARS	95 (36.1)
RCMD	63 (24.0)
RCMD-RS	26 (9.9)
RAEB-I	7 (2.7)
MDS-U	3 (1.1)
Myelodysplastic syndrome associated to isolated del(5q)	19 (7.2)
CMML	9 (3.4)
IPSS, *n* (%):[d]	
IPSS low risk	218 (82.9)
IPSS intermediate-1 risk	0 (0.0)
SPI, *n* (%):[e]	
SPI low risk	204 (77.6)
SPI intermediate risk	30 (11.4)
Hemoglobin level, mean±SD, g/dL[b]	9.2±1.8
Leukocyte blood count, mean±SD, × 10^9/L[f]	5.6±3.9
Monocyte blood count, mean±SD, × 10^9/L[g]	0.6±1.4
Neutrophil blood count, mean±SD, × 10^9/L[h]	3.1±2.5
Platelet count, mean±SD, × 10^9/L[i]	231.1±133.6
Transfusion frequency, mean±SD, PRBC/month:	
Overall transfusion frequency[j]	2.8±3.9
Transfusion frequency chelated patients[k]	2.5±1.6
Transfusion frequency nonchelated patients[l]	3.0±4.9
Sorror comorbidity index:[m]	
Median (interquartile range)	1.0 (0.0–2.0)
Sorror index ≥3, *n* (%)	57 (21.7)

CMML chronic myelomonocytic leukemia, *del(5q)* chromosome 5q deletion, *IPSS* International Prognostic Scoring System, *MDS-U* myelodysplastic syndrome not otherwise specified, *RA* refractory anemia, *RAEB* refractory anemia with excess blasts, *RAEB-I* refractory anemia with excess blasts type I, *RARS* refractory anemia with ringed sideroblasts, *RCMD* refractory cytopenia with multilineage dysplasia, *RCMD-RS* refractory cytopenia with dysplasia and ringed sideroblasts, *SD* standard deviation, *SPI* Spanish Prognostic Index, *PRBC* packed red blood cells

[a] Missing data, n=11
[b] Missing data, n=6
[c] Missing data, n=2
[d] Missing data, n=45
[e] Missing data, n=29
[f] Missing data, n=7
[g] Missing data, n=20
[h] Missing data, n=18
[i] Missing data, n=9
[j] Missing data, n=16
[k] Missing data, n=1
[l] Missing data, n=15
[m] Missing data, n=4

LFS than those nonchelated (median survival was not reached in both groups; p=0.007) (Fig. 1b).

In a multivariable analysis, the independent variables predicting LFS were IPSS (p=0.014) and transfusion frequency (p=0.001) (Table 4).

Organ complications and event-free survival

The information on organ complications is summarized in Table 5. Interestingly, the number of PRBC transfused (53.6 ±61.2) and the SF levels (1945.4±1527.6 μg/L) at the onset of cardiac complications were lower than those observed at the onset of hepatic complications (58.7±73.7 and 2387.2± 1722.2 μg/L, respectively). According to the opinion of investigators who collected the data, iron overload was the main factor related to hepatic complications (21 subjects, 70.0 %), followed by drugs (7 subjects, 23.3 %), viral infections (3 subjects, 10.0 %), alcohol abuse (1 subject, 3.3 %), and others (6 subjects, 20.0 %); more than one cause was reported in 9 (30.0 %) subjects. For arthropathy, arthrosis was the main cause of complications (7 subjects, 70.0 %). For endocrine complications, diabetes (8 subjects, 30.8 %) and iron overload (7 subjects, 26.9 %) were described as the main causes of complications. In the case of cardiac complications, the cause

Table 2 Overall iron metabolism (N=263)

Parameter	Value
TSI at MDS diagnosis:[a]	
Mean±SD	57.4±25.0
<50 %, *n* (%)	87 (33.1)
50–75 %, *n* (%)	45 (17.1)
≥75 %, *n* (%)	55 (20.9)
SF at MDS diagnosis:[b]	
Mean±SD, μg/L	515.6±470.8
<500 μg/L, *n* (%)	144 (54.8)
500–1000 μg/L, *n* (%)	67 (25.9)
1000–2500 μg/L, *n* (%)	20 (7.6)
≥2500 μg/L, *n* (%)	3 (1.1)
SF over the course of disease:[c]	
≤1000 μg/L, *n* (%)	41 (15.6)
1000–2500 μg/L, *n* (%)	94 (35.7)
>2500 μg/L, *n* (%)	95 (36.1)

MDS myelodisplastic syndrome, *SF* serum ferritin, *TSI* transferrin saturation index

[a] Missing data, n=76

[b] Missing data, n=29

[c] Missing data, n=33

was unknown in most cases (heart failure, 43 subjects, 93.5 %; heart arrhythmia, 23 subjects, 95.8 %). Iron overload was not reported as a cause for cardiac complication in any of the described cases.

