Leukemia Research 76 (2019) 53–57

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Hepatic and cardiac and iron overload detected by T2* magnetic resonance (MRI) in patients with myelodisplastic syndrome: A cross-sectional study

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ARTICLE INFO

Keywords:
Myelodysplastic-myeloproliferative diseases
Iron overload
Magnetic resonance

ABSTRACT

Introduction: Transfusion-dependent anemia and iron overload are associatedwith reduced survival in myelodysplastic syndrome (MDS). This cross-sectional study aimed to evaluate the prevalence of hepatic and cardiac overload in patients with MDS as measured by T2* magnetic resonance imaging (MRI), and its correlation with survival.

Methods: MDS or chronic myelomonocytic leukemia patients had iron overload evaluated by T2* MRI. HIO was considered when hepatic iron concentration ≥ 2 g/mg. Cardiac iron overload was considered with a T2*-value < 20 ms.

Results: Among 71 patients analyzed, median hepatic iron concentration was 3.9 g/mg (range 0.9–16 g/mg), and 68%of patients had hepatic iron overload. Patients with hepatic iron overload had higher mean ferritin levels (1182 ng/mL versus 185 ng/mL, $p < 0.0001$), transferrin saturation (76% versus 34%, $p < 0.0001$) and lower survival rates. Median cardiac T2*value was 42 ms (range 19.7–70.1 ms), and only one patienthad a T2* value indicative of cardiac iron overload.

Conclusions: Hepatic iron overload is found in two thirds of patients, even in cases without laboratory signs of iron overload. Hepatic iron overload by T2* MRI is associated with a decreased risk of survival in patients with MDS.

1. Introduction

Myelodysplastic syndrome (MDS) is a heterogeneous group of disorders characterized by clonal, dysplastic, ineffective hematopoiesis and an increased propensity to develop acute myeloid leukemia (AML) [1]. Approximately 60%–80% of patients with MDS experience symptomatic anemia, and 40%–50% may develop transfusion-dependent anemia. Transfusion-dependent anemia is associated with the development of iron overload and decreased survival. However, iron overload may occur before patients become transfusion-dependent, since ineffective erythropoiesis suppress hepcidin production in the liver and may lead to increased iron absorption in the gut. The deleterious role of iron overload in the survival of patients with MDS has been extensively reported, with an approximate increase of 30% in risk of death for every 500 ng/ml increase in serum ferritin above the 1000 ng/ml threshold [2].

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https://doi.org/10.1016/j.leukres.2018.12.001
Received 16 March 2018; Received in revised form 17 November 2018; Accepted 3 December 2018
Available online 04 December 2018
0145-2126/

The gold standard exam for detection of iron overload is tissue biopsy with Prussian blue staining, most commonly done in the liver. However, this procedure is associated with a risk of bleeding and infection, even more in patients with MDS, who are often thrombocytopenic. A variety of non-invasive methods for measuring iron overload exist, including serum ferritin, labile plasma iron and magnetic resonance imaging (MRI). serum ferritin is the most commonly used parameter for assessing body ironcontent [1]. However, since serum ferritin is also a marker of inflammation and acute-phase reactant, it may falsely be elevated and it correlates poorly with iron overload in specificorgans [1,3]. Labile plasma iron > 0.4 μM is highly correlated with iron overload, and has been validated in patients with β-thalassemia [4]. However, the methodology for measurement of labile plasma iron has not been standardized outside of a few laboratories, and as such it is rarely used in daily clinical practice.

MRI is an effective method for evaluating iron overload in specific organs such as the heart and liver [5–8]. MRI can achieve high sensitivity and specificity in the analysis of liver iron content [9], and it is considered the best surrogate marker of total body iron content available [10]. Cardiac T2* MRI provides an accurate measure of cardiac iron overload [4], although it correlates poorly with serum ferritin and liver iron concentration, suggesting a different mechanism of iron overload [6]. In one study with T2* MRI in patients with MDS, it was demonstrated that 19% of patients had evidence of cardiac iron overload [11].

