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Research paper

Delayed time from RBC transfusion dependence to first cardiac event in lower IPSS risk MDS patients receiving iron chelation therapy

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ABSTRACT

Transfused MDS patients are at risk for iron overload (IOL). IOL may exacerbate congestive heart failure (CHF), coronary artery disease (CAD) and arrythmias (ARR). We retrospectively examined cardiac events (CE) in red blood cell (RBC) transfusion dependent (TD) lower IPSS risk MDS patients. Patients were censored at death or MDS progression. 151 MDS patients were lower IPSS risk and RBC TD. Median number of cardiac risk factors (RF) per patient was 1 (1–4). CE following RBC TD occurred in 48 (32%) and were: CHF, n = 20; CAD, n = 15; ARR, n = 11. In univariate analysis factors significant for time to (TT) CE were: age at 1st RBC transfusion; number of RBCU transfused while lower IPSS risk; received iron chelation therapy (ICT); MDS treatment received; and number of cardiac RF/patient ($p \leq 0.02$). Receiving ICT remained significant for TTCE in multivariate analysis ($p = 0.03$). Median TTCE in patients not receiving and receiving ICT was 7.0 (0.1–65.0) and 20.0 (0.1–148.6) months, respectively ($p = 0.02$). For lower IPSS risk RBC transfusion dependent MDS patients, time to first cardiac event following RBC TD was significantly longer in patients receiving ICT. These results suggest ICT may delay cardiac events in transfused patients. The results should be confirmed in larger numbers in prospective analyses.

1. Introduction

The myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell disorders in which ineffective hematopoiesis leads to peripheral blood cytopenias and an increased risk of progression to acute myelogenous leukemia (AML) [1]. Classification of MDS was previously based on the French-America-British (FAB) system and more recently the World Health Organization (WHO) system [2–4]. The International Prognostic Scoring System (IPSS) and Revised IPSS (IPSS-R) are commonly used to assess MDS risk, risk of AML progression and overall survival (OS) prediction [5,6].

The median age at MDS diagnosis is in the 70's; from the United States Surveillance Epidemiology and End Results (SEER) data, the median age in 7131 patients diagnosed with MDS in 2001 to 2003 was 76 years [7]. Patients in this age group have a higher incidence of risk factors for cardiac events than do younger patients with transfusion dependent anemias such as beta-thalassemia major. Anemia itself may contribute to cardiac comorbidities, for example in one analysis cardiac remodelling was seen in MDS patients with a hemoglobin of 87 g/dL while there was no cardiac remodelling seen at a hemoglobin of 113 [8]. Studies show that a leading cause of non-leukemic death in MDS patients is from cardiac causes [9,10].

Because of significant anemia, many lower risk MDS patients receive red blood cell (RBC) transfusions as supportive care. Over time, transfusion dependent patients develop iron overload (IOL), which has been shown in multiple previous analyses to be associated with clinical endpoints in MDS [11–15]. In a nationwide survey from Japan 37 of 38 transfusion dependent MDS patients who died from cardiac or hepatic failure had a serum ferritin level of 1000 ng/mL or greater [16]. In a United States Medicare population, MDS patients who were transfusion dependent had a higher incidence of cardiac comorbidities than did MDS patients who were not transfusion dependent [17].

Reducing IOL with iron chelation therapy (ICT) in beta-thalassemia major has beneficial effects on cardiac endpoints, including reduction in arrythmias, and stabilization and even improvement in congestive heart failure (CHF) [18]. One study showed that patients whose serum ferritin level was kept consistently less than 2500 ng/mL had superior cardiac disease-free survival compared to those whose ferritin ran higher [19]. In MDS, a previous study showed a decreased incidence of cardiac events (CHF and arrythmias) in patients receiving ICT [14]. In this analysis, cardiac event-free survival was 137.0 (108.5–165.5) months and 96.0 (84.1–107.9) months in patients receiving and not receiving ICT, respectively [14]. In another study, newly diagnosed or

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progressive cardiac conditions (coronary artery disease [CAD], cardiomyopathy, rhythm abnormalities, structural abnormalities, and infectious/inflammatory conditions) appeared to be increased in non-chelated patients compared to patients who were chelated or chelated for 6 months or longer, though this result was not statistically significant, and it is not clear whether all patients were RBC transfusion dependent [15]. Given this limited background examining cardiac events in MDS with IOL, we wished to determine whether cardiac events, including clinical episodes of CHF, CAD, and arrythmias were attenuated in transfusion dependent patients with lower risk MDS receiving ICT.

2. Methods

We performed a retrospective analysis of patients with MDS seen at St. Paul's Hospital in Vancouver, Canada. The Providence Hematology clinical database was searched for patients with a bone marrow biopsy confirmed diagnosis of MDS; patients diagnosed between January 1, 1981 and December 31, 2018 were included. Patient charts were reviewed and clnical data extracted. Patients who were not lower IPSS risk MDS, or who were not RBC transfusion dependent were excluded, as were patients with insufficient information regarding clinical characteristics, course and outcomes. Disease specific outcomes and prognostic factors including age, gender, time from MDS diagnosis to first RBC transfusion, FAB or WHO MDS diagnosis, bone marrow blast count, hemoglobin (Hb) at RBC transfusion dependence, platelet count at RBC transfusion dependence, IPSS and IPSS-R cytogenetic risk group, IPSS and IPSS-R risk group, number of RBC units transfused while lower IPSS risk and transfusion dependent, transfusion intensity (number of RBC units transfused per 4 week period), ICT use and duration and ICT agent, time to ICT from transfusion dependence, number of patients with cardiac risk factors, type of cardiac risk factors, number of cardiac risk factors per patient, number of cardiac episodes in patients with cardiac events, number of patients with cardiac events preceding transfusion dependence, number of patients with cardiac events following the onset of transfusion dependence, Hb and platelet count at first cardiac event following transfusion dependence, serum ferritin at onset of transfusion dependence and at first cardiac event following onset of transfusion dependence, time to first cardiac event following onset of transfusion dependence, MDS treatment received, and cause of death were recorded (see Table 1).