Patients receiving chelation treatment had longer cardiac event-free survival in comparison with nonchelated patients (137.0 [108.5–165.5] vs 96.0 [84.1–107.9] months; p=0.017) (Fig. 1c); in a multivariable analysis, the independent variables predicting cardiac event-free survival were chelation treatment (p=0.040) and Sorror comorbidity index (p=0.039) (Table 4). Differences between chelated and nonchelated patients were not observed in terms of hepatic, endocrine, or arthropathy event-free survival (Table 5).

Discussion

This observational retrospective study shows that the administration of iron chelation therapy for ≥6 months results in longer patients' survival and cardiac event-free survival. Almost 64 % of patients in our study reached SF levels higher than 1000 μg/L and 36 % higher than 2500 μg/L, while 36.5 % received chelation therapy for ≥6 months. Both the number of PRBC transfused and SF levels were over those recommended by current guidelines on MDS management [23–25]. Nonetheless, our data show an improvement on these parameters in comparison with previous assessments in Spain, where SF levels in the last follow-up reached 2480±1648 μg/L [26]. Our findings are consistent with previous analyses evaluating the benefit of iron chelation therapy on patients' survival [9, 11, 27, 28]. Adequate chelation therapy administered for ≥6 months has shown to improve OS [29, 30], and it has also been identified as a factor predicting for OS [8, 29], along with other variables such as age [4, 31], IPSS [4, 8, 31], transfusion requirements [3, 4, 8, 31], and the development of secondary iron overload [3, 4]. The increased risk of progression to acute myeloid leukemia under conditions of oxidative stress, characteristic of iron overload, has been validated by indirect data from preclinical studies showing the effect of iron modifying cell growth and differentiation [32]. Indeed, the analysis of risk transformation to acute myeloid leukemia has suggested that iron overload and transfusion dependence have a significant impact on this endpoint [33]. Although our survival analysis showed longer LFS in chelated patients, iron chelation therapy was not identified as an independent variable predicting for LFS. There is no agreement with regard to the effect of chelation therapy on the risk of progressing to acute myeloid leukemia, though Lyons et al. reported a trend to longer time in patients receiving iron chelation therapy [30]. Thus, further research is still needed to clarify its effect on LFS.

In addition to the positive effect of chelation therapy on patients' survival, our results also support the benefit of chelation cherapy on cardiac event-free survival. The assessment of prevalence and impact of comorbidities in over 1700 pa-

Table 3 Iron balance in patients who received deferasirox as first chelation treatment

Iron balance	Mean±SD PRBC transfusion frequency (PRBC/month)	Mean±SD deferasirox dose (mg/kg/day)	Mean±SD treatment duration (months)	Mean±SD SF before treatment (μg/L)	Mean±SD SF after treatment (μg/L)
Increased SF levels (n=27)	2.7±2.2	16.8±5.6[a]	20.8±10.7	1,634.9±673.1 p<0.001	3,094.0±1,855.2
Decreased SF levels (n=40)	2.2±1.0	18.3±3.6	24.6±11.3	2,032.3±1,143.1 p<0.001	1,056.2±634.1