The primary objective of this study was to evaluate the prevalence of hepatic and cardiac iron overload detected by MRI in a cohort of patients with MDS not receiving iron chelation therapy (confounding factor). Secondary objectives were: to investigate the correlation of hepatic and cardiac iron overload detected by MRI with baseline clinical features, including transfusion requirements, and with laboratory iron indexes (serum iron, serum ferritin and labile plasma iron); and to evaluate the impact of iron overload as detected by MRI on survival and leukemic transformation.

2. Patients and methods

2.1. Study design, ethics and participants

This was a cross-sectional study, conducted in a private hospital in Brazil, according to the Declaration of Helsinki guidelines. The local Institutional Review Board approved the study protocol and we obtained written informed consent from all subjects.

We recruited eligible participants among all consecutive patients who underwent MRI evaluation of cardiac and hepatic iron overload in our hospital (even those referred by other institutions) between May 2009 and March 2012. All patients underwent MRI in the same setting and with the same equipment and protocol for imaging. We invited to participate in this study all patients with a diagnosis of WHO-2008 defined MDS and MDS/MPD, irrespectively of transfusion requirements. We reclassified the patients according to the latest WHO Classification (2016). We excluded patients under 18 years old and those undergoing iron chelation therapy (because chelation therapy would be a confounding factor in statistical analysis).

2.2. Outcomes and measurements

We collected detailed characteristics of disease and transfusion dependency, and risk-classified patients using the WHO-based prognostic scoring system (WPSS), to confirm the initial diagnosis and the eligibility for the study. We collected blood samples at the same day of MRI examination for serum ferritin and labile plasma iron measurements. We investigated the number of transfused RBC units via chart reviews, and the patients informed their clinical history by filling data collection forms. We extracted data on follow-up outcomes from the medical record and contacted the physicians in charge of patient care at referring centers for details and confirmations.

2.3. Magnetic resonance imaging

We examined all patients using T2* MRI on a 1.5 T scanner (General Electric Healthcare - Milwaukee, Wisconsin- USA) with the combination of body-matrix and spine-matrix surface coils. Post processing was performed on ReportCARD software (version 4.4, General Electric Healthcare – Milwaukee, Wisconsin – USA). We used a validated $T2^*$ method first introduced by Andersson et al. [6] ECG-gated breath-hold spoiled gradient recalled echo sequence was applied at different echo times (TE 3, 5, 6.5, 8, 10, 12, 14, 17, 20, 23, 26 and 29 ms) with the following parameters: repetition time 500 ms, flip angle 20°, slice thickness 10 mm, matrix size 128 × 256, field of view 350 mm, seven phase encoding steps per cardiac cycle and time of acquisition 15–25 s. A single short-axis mid-ventricular slice was acquired with constant imaging parameters for each subject. The radiologist, an experienced reader, chose a region of interest of 1.0-1.3 cm^2 for the signal intensity measurement from the left ventricular septum. A mono-exponential fitting was used in the cardiac $T2^*$ ($1/R2^*$) measurement analysis. We chose $R2^*$ as a primary cardiac iron indicator, as it is directly proportional to iron concentration [12]. For this study, we defined cardiac iron overload as $R2^* \geq 01$/second (corresponding $T2^* \leq 20$ ms), and used this value as a cutoff point for normal and pathologically elevated cardiac iron.

For assessing liver iron overload, we used a spoiled gradient recalled echo imaging sequence with fat suppression for liver iron assessment at 8 different echo times (TE 2–16 ms, 2 ms interval) with the following parameters: repetition time 34 ms, flip angle 20°, slice thickness 10 mm, matrix size 192 × 256 voxels, field of view 400 mm and time of acquisition 4.50 min. An experienced reader chose a region of interest, freehand, for signal intensity measurement from the right part of the right liver lobe in segments 6 and 7 to avoid vessels and possible artifacts. A mono-exponential fitting with truncation method was applied to the data for calculation of T2*/R2* [13]. R2* values were converted into liver iron concentration by applying a conversion equation described elsewhere [14].