For patients that received MDS treatments such as erythropoiesis stimulating agents or lenalidomide, only the periods during which they were RBC transfusion dependent were included. Similarly, for patients who achieved transfusion independence with ICT, only the periods of RBC transfusion dependence were included. In order to minimize confounding factors while capturing the effect of transfusions and IOL, patients were censored at the time of progression to either higher IPSS risk MDS or AML, or at the achievement of transfusion independence.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows, version 25. Baseline factors of patients with cardiac events were compared to those of patients without cardiac events. Basline factors of patients receiving ICT were compared to those of patients not recieiving ICT. Kaplan-Meier and Cox regression analyses for overall survival (OS) were performed from time of first RBC transfusion to December 31, 2018, death, or last known date the patient was lower IPSS risk and RBC transfusion dependent, and from first RBC transfusion to first cardiac event following transfusion dependence (TTCE), or as above in patients with no cardiac events following the onset of transfusion dependence.

This study was approved by the Univeristy of British Columbia Research Ethics Board.

3. Results

Of 453 patients in the clinical database with a bone marrow aspirate and biopsy confirmed diagnosis of MDS, 151 were lower IPSS risk at RBC transfusion dependence. Patients were excluded from the total for the following reasons: not transfused as lower IPSS risk MDS, n = 131; higher IPSS risk MDS, n = 125; and insufficient information, n = 46.

Baseline features of the included patients at RBC transfusion dependence are shown in Table 1. Three groups are shown: all patients, patients experiencing cardiac events following transfusion dependence (n = 48 [32%]) and patients receiving ICT (n = 58 [38%]). Features differing between groups are indicated by the p-values. The p-values for patients with cardiac events following transfusion dependence indicate comparison to patients not experiencing cardiac events following transfusion dependence. Similarly, the p-values for patients receiving ICT indicate comparison to patients not receiving ICT. The median (range) age at first RBC transfusion in all patients was 74.5 (32–93) years. Median time from MDS diagnosis to first RBC transfusion was: 1.7 (−169.7–161.9) months. Median (range) ferritin level at first cardiac event following RBC transfusion dependence was 1682.5 (20–8400) ng/mL in all patients with cardiac events, and was 2246.5 (345–8400) ng/mL in patients with cardiac events receiving ICT.

Clinical factors differing significantly between patients with cardiac events following the onset of transfusion dependence and patients without cardiac events following transfusion dependence, were: number of patients with cardiac risk factors; number of cardiac risk factors per patient; and MDS treatment received, $p \leq 0.02$ for all. Cinical factors differing significantly between ICT and non-ICT patients, were: age at first RBC transfusion, $p = 0.0001$; number of RBC units transfused while lower IPSS risk, $p = 0.0001$; and transfusion intensity, $p \leq 0.04$ for all.

Looking for clinical factors significant for TTCE and OS, univariate analyses were done for all clinical factors listed in Table 1. Those that were significant for the relevant endpoints are shown in Table 2. They include, for TTCE: age at first RBC transfusion; number of RBC units transfused while lower IPSS risk; receiving ICT; number of cardiac risk factors per patient; and MDS treatment received, $p \leq 0.02$ for all. Factors significant for OS in univariate analyses include: age at first RBC transfusion, number of RBC units transfused while lower IPSS risk; receiving ICT; and TTCE, $p \leq 0.048$ for all.

Factors significant for TTCE in univariate analyses were entered into a multivariate analysis, and this is shown in Table 3. The only factor remaining significant for TTCE was receiving ICT (hazard ratio (HR) for shorter TTCE was 0.93 and 95% confidence intervals [CI] were 0.87 to 0.99, $p = 0.03$). The median TTCE in all patients was 7.0 (0.1–148.6) months. The median TTCE in patients receiving and not receiving ICT was 20.0 and 7.0 months, respectively, $p = 0.02$. Because we suspected that older patients receiving ICT might be more subject to selection bias (less likely to receive ICT), we looked at TTCE in patients 75 years or less, which is at the median age of all patients (Fig. 1a). In all patients ≤75 years, the median TTCE was 18.4 (0.1–148.6) months. In patients ≤75 years receiving and not receiving ICT, the median TTCE was 37.0 and 9.0 months, respectively, $p = 0.07$ (Fig. 1b). Time to cardiac event by type of cardiac event is shown in Fig. 2a, and time to CHF, CAD and arrythmia by receipt of ICT are shown in Fig. 2b-d.

The 84 patients 75 years of age or less were examined more closely. In this subgroup of patients, the median age of patients receiving ICT was 65 (32–74) years compared to 69 (44–75) years in non-ICT patients ($p = 0.04$). Other baseline clinical features that differed significantly between ICT and non-ICT patients included: MDS subtype; number of RBC units transfused while lower IPSS risk; transfusion intensity; hemoglobin; and ferritin level at first post-transfusion dependence cardiac event ($p \leq 0.048$ for all). In univariate analyses, however, only number of RBC units was significant for TTCE when using a transfusion threshold of 20 units ($p = 0.015$), and further analysis was restricted by small numbers of events in the group receiving less than 20 RBC units.

Factors significant for OS in univariate analyses were entered into a multivariate analysis, which is shown in Table 4. The only factor remaining significant for OS was receiving ICT (HR for death in those

Table 1
Baseline characteristics, treatment and outcome of 151 patients with lower IPSS risk MDS receiving red blood cell transfusions: all patients, by cardiac status and by receipt of iron chelation therapy.