PRBC packed red blood cells, *SF* serum ferritin

[a] Missing data, n=5

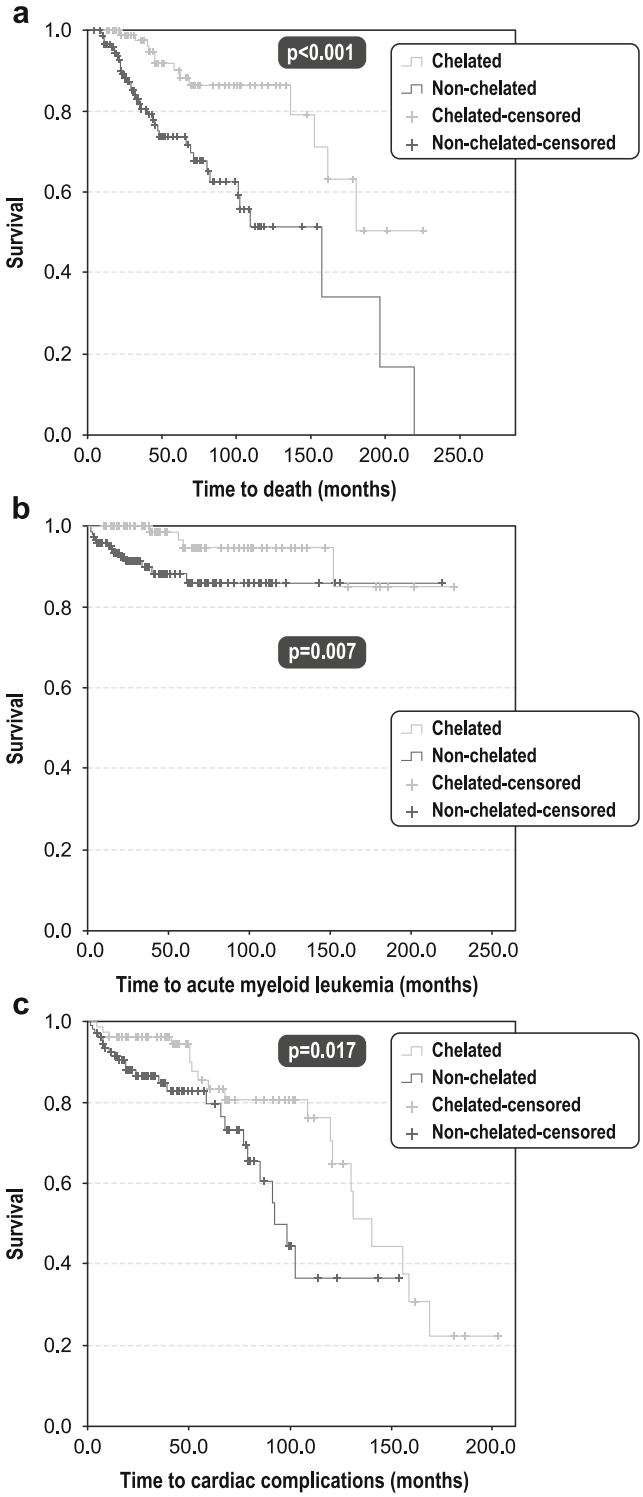

Fig. 1 Overall survival (**a**), leukemia-free survival (**b**), cardiac event-free survival (**c**)

tients from a US medical database revealed that 51 % of patients with newly diagnosed MDS suffered from comorbidities, and those with comorbidities had an increased risk of death [34]. Specifically, hepatic and cardiac dysfunctions associated to iron damage in transfusion-dependent low-risk

Table 4 Multivariable proportional hazard regression models for overall survival, leukemia-free survival, and cardiac event-free survival

Parameter	Hazard ratio	95 % CI	*p*-value
Overall survival:			
Age	1.073	1.016–1.133	0.011
IPSS	6.859	2.498–18.833	<0.001
Chelation treatment	0.361	0.159–0.822	0.015
Leukemia-free survival:			
IPSS	9.415	1.582–56.050	0.014
Transfusion frequency	1.095	1.038–1.154	0.001
Cardiac event-free survival:			
Chelation treatment	0.405	0.170–0.961	0.040
Sorror comorbidity index	1.240	1.011–1.521	0.039

CI confidence interval

MDS patients have been extensively reported to carry along a higher mortality rate [2–4]. In light of the high incidence of cardiac and hepatic comorbidities in MDS patients, efforts have been made to include these complications in specific indexes to predict the risk of nonleukemic death in MDS patients [35]. Furthermore, Hoffbrand et al. [36] recommended considering liver and cardiac iron concentrations as additional valuable parameters at the moment of deciding whether or not to start chelation treatment in low-risk PRBC transfusion-dependent MDS patients.