2.4. Endpoint definition

We defined hepatic iron overload in this study as the presence of a hepatic iron concentration ≥ 2.2 mg/g of liver tissue as estimated by MRI. We considered a patient as having cardiac iron overload when T2* value was < 20 ms.

We defined overall survival (OS) as the time from MRI evaluation until death from any cause, considering patients who were alive at last follow-up as censored. We defined cumulative incidence of transformation to AML considering the competing risk of death without transformation.

2.5. Statistical analysis

We used Wilcoxon rank sum and Chi-square/Fischer's exact test to compare continuous and categorical variables, respectively. OS was estimated using the Kaplan-Meier method, and differences in survival curves were compared by the log rank test. A Cox model was fit to determine variables associated with OS. Impact of hepatic iron overload on incidence of transformation to AML was determined by a Fine Gray regression model. A univariate Cox model was fit to estimate the hazard ratio (HR) for hepatic iron overload. The HR for hepatic iron overload was further adjusted by a multivariate model including hepatic iron overload and the Revised International Prognostic Scoring System for myelodysplasia (R-IPSS).

Statistical analysis was performed with STATA (v14.0), and with R (version 34.3) and alpha error was set at 5%.

Table 1
Baseline clinical features of patients.

Feature	Median [range] or N (%)
Age, years	66 [18–89]
Male sex	39 (54)
Hemoglobin, g/dL	10.6 [5–12.6]
ANC, x 10^9/L	2.15 [0–14.78]
Platelets, x 10^9/L	109 [8–1046]
Bone marrow blasts, %	1.2 [0–19]
WHO 2016 Classification	
• RC (MDS-SLD)	4 (6)
• RARS (MDS-RS-SLD)	10 (14)
• RCMD (MDS-MLD)	27 (39)
• RAEB-I/II (MDS-EB-1/2)	17 (22)
• MDS with chromosome 5 abnormalities (MDS with isolated del(5q)	4 (6)
• CMML	3 (4)
• Therapy-related MDS (t-MN)	2 (3)
• RARS-T (MDS/MPN with ring sideroblasts and thrombocytosis)	2 (3)
• MDS-U	2 (3)
Karyotype risk (WPSS)	
• Good	52 (73)
• Intermediate	6 (9)
• Poor	5 (7)
• No metaphases	8 (11)
Transfusion dependency	
• Yes	42 (59)
• No	29 (41)
Number of transfusions	5 [0–84]
Iron saturation, %	59.5 [5–100]
Ferritin, ng/ml	849.9 [44.3–12,738]
LPI, microM	0.23 [−0.21 to 12.93]

ANC, absolute neutrophil count; BM, bone marrow; CMML, chronic myelomonocytic leukemia; LPI, labile plasma iron; MDS, myelodysplastic syndrome; MDS-U, myelodysplastic syndrome-unclassified; RAEB, refractory anemia with excess blasts; RARS, refractory cytopenia with ring sideroblasts; RARS-T, refractory cytopenia with ring sideroblasts and thrombocytosis; RC, refractory cytopenia; RCMD, refractory cytopenias with multilineage dysplasia; WHO, World Health Organization; WPSS, WHO-based Prognostic Scoring System.

3. Results

3.1. Baseline features and serum markers of iron overload

During the study period, we recruited 77 patients, but we had to exclude 5, because they could not undergo MRI due to claustrophobia, and 1 patient in whom MDS was discarded after revision of clinical and laboratory data, so 71 patients remained for analysis. None of the patients were receiving iron-chelating therapy at the time of inclusion in the study. Patients' characteristics are described in Table 1. Among these, 28 patients received modifying therapy, including thalidomide (11), cyclosporine (6), hypomethilant therapy (azacytidine, 7 and decitibine, 8), with some patients receiving two therapies.

Sixty-two patients could be classified by the WPSS risk score, and the majority had either very low risk or low risk disease (N = 22; 41%). Twelve patients (22%) had intermediate risk disease, high-risk disease was present in 19 patients (35%) and only one (2%) had very high risk MDS. A total of 42 patients (59%) had transfusion dependency according to the WPSS criteria. The median total number of RBC packs transfused was 5 (range 0–84). Serum biomarkers of iron overload were collected at the day of MRI imaging. Median SF of all patients was 849.9 (44.3-12,738 ng/ml), but for transfused patients was 968 ng/ml versus 947.7 ng/ml for non-transfused patients (p = 0.99).