Patient Characteristic at time of first RBC transfusion	All patients n = 151	Cardiac events post onset of TD n = 48	p-value[1]	ICT patients n = 58	p-value[2]
Age at 1st RBC transfusion (median [range]), years	74.5 (32-93)	77 (53-89)	NS	68 (32-89)	**0.0001**
Gender (n [%])			NS		NS
Male	90 (59.6%)	24 (50.0%)		34 (58.6%)	
Female	61 (40.4%)	24 (50.0%)		24 (41.4%)	
Time from MDS dx to 1st RBC TD (months)	1.7 (-169.7-161.9)	1.6 (-169.7-161.9)	NS	5.8 (-169.7-161.9)	NS
FAB or WHO MDS dx (n [%])			NS		NS
RA/MDS-SLD	29 (19.2%)	13 (27.1%)		12 (20.7%)	
RARS/RARS-t/MDS-RS-SLD	52 (34.4%)	13 (27.1%)		25 (43.1%)	
RCMD/RCMD-RS	43 (28.5%)	13 (27.1%)		15 (25.9%)	
Other[3]	27 (17.9%)	9 (18.7%)		6 (10.3%)	
Hb at TD (g/dL, median [range])	85 (43-121)	86 (43-119)	NS	85 (50-121)	NS
Plts at TD (x10^9/L, median [range])	192 (13-53000)	191 (23-50000)	NS	212 (19-1173)	NS
Marrow blast count (%, median [range])	1 (0-10)	1 (0-8)	NS	1 (0-7)	NS
IPSS cytogenetic risk group (n[%])			NS		NS
Favorable	112 (74.2%)	36 (75.0%)		42 (72.4%)	
Intermediate	19 (12.6%)	6 (12.5%)		8 (13.8%)	
Poor	4 (2.6%)	2 (4.2%)		1 (1.7%)	
Not available	16 (10.6%)	4 (8.3%)		7 (12.1%)	
IPSS Risk Group			NS		NS
Low	73 (48.3%)	22 (45.8%)		27 (46.6%)	
Intermediate-1	70 (46.4%)	25 (52.1%)		26 (44.8%)	
≤ Intermediate-1	8 (5.3%)	1 (2.1%)		5 (8.6%)	
IPSS-R cytogenetic risk group			NS		**0.06**
Very good	6 (4.0%)	4 (8.3%)		2 (3.5%)	
Good	111 (73.5%)	34 (70.8%)		41 (70.7%)	
Intermediate	13 (8.6%)	2 (4.2%)		8 (13.8%)	
Poor	3 (2.0%)	2 (4.2%)		1 (1.7%)	
Very poor	1 (0.6%)	0 (0%)		0 (0%)	
Not available	17 (11.3%)	6 (12.5%)		6 (10.3%)	
IPSS-R risk group			NS		NS
Very low	26 (17.2%)	8 (16.7%)		13 (22.4%)	
Low	80 (53.0%)	25 (52.1%)		28 (48.3%)	
Intermediate	24 (15.9%)	8 (16.7%)		8 (13.8%)	
High	4 (2.6%)	1 (2.1%)		1 (1.7%)	
Very high	0 (0%)	0 (0%)		0 (0%)	
Not available	17 (11.3%)	6 (12.5%)		8 (13.8%)	
Number of RBCU transfused while lower IPSS risk (median [range])	43 (2-675)	54.5 (2-330)	NS	81 (10-675)	**0.0001**
Transfusion intensity (n RBCU/4 weeks, median [range])	2 (0.5-9)	2 (1-4)	NS	2 (1-9)	**0.04**
Iron chelation therapy			NS		NA
deferasirox	45 (29.8%)	12 (25.0%)		45 (77.6%)	
deferoxamine	12 (8.0%)	5 (10.4%)		12 (20.7%)	
deferiprone	1 (0.7%)	0 (0%)		1 (1.7%)	
Duration of ICT (median [range]), months	19 (1-164)	9 (1-164)	NS	19 (1-164)	NA
Time to ICT from TD	22.0 (1.4-209.0)	18.7 (1.4-209.0)	NS	22.0 (1.4-209.0)	NA
n (%) with cardiac risk factors	119 (78.8%)	43 (89.6%)	**0.009**	47 (81.0%)	NS
Cardiac risk factors			NA		NA
Smoking	69	26		27	
Hypertension	65	28		23	
Hyperlipidemia	25	11		10	
Diabetes	32	12		11	
n (%) of cardiac risk factors per patient			**0.003**		NS
0	29	4		11	
1	67	21		30	
2	30	11		11	
3	18	9		5	
4	2	2		1	
Median n cardiac risk factors/patient	1 (0-4)	1 (0-4)	**0.003**	1(0-4)	NS
n cardiac episodes in patients with cardiac events (median [range])	1 (1-4)	1 (1-4)	NS	1 (1-4)	NS
n (%) with cardiac events preceding TD	30 (19.9%)	26 (54.2%)	NA	1 (1.7%)	NA
n (%) with cardiac events post TD[4]	48 (31.8%)	48 (100%)	NA	21 (36.2%)	NS
Hb at 1st cardiac event post TD (g/dL; median [range])	90 (60-139)	89 (67-128)	NS	87 (60-104)	NS
Plts at 1st cardiac event post TD (x10^9/L; median [range])	164 (5-50000)	133 (14-505)	NS	243 (5-50000)	NS
Ferritin at 1st cardiac event following onset of TD (median [range] ng/mL)	1682.5 (20-8400)	1682.5 (20-8400)	NS	2246.5 (345-8400)	NS
Time to 1st cardiac event following onset of TD (median, range)	7.0 (0-148.6)	7.0 (0-148.6)	NS	29.6 (1-148.6)	NS
MDS treatment received			**0.02**		NS
ESA	58 (38.4%)	19 (39.6%)		25 (43.1%)	
LEN	8 (5.3%)	2 (4.2%)		3 (5.2%)	
Immunosuppressive[5]	4 (2.7%)	2 (4.2%)		3 (5.2%)	
Other[6]	12 (8.0%)	4 (8.3%)		5 (8.6%)	
Chemotherapy[7]	7 (4.6%)	2 (4.2%)		2 (3.4%)	
Cause of death			NS		NS

(*continued on next page*)

Table 1 (*continued*)

Patient Characteristic at time of first RBC transfusion	All patients n = 151	Cardiac events post onset of TD n = 48	p-value[1]	ICT patients n = 58	p-value[2]
Infection	5 (3.3%)	4 (8.3%)		1 (1.7%)	
Cardiac[8]	5 (3.3%)	3 (6.3%)		2 (5.2%)	
MDS/AML[9]	13 (8.6%)	3 (6.3%)		8 (14.0%)	
Other[10]	6 (4.0%)	0 (0%)		2 (5.2%)	
Unknown	11 (7.3%)	3 (6.3%)		4 (6.9%)	