Our study's assessment of organ complications during the course of the disease is a novel approach. In this regard, iron overload was reported as the main factor related to hepatic complications. Nonetheless, we did not find significant differences in hepatic event-free survival for chelated and nonchelated patients. One of the limitations of our study was the low number of hepatic events reported (n=30), as this may have prevented statistically significant differences between groups to appear. In contrast, although researchers in our study did not relate cardiac complications to iron overload, the results showed a significant difference between those treatment groups for cardiac event-free survival (137 months in chelated vs 96 months in nonchelated patients; p=0.017). Interestingly, the number of PRBC transfused and SF levels at the onset of cardiac complications (54 PRBC and 1945 μg/L) were lower than those observed at the onset of hepatic complications (59 PRBC and 2387 μg/L). Differences are even more striking when compared with evidence from thalassemic patients where the onset of cardiac complications is associated to PRBC values ranging from 75 to 100 and SF levels above 2500 μg/L [37].

As MDS is primarily a hematologic malignancy of the elderly [38], with 86 % of cases diagnosed in individuals older than 60 years [25], comorbidities may compromise elderly patients to a greater degree, and they become more susceptible to the deleterious effect of iron overload. This can be

Table 5 Baseline and evolution of organ complications (N=263)

Complication	Total, n (%)	Mean±SD number of PRBC transfusions at start of complication	Mean±SD SF levels at start of complication, μg/L	Median (95 % CI) event-free survival, months	
				Chelated patients	Non-chelated patients
Cardiac	53 (20.2 %)[a]	53.6±61.2[b]	1945.4±1527.6[c]	137.0 (108.5–165.5)	96.0 (84.1–107.9)[*]
Hepatic	30 (11.4 %)[d]	58.7±73.7[e]	2387.2±1722.2[f]	–[**]	208.0 (– – –)
Endocrine	26 (9.9 %)[g]	60.7±59.2[f]	1839.2±1593.7[e]	–[**]	–[**]
Arthropathies	10 (3.8 %)[f]	48.1±42.4[h]	4718.2±6094.7[i]	–[**]	–[**]

CI confidence interval, *PRBC* packed red blood cells, *SD* standard deviation, *SF* serum ferritin

[*] p=0.017 versus chelated patients

[**] Median was not reached

[a] Missing data, n=48

[b] Missing data, n=18

[c] Missing data, n=20

[d] Missing data, n=10

[e] Missing data, n=8

[f] Missing data, n=6

[g] Missing data, n=25

[h] Missing data, n=9

[i] Missing data, n=4

particularly relevant for cardiac complications and might partly explain the differential thresholds in PRBC and SF levels observed for cardiac versus hepatic events in our population. In addition, our study pointed out comorbidities—Sorror comorbidity index—as predictive for cardiac event-free survival, along with chelation treatment; although chelated patients showed less comorbidities, the benefit of chelation treatment remained irrespective of comorbidity occurrence. Furthermore, cardiac complications in MDS patients may be compounded by several factors (e.g., hypertension and coronary artery disease) and may easily hide behind the usual causes of death in the elderly [39].

One caveat of this study is common to the potential biases and confounding effects of all retrospective analyses. Thus, these findings—especially those on cardiac complications and cardiac event-free survival—must be confirmed in prospective trials.

Nevertheless, the study results provide further evidence on the deleterious effect of iron overload and support the potential survival benefit of iron chelation therapy in lower risk MDS patients. Indeed, chelation-treated patients showed longer OS, LFS, and cardiac event-free survival. Therefore, we believe that this study provides physicians with meaningful information to take into account when managing MDS patients.

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Ethical standards This study was conducted in accordance with the Guidelines for Ethical Review of Epidemiological Studies, Spanish Society of Epidemiology, the principles of the Helsinki Declaration, and its subsequent amendments. The study was approved by the Ethics Committee from Hospital Clínico Universitario San Carlos (Madrid, Spain). Written informed consent was obtained from patients prior to their inclusion in the study. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation, and with the Helsinki Declaration of 1975 and its later revisions.

Conflict of interest The authors declare that Dr. Maria Diez Campelo has received research funding and honoraria from Novartis; and Dr. Guillermo Sanz has received research funding from Celgene and Novartis, and serves as a consultant to Celgene, Amgen, Novartis and Boehringer Ingelheim Pharma GmbH. The remaining authors have no conflict of interest to disclose.

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