3.2. Prevalence of iron overload by MRI and correlation with baseline clinical features

Four patients could not have hepatic iron concentration measured by MRI due to technical errors or artifacts during imaging acquisition.

Table 2
Clinical features of patients according to the presence of hepatic iron overload.

Feature	Mean (95% CI) or N (% and 95% CI)		P
	N-HIO	HIO	
Age, years	65 (60–71)	62 (58–67)	0.42
Male sex	11 (52%; 30–74%)	25 (54%; 39–69%)	1.00
Hemoglobin, g/dL	10 (9.2–10.7)	8.66 (8.1–9.1)	0.008
ANC, x 10^9/L	2.59 (1.75–3.44)	2.76 (1.93–3.58)	0.79
Platelets, x 10^9/L	175 (116–234)	176 (109–243)	0.98
Bone marrow blasts, %	2 (0-4)	3 (2-5)	0.10
WHO 2016 Classification			0.96
MDS-SLD	2 (9%; 1–32%)	2 (4%; 0.7–16%)	
MDS-RS-SLD	4 (19%; 6–42%)	6 (13%; 5–27%)	
MDS-MLD	8 (39%; 19–61%)	17 (38%; 24–52%)	
MDS-EB-1	2 (9%; 1–32%)	7 (15%; 7–29%)	
MDS-EB-2	2 (9%; 1–32%)	5 (11%; 4–24%)	
MDS with isolated del(5q)	1 (5%; 0.1–18%)	3 (7%; 2–19%)	
MDS-U	1 (5%; 0.1–18%)	1 (2%;0.1–13%)	
t-MN	0 (0%; 0–19%)	2 (4%; 0.7–16%)	
MDS/MPN with ring sideroblasts and thrombocytosis	1 (5%; 0.1–18%)	1 (2%;0.1–13%)	
CMML	0 (0%; 0–19%)	2 (4%; 0.7–16%)	
Karyotype risk (IPSS-R)			0.91
Good	18 (90%; 66–98%)	34 (85%; 69–94%)	
Intermediate	1 (5%; 0.2–27%)	1 (2.5%; 0.1–15%)	
Poor	1 (5%; 0.2–27%)	3 (7.5%; 2–21%)	
Very Poor	0 (0%; 0–20%)	2 (5%; 0.8–18%)	
Transfusion dependency			0.02
Yes	9 (42%; 22–65%)	34 (74%; 58–85%)	
No	12 (58%; 34–77%)	12 (26%; 15–41%)	
Number of transfusions	4 (0–10)	15 (9–21)	0.011
Iron saturation, %	40 (33–48)	67 (59–75)	8.05e-06
Ferritin, ng/ml	364 (222–505)	1373 (1067–1680)	2.12e-07
LPI, microM	0.29 (0.07–0.52)	1.47 (0.66–2.29)	8.7e-03

ANC = absolute neutrophil count; HIO = hepatic iron overload; N-HIO = without hepatic iron overload; LPI = labile plasma iron.

In the remaining 67 patients, median hepatic iron concentration was 3.3 mg/g (range 0.4–16 mg/g), and 45 patients (67%, 95% confidence interval [CI] 55–78%) had hepatic iron overload. Clinical features by hepatic iron overload are summarized in Table 2. Patients with hepatic iron overload were more likely to be transfusion-dependent by WPSS criteria (76% vs. 41%; p = 0.006), have higher percentage of bone marrow blasts (median 2% vs. 0%; p = 0.03), higher serum ferritin level (median 1184.2 ng/ml vs. 228.8 ng/ml; p < 0.00001), higher transferrin saturation (median 76% vs. 37.5%, p = 0.0001), lower hemoglobin (median 8.4 g/dL vs. 10.6 g/dL, p = 0.0036) and a higher number of prior transfused RBC units (median 9 vs. 0, p = 0.0004). There was no difference in WPSS risk categories (p = 0.52), karyotype risk (p = 0.65) nor in serum levels of labile plasma iron (median 0.29 microM vs. 0.15 microM, p = 0.10). Patients with hepatic iron overload neither had higher serum levels of aspartate aminotransferase (AST; p = 0.34) nor alanine aminotransferase (ALT; p = 0.32).