Abbreviations: 1st, first; AML, acute myeloid leukemia; AFIB, atrial fibrillation; aflutter, atrial flutter; ATG, anti-thymocyte globulin; AZA, azacitidine; ARR, arrhythmia; CAD, coronary artery disease; CHF, congestive heart failure; dx, diagnosis; dL, decilitre; ESA, erythropoiesis stimulating agent; FAB, French-American-British; g, grams; GVHD, graft versus host disease; Hb, hemoglobin; HU, hydroxyurea; ICT, iron chelation therapy; IPSS, International Prognostic Scoring System; IPSS-R, Revised IPSS; L, litre; LEN, lenalidomide; MDS, Myelodysplastic Syndrome; MI, myocardial infarction; mL, milliliter; n, number; NA, not applicable; ng, nanograms; NOS, not otherwise specified; NS, not significant; p, probability; Plts, platelets; RA, refractory anemia; RBC, red blood cell; RS, ringed sideroblasts; t, RARS with thrombocytosis; RCMD, refractory cytopenia with multilineage dysplasia; SLD, single lineage dysplasia; TD, transfusion dependent; U, units; WHO, World Health Organization.

[4]Cardiac events, ALL: CHF, n = 26; CAD, n = 35; ARR, n = 35 (AFIB, n = 31; aflutter, n = 1, NOS, n = 3). Cardiac: CHF, n = 26; CAD, n = 35; ARR, n = 35 (AFIB, n = 31, aflutter, n = 1, NOS, n = 3). ICT: CHF, n = 8; CAD, n = 12; ARR, n = 13 (AFIB, n = 10; aflutter, n = 1, NOS, n = 2).

[1] compared to patients without cardiac events following TD.

[2] compared to patients not receiving ICT.

[3] All: MDSU/MDS-MPNU, n = 12; del(5q)MDS, n = 8; del(5q)MDS + 1 additional abnormality, n = 3 RAEB-1, n = 4. Cardiac events: MDSU/MDS-MPNU, n = 4; del(5q)MDS, n = 2; del(5q)MDS + (+8), n = 2; RAEB-1, n = 1. ICT: MDSU/MDS-MPNU, n = 2; del(5q)MDS, n = 2; del(5q)MDS + (+8); RAEB-1, n = 1 each.

[5] All: prednisone, n = 4. Cardiac event: prednisone, n = 2. ICT: prednisone, n = 2; ATG, n = 1.

[6] All: pyridoxine, n = 9; delalestryl; anagrelide; ruxolitinib; n = 1 each. Cardiac event: pyridoxine, n = 3; delalestryl, n = 1. ICT: pyridoxine, n = 4; delalestryl, n = 1.

[7] All: AZA, n = 3; HU, n = 3; NOS, n = 1. Cardiac event: AZA; HU; n = 1 each. ICT: AZA; HU, n = 1 each.

[8] All: CHF from IOL, n = 2; CHF, n = 2; MI, n = 1. Cardiac: CHF from IOL, n = 2; MI, n = 1. ICT: CHF, n = 2.

[9] All: MDS, n = 7; AML, n = 6. Cardiac event: MDS, n = 2; AML, n = 1. ICT: MDS, n = 2; AML, n = 6.

[10] All: intracranial malignancy; intracranial bleed; pulmonary fibrosis; hepatic cirrhosis; GVHD; dementia; n = 1 each. Cardiac: NA. ICT: cirrhosis; pulmonary fibrosis; n = 1 each.

Table 2
Factors significant in univariate analysis for time from first RBC transfusion to first cardiac event following onset of transfusion dependence and for overall survival in transfusion dependent patients with lower IPSS risk MDS.

Factor	TTCE p-value	OS p-value
Age at 1st RBC transfusion	**0.0009**	**0.048**
# of RBCU transfused while lower IPSS risk	**0.01**	**0.0001**
Received iron chelation therapy	**0.02**	**0.003**
# of cardiac risk factors per patient	**0.003**	NS
Time to 1st cardiac event following onset of TD	NS	**0.007**
MDS treatment received	**0.02**	NS

1st, first; #, number; ICT, iron chelation therapy; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; OS, overall survival; p, probability; TD, transfusion dependence; TTCE, time from 1st RBC transfusion to 1st cardiac event following onset of TD; RBC, red blood cell; U, units.

receiving ICT 0.48, 95% CI 0.22 to 0.84, p = 0.02). The median OS in all patients was 86.3 (2.0–257) months, and in patients receiving and not receiving ICT, the median OS was 101.6 and 53.9 months, respectively, p = 0.002 (Fig. 3a). In patients ≤75 years, the median OS in all patients was 95.4 (2.8–257) months, and in patients receiving and not receiving ICT, the median OS was 101.6 and 44.1 months, respectively, p = 0.02 (Fig. 3b). In the subgroup of patients 75 years of age or less, no baseline factors differing between ICT and non-ICT patients were significant for OS.

4. Discussion

In this retrospective analysis, for lower IPSS risk MDS patients receiving RBC transfusions, the time to first cardiac event following RBC transfusion dependence was significantly longer in patients receiving ICT. Receiving ICT remained an independent predictor for TTCE in a multivariate analysis. The cardiac events considered in this analysis were clinical episodes of CHF, arrythmias and CAD. The former two cardiac events are well known to occur with increased incidence in patients with congenital transfusion dependent anemias with IOL such as beta-thalassemia major, and to be prevented and improved using ICT. Coronary artery disease has been shown to occur in IOL in animal models. Two published clinical studies show what appears to be an attenuation of cardiac events in MDS patients receiving ICT, however,

Table 3
Multivariate analysis of factors significant for time from first red blood cell transfusion to first cardiac event following onset of transfusion dependence in patients with lower IPSS risk MDS, while still lower IPSS risk and transfusion dependent.

Variables in the Equation								
	B	SE	Wald	df	Sig.	HR	95.0% CI	
							Lower	Upper
Age at 1st RBC transfusion	−0.04	0.08	0.74	1	0.39	0.96	0.88	1.05
# RBCU received while lower IPSS risk	−0.002	0.01	0.03	1	0.86	0.99	0.98	1.02
Received ICT	−0.08	0.04	4.68	1	**0.03**	0.93	0.87	0.99
MDS treatment received	−0.20	0.19	1.19	1	0.28	0.82	0.57	1.18
# of cardiac risk factors per patient	−0.40	0.39	1.08	1	0.30	0.67	0.31	1.42

#, number; 1st, first; CI, confidence intervals; df, degrees of freedom; HR, hazard ratio; ICT, iron chelation therapy; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; RBC, red blood cell; SE, standard error; Sig, significance; TD, transfusion dependent; U, units.

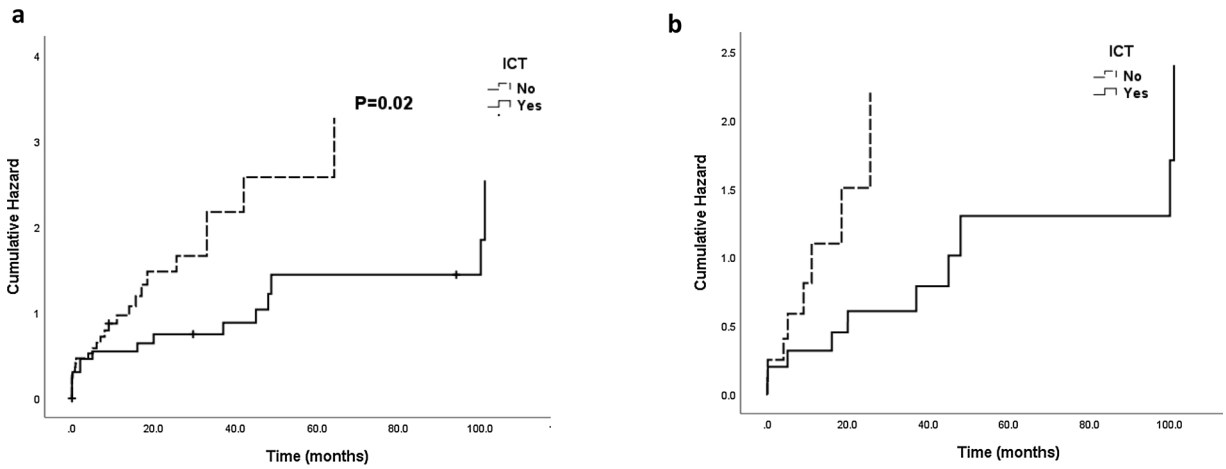

Fig. 1. Time from first RBC transfusion to first cardiac event following onset of RBC transfusion dependence by receipt of ICT in lower IPSS risk MDS. A) all patients B) patients ≤75 years of age.

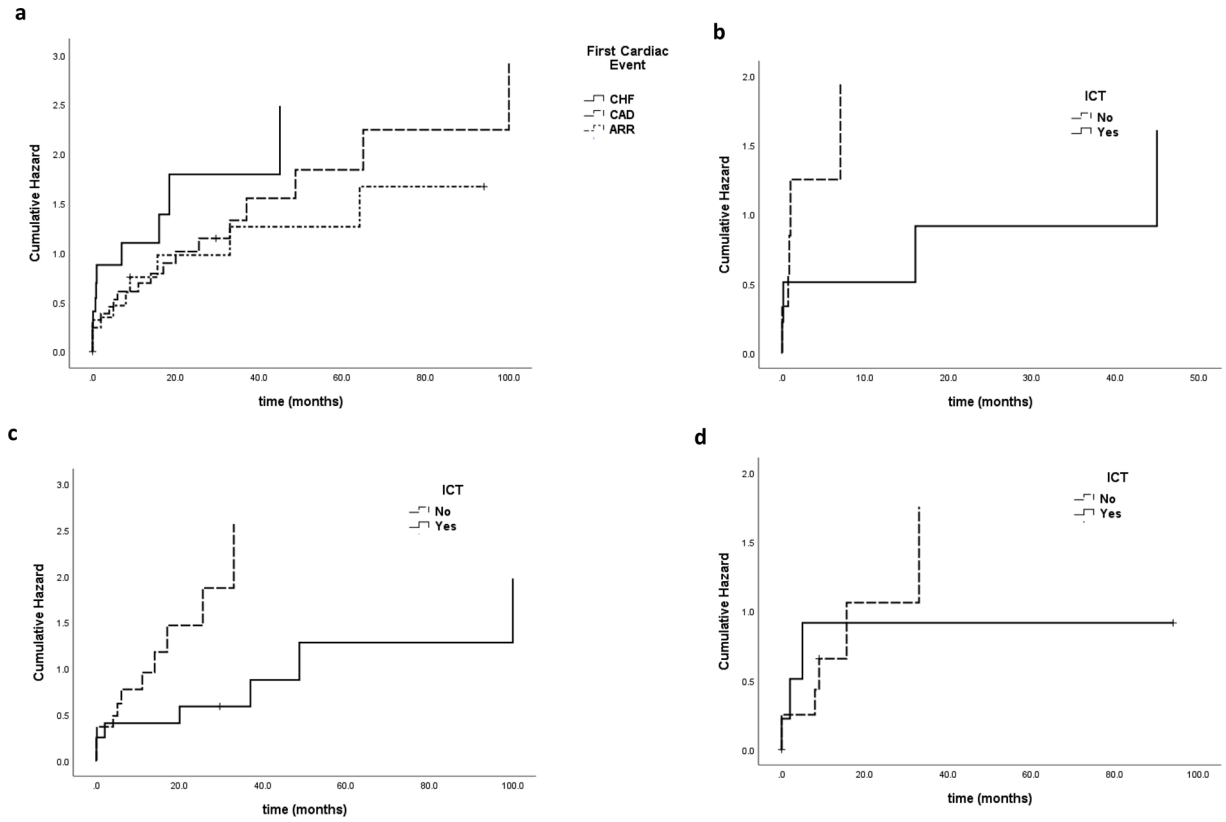

Fig. 2. Time from first RBC transfusion to first cardiac event following transfusion dependence in lower IPSS risk MDS patients by type of cardiac event. A) all cardiac events B) congestive heart failure by receipt of iron chelation therapy C) coronary artery disease by receipt of iron chelation therapy D) arrythmias by receipt of iron chelation therapy.

the first of these studies considered CHF and arrythmias, but not CAD, and the second did not show a statistically significant difference in events between ICT and non-ICT patients [14,15]. Three other studies examined cardiac endpoints in relation to ICT; of these, two (n = 97 and n = 127 lower risk MDS) found no significant difference in cardiac mortality and the third study of 4226 patients found no altered risk of CHF with ICT [20–22].

In the randomized, placebo controlled TELESTO trial of ICT in lower risk MDS reported at the annual meeting of the American Society of Hematology in December 2018, although there was a difference in event-free survival between patients randomized to receive ICT or placebo, this trial used a composite endpoint of cardiac and liver events and AML progression, and there was no difference in cardiac events between ICT and placebo patients [23]. However, the mean age of TELESTO patients was only 61 years, compared to the considerably higher median age of 75 years in the current study. It is possible and even likely that the older patients in the current study might be more susceptible to a contribution of IOL to cardiac events than the younger patients in the TELESTO trial. In addition, half of TELESTO patients randomized to placebo withdrew from the trial and subsequently received ICT. For this reason, a difference in cardiac events between ICT and placebo patients might have been obscured. In the current study,

Table 4
Multivariate analysis of factors significant for OS from first red blood cell transfusion in patients with lower IPSS risk MDS, while still lower IPSS risk and transfusion dependent.

Variables in the Equation

	B	SE	Wald	df	Sig.	HR	95.0% CI	
							Lower	Upper
Age at 1st RBC transfusion	−0.02	0.05	0.16	1	0.69	0.98	0.89	1.08
# RBCU received while lower IPSS risk	−0.05	0.03	3.25	1	0.07	0.95	0.89	1.01
TTCE	−0.07	0.04	3.48	1	0.06	0.93	0.87	1.00
Received ICT	−3.60	1.67	4.68	1	**0.01**	0.48	0.22	0.84

#, number; 1st, first; CI, confidence intervals; df, degrees of freedom; HR, hazard ratio; ICT, iron chelation therapy; MDS, myelodysplastic syndrome; OS, overall survival; RBC, red blood cells; SE, standard error; Sig, significance; TD, transfusion dependent; TTCE, time from 1st RBC transfusion to 1st cardiac event following onset of TD; U, units.

patients either received ICT or did not at any point. Patients receiving ICT at any point were categorized in the ICT group, regardless of duration of treatment.

We attempted to determine a ferritin threshold that predicted cardiac events in our MDS patients, but these analyses were unrewarding. In retrospect, in regard to the ferritin threshold of 2500 in beta-thalassemia major, under which superior cardiac disease-free survival is seen, the major risk factor for younger beta-thalassemia major patients for cardiac events is IOL. In contrast, older MDS patients may have multiple risk factors for cardiac events to which IOL may contribute. A previous study made an attempt to address this issue in MDS. In a Spanish registry, the mean +/- standard deviation (SD) number of RBC units at the onset of the cardiac event was 53.6 ± 61.2 while the mean +/- SD serum ferritin level was 1945.4 ± 1527.6 ng/mL, giving a wide range of ferritin values [14]. Similarly, the median ferritin level in our patients experiencing cardiac events was 1682.5 (20–8400) ng/mL. While a ferritin threshold to predict cardiac events in transfused MDS patients would be extremely useful in clinical practice and is almost certainly lower than in beta-thalassemia major, this threshold might vary widely between groups of MDS patients depending on other cardiac risk factors present, degree of anemia, and other considerations such as comorbidities and performance status.

Because of the ability of iron to transfer electrons, through Fenton chemistry, IOL results in the generation of oxygen free radicals or reactive oxygen species (ROS), which have been shown in multiple studies to damage lipids, proteins, and nucleic acids, leading to cellular consequences (reviewed in [24]). Cardiac cells may be particularly sensitive to damage from iron-induced oxidative stress for several reasons. Non-transferrin bound iron enters cardiac cells in an unregulated manner, where it gives rise to oxidative species [25–27]. Cardiomyocytes are rich in mitochondria, and mitochondrial DNA may be particularly sensitive to oxidative damage as it lacks histones for protection. In addition, protein and lipid damage may result in disruption of the electron transport chain, leading to impaired energy production and ultimately resulting in cell death. In transfused beta-thalassemia major with IOL, histologic studies of cardiac tissue have shown damage to lysosomes, disruption of mitochondria, and loss of myofilaments [28]. Such cellular damage, if widespread, could lead to impaired left ventricular ejection fraction and clinical CHF. Moreover, in beta-thalassemia major, IOL is recognized to lead to cardiac arrythmias [18]. More recently, Vinchi et al showed, using a mouse model, that IOL can exacerbate CAD [29]; IOL in macrophages results in cholesterol accumulation, progression to foam cells, inflammation, apoptosis, and plaque destabilization [30].

In the current study, superior overall survival in patients receiving ICT was also seen, and was an independent predictor of OS in multivariate analysis, in keeping with previous analyses from our group and others [11,13,20,31–33]. While the TELESTO trial did not show an OS difference between patients receiving and not receiving ICT, it was not powered to detect such a difference due to the sample size being reduced by two thirds because of slow enrollment. A difference in OS may not have been apparent in TELESTO for the same reasons discussed above for cardiac events; namely the younger age of the patients, and the fact that half of placebo patients went on to receive ICT.

In conclusion, in this retrospective analysis, for lower IPSS risk MDS patients receiving RBC transfusions, time to first cardiac event following RBC transfusion dependence was significantly longer in patients receiving ICT, and receiving ICT was an independent predictor for TTCE in multivariate analysis. These results suggest that ICT may delay cardiac events in transfused MDS patients, a finding that could be clinically significant. As another randomized controlled trial of ICT in MDS is unlikely to be performed at this point, though the results should be confirmed in larger numbers, the best source of such data might be prospective MDS patient registries [11,13–15].

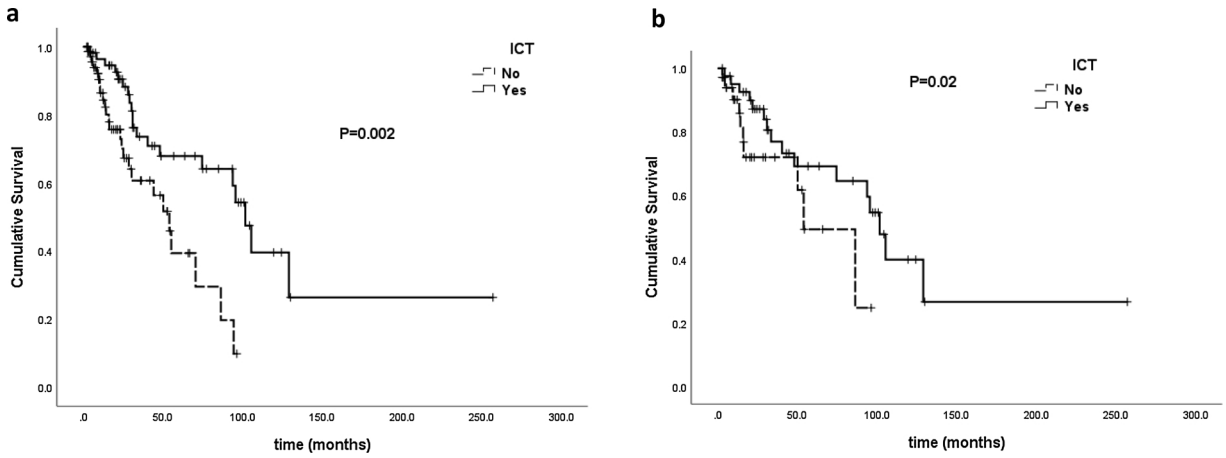

Fig. 3. Overall survival from time of first RBC transfusion of patients with transfusion dependent lower IPSS risk MDS by receipt of ICT. A) all patients B) patients ≤75 years of age.

Declaration of Competing Interest

CACW: no conflicts. HAL: honoraria, research funding: Alexion, Celgene, Novartis, Otsuka, member of the Exjade Speaker's Bureau.

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References

[1] D.P. Steensma, Myelodysplastic syndromes: diagnosis and treatment, Mayo Clinic proceedings. [Review] 90 (7) (2015) 969–983 Jul.

[2] J.M. Bennett, D. Catovsky, M.T. Daniel, G. Flandrin, D.A. Galton, H.R. Gralnick, et al., Proposals for the classification of the myelodysplastic syndromes, Br. J. Haematol. 51 (2) (1982) 189–199 Jun.

[3] J.W. Vardiman, The World Health Organization (WHO) classification of tumors of the hematopoietic and lymphoid tissues: an overview with emphasis on the myeloid neoplasms, Chem Biol Interact. [Review]. 184 (1–2) (2010) 16–20 Mar 19.

[4] C. Strupp, K. Nachtkamp, B. Hildebrandt, A. Giagounidis, R. Haas, N. Gattermann, et al., New proposals of the WHO working group (2016) for the diagnosis of myelodysplastic syndromes (MDS): characteristics of refined MDS types, Leuk. Res. 57 (2017) 78–84 Jun.

[5] P. Greenberg, C. Cox, M.M. LeBeau, P. Fenaux, P. Morel, G. Sanz, et al., International scoring system for evaluating prognosis in myelodysplastic syndromes, Blood. 89 (6) (1997) 2079–2088 Mar 15.

[6] P.L. Greenberg, H. Tuechler, J. Schanz, G. Sanz, G. Garcia-Manero, F. Sole, et al., Revised international prognostic scoring system for myelodysplastic syndromes, Blood. [Research Support, Non-U.S. Gov't]. 120 (12) (2012) 2454–2465 Sep 20.

[7] X. Ma, M. Does, A. Raza, S.T. Mayne, Myelodysplastic syndromes: incidence and survival in the United States, Cancer. 109 (8) (2007) 1536–1542. Apr 15.

[8] E.N. Oliva, B.D. Dimitrov, F. Benedetto, A. D'Angelo, F. Nobile, Hemoglobin level threshold for cardiac remodeling and quality of life in myelodysplastic syndrome, Leuk. Res. 29 (10) (2005) 1217–1219 Oct.

[9] L. Malcovati, M.G. Porta, C. Pascutto, R. Invernizzi, M. Boni, E. Travaglino, et al., Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making, J. Clin. Oncol. 23 (30) (2005) 7594–7603 Oct 20.

[10] R.M. Lyons, B.J. Marek, C.S. Paley, J. Esposito, K. McNamara, L. Garbo, et al., 48-month update on survival and AML transformation in a 600-patient registry of lower-risk MDS patients, Blood. [Annual Meeting Abstracts]. 122 (November (21)) (2013) Abstract 2775.

[11] H.A. Leitch, A. Parmar, R.A. Wells, L. Chodirker, N. Zhu, T.J. Nevill, et al., Overall survival in lower IPSS risk MDS by receipt of iron chelation therapy, adjusting for patient-related factors and measuring from time of first red blood cell transfusion dependence: an MDS-CAN analysis, Br. J. Haematol. 179 (1) (2017) 83–97 Oct.

[12] C.A.C. Wong, S.A.Y. Wong, H.A. Leitch, Iron overload in lower international prognostic scoring system risk patients with myelodysplastic syndrome receiving red blood cell transfusions: relation to infections and possible benefit of iron chelation therapy, Leuk. Res. 67 (2018) 75–81 Feb 10.

[13] M. Hoeks, G. Yu, S. Langemeijer, S. Crouch, L. De Swart, P. Fenaux, et al., Impact of treatment with iron chelation therapy in lower-risk MDS patients participating in the European Leukemianet MDS (EUMDS) Registry, Blood. [ASH Annual Meeting Abstracts]. (2017) 130:abstract 425.

[14] A.F. Remacha, B. Arrizabalaga, A. Villegas, M.S. Duran, L. Hermosin, R. de Paz, et al., Evolution of iron overload in patients with low-risk myelodysplastic syndrome: iron chelation therapy and organ complications, Annals of hematology. [Multicenter Study Research Support, Non-U.S. Gov't]. 94 (5) (2015) 779–787 May.

[15] R.M. Lyons, B.J. Marek, S. Sharma, C. Paley, J. Esposito, L. Garbo, et al., 24-month analysis of the impact of chelation on clinical outcomes in a 600 patient registry of lower-risk MDS patients, Blood. 118 (21) (2011) 1207-8a, abstract 2800.

[16] M. Takatoku, T. Uchiyama, S. Okamoto, Y. Kanakura, K. Sawada, M. Tomonaga, et al., Retrospective nationwide survey of Japanese patients with transfusion-dependent MDS and aplastic anemia highlights the negative impact of iron overload on morbidity/mortality, Eur. J. Haematol. 78 (6) (2007) 487–494 Jun.

[17] S.L. Goldberg, E. Chen, M. Corral, A. Guo, N. Mody-Patel, A.L. Pecora, et al., Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries, J. Clin. Oncol. 28 (17) (2010) 2847–2852 Jun 10.

[18] B.A. Davis, J.B. Porter, Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia, Blood. 95 (4) (2000) 1229–1236 Feb 15.

[19] B.A. Davis, C. O'Sullivan, P.H. Jarritt, J.B. Porter, Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major, Blood. 104 (1) (2004) 263–269 Jul 1.

[20] C. Rose, S. Brechignac, D. Vassilief, L. Pascal, A. Stamatoullas, A. Guerci, et al., Does iron chelation therapy improve survival in regularly transfused lower risk MDS patients? A Multicenter Study by the GFM, Leuk. Res. 34 (7) (2010) 864–870.

[21] M. Delforge, D. Selleslag, Y. Beguin, A. Triffet, P. Mineur, K. Theunissen, et al., Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes, Leukemia Research. [Multicenter Study Research Support, Non-U.S. Gov't]. 38 (5) (2014) 557–563 May.

[22] A.M. Zeidan, F. Hendrick, E. Friedmann, M.R. Baer, S.D. Gore, M. Sasane, et al., Deferasirox therapy is associated with reduced mortality risk in a medicare population with myelodysplastic syndromes, J Comp Eff Res. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 4 (4) (2015) 327–340. Aug.

[23] E. Angelucci, J. Li, P.L. Greenberg, W. Depei, M. Hou, E. Montaño Figueroa, et al., Safety and efficacy, including event-free survival, of deferasirox versus placebo in iron-overloaded patients with low- and int-1-risk myelodysplastic syndromes (MDS): outcomes from the randomized, double-blind Telesto study, Blood. (2018) 132:abstract 234.

[24] N. Gattermann, E.A. Rachmilewitz, Iron overload in MDS-pathophysiology, diagnosis, and complications. Annals of hematology. [Review]. 90 (1) (2011) 1–10 Jan.

[25] Y. Liu, J.G. Parkes, D.M. Templeton, Differential accumulation of non-transferrin-bound iron by cardiac myocytes and fibroblasts, J. Mol. Cell. Cardiol. 35 (5) (2003) 505–514 May.

[26] E.W. Randell, J.G. Parkes, N.F. Olivieri, D.M. Templeton, Uptake of non-transferrin-bound iron by both reductive and nonreductive processes is modulated by intracellular iron, J. Biol. Chem. 269 (23) (1994) 16046–16053 Jun 10.

[27] J.G. Parkes, R.A. Hussain, N.F. Olivieri, D.M. Templeton, Effects of iron loading on uptake, speciation, and chelation of iron in cultured myocardial cells, J. Lab. Clin. Med. 122 (1) (1993) 36–47 Jul.

[28] A. Kolnagou, Y. Michaelides, C. Kontos, K. Kyriacou, G.J. Kontoghiorghes, Myocyte damage and loss of myofibers is the potential mechanism of iron overload toxicity in congestive cardiac failure in thalassemia. Complete reversal of the cardiomyopathy and normalization of iron load by deferiprone, Hemoglobin. [Case Reports]. 32 (1–2) (2008) 17–28.

[29] F. Vinchi, A. Simmelbauer, S. Altamura, S. Spaich, R. Sparla, B. Galy, et al., Low-iron diet and chelation therapy rescue severe atherosclerosis associated with high circulating iron levels, Blood. (2016) 128:abstract 199.

[30] F. Vinchi, M.U. Muckenthaler, M.C. Da Silva, G. Balla, J. Balla, V. Jeney, Atherogenesis and iron: from epidemiology to cellular level, Front Pharmacol. [Review] 5 (2014) 94.

[31] H.A. Leitch, C. Chan, C.S. Leger, L.M. Foltz, K.M. Ramadan, L.M. Vickars, Improved survival with iron chelation therapy for red blood cell transfusion dependent lower IPSS risk MDS may be more significant in patients with a non-RARS diagnosis, Leukemia Research. [Research Support, Non-U.S. Gov't]. 36 (11) (2012) 1380–1386 Nov.

[32] H.A. Leitch, C.S. Leger, T.A. Goodman, K.K. Wong, D.H.C. Wong, K.M. Ramadan, et al., Improved survival in patients with myelodysplastic syndrome receiving iron chelation therapy, Clin. Leuk. 2 (3) (2008) 205–211. August 2008.

[33] J. Neukirchen, F. Fox, A. Kundgen, K. Nachtkamp, C. Strupp, R. Haas, et al., Improved survival in MDS patients receiving iron chelation therapy - a matched pair analysis of 188 patients from the Dusseldorf MDS registry, Leukemia