A total of 11 patients (16.4%, 95% CI 9%–27%) had no prior history of RBC transfusion dependency by WPSS criteria but presented with hepatic iron overload by T2* MRI evaluation. Compared to the remaining cohort, none of these 11 patients had high risk or very high risk MDS by WPSS (0% versus 32%, p = 0.023).

Moderate/severe hepatic iron overload was found in 20 patients (30%, 95% CI 20–42%). These patients were more likely to be transfusion-dependent (85% vs. 55%, p = 0.018), had higher serum ferritin (1398.95 vs. 593.5 ng/ml, p = 0.0002), higher transferrin saturation (89.5% versus 44%, p < 0.00001) and higher labile plasma iron (median 0.83 microM versus 0.15 microM, p = 0.038). They also had

received a higher number of RBC units prior to MRI evaluation (median 12 versus 2 units, p = 0.0088).

Only one patient presented with a T2* relaxation time compatible with heart iron overload. This patient had a diagnosis of transfusion-dependent RAEB-I, and had a prior history of having received transfusion of 40 units of RBCs. Serum ferritin was 12,738.6 ng/ml, transferrin saturation was 96%, and labile plasma iron was 7.66 microM. No abnormality of cardiac function was seen in this patient (left ventricle ejection fraction 60%).

3.3. Hepatic iron overload detected by MRI and survival and risk of transformation to acute myeloid leukemia

Information on OS outcomes and hepatic iron overload was available for 60 patients (84.5% of the cohort). Median follow-up was 45 months. By univariate Cox analysis, when analyzed as a continuous variable, hepatic iron concentration detected by T2* MRI was significantly associated with inferior OS (Hazard Ratio [HR] 1.20, 95% CI 1.06–1.35, p = 0.003). Similarly, any degree of hepatic iron overload (hepatic iron concentration ≥ 2.2 mg/g) was associated with inferior OS (HR 3.26, 95% CI 1.11–9.53, p = 0.031), with an observed power of 76%, as well as moderate/severe hepatic iron overload (hepatic iron concentration ≥ 3.6 mg/g; HR 2.23, 95% CI 1.02–4.86, p = 0.043). We next evaluated what would be the optimal cut-point of hepatic iron concentration for association with decreased OS in our data. In a ROC curve analysis, the cut-point of 3.6 mg/g of hepatic iron concentration was chosen as the one with the highest sensitivity/specificity for mortality (sensitivity 73%; specificity 67.6%) Patients with ≥ 3.6 mg/g of hepatic iron concentration had significantly inferior OS (HR 3.24, 95% CI; 1.35–7.76, p = 0.008; Fig. 1). This increased risk remained even after adjusting for WPSS risk (HR 2.81, 95% CI 1.16–6.80, p = 0.022).

We also evaluated whether hepatic iron concentration was associated with an increased risk of transformation to acute myeloid leukemia (AML). Information on AML evolution was available for 56 patients (78.8%). After 45 months, 12 patients (21%) transformed to AML. The subhazard ratio (SHR) for hepatic iron concentration (as a categorical variable, considering a cut-point of 3.6 mg/g) and evolution to AML was 1.52 (95% CI 0.48–4.77, p-value 0.48; Fig. 2), indicating no statistical effect of hepatic iron concentration on risk of AML transformation. At 4 years, cumulative incidence of AML transformation (with competing risk of death) was 27.8% in patients with hepatic iron concentration ≥ 3.6 mg/g, versus 19.3% for patients with hepatic iron concentration 3.6 mg/g.

4. Discussion

The decision to submit or not a patient to T2* MRI is generally based on the finding of elevated serum ferritin levels and other laboratorial signs of iron overload. However, this study has shown that MRI can show early signs of organ overload before the elevation of serum ferritin. These patients could potentially benefit from early introduction of iron chelation, a hypothesis that needs to be evaluated in clinical trials. In this study, patients with hepatic iron concentration ≥ 3.6 mg/g of liver tissue as estimated by T2* MRI had three times higher chance of dying than patients with results below this level. This indicates situations in which an intervention such as chelation or a more aggressive disease management may be needed. MRI is widely available and is not an invasive exam, much safer than biopsy for patients with MDS.

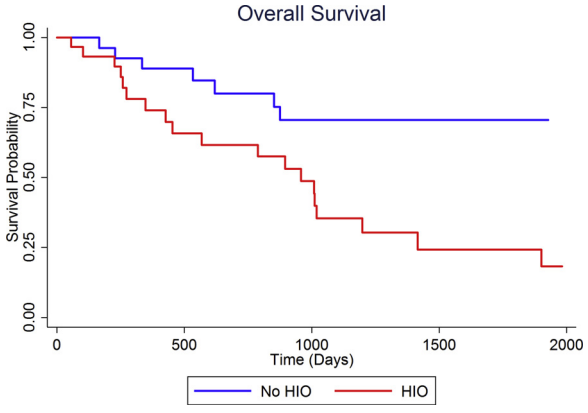

Fig. 1. Overall survival probability of patients with or without iron overload.

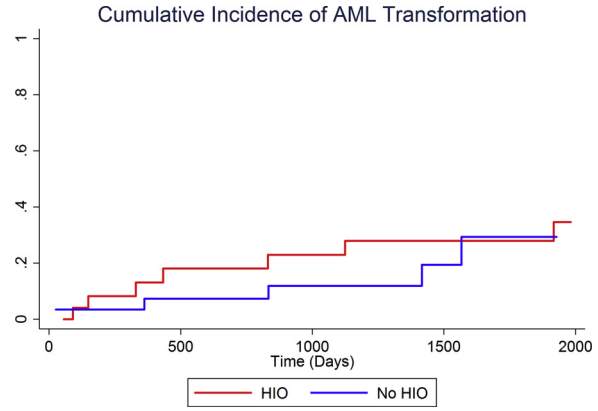

Fig. 2. Cumulative incidence of acute myeloid leukemia transformation in patients with or without iron overload.

We also found an association between hepatic iron overload and a lower overall survival, independent of the overall prognosis of the patient as assessed by the WPSS risk score. It has been previously reported [2] that increased serum ferritin is a risk factor for mortality in MDS. However, it is still unknown how increased iron overload leads to worse outcomes in these patients, whether it is a marker associated with more aggressive disease or whether iron overload per se leads to decreased outcome. We could not detect an association between iron overload and leukemic transformation in our cohort, but the number of events was small. Studies with larger cohorts of patients with MDS patients who are evaluated by MRI could possibly shed some light on this issue.

Something to be planned in further studies is the collection of data on larger follow-ups, allowing the detection of cause of deaths. The previous clinical history of our patients was evaluated, as per the hospital routine, by means of forms that were filled in by the patients themselves, which is subject to memory errors. We had a very large range of transfusions in our sample, with the history varying from zero to more than 80 transfusions. This evidenced a large heterogeneity in terms of clinical status in these MDS patients, which probably limited the identification of confusion variables. On the other hand, we included only adult patients, who have clearly different clinical evolution than children with MDS. Future studies should discern patients at different age groups and different disease status.

In conclusion, in a small cohort of patients with MDS evaluated by T2* MRI, we could demonstrate that hepatic iron overload is found in approximately two thirds of patients, even in cases without a history of transfusion dependency. Hepatic iron overload by T2* MRI is associated with a decreased risk of survival in patients with MDS. Future studies should confirm these findings in a larger cohort of patients and try to determine the mechanism behind the development of hepatic iron overload in patients without a history of transfusion dependency.

Acknowledgement

This study received no funding. There is no acknowledgement to be made.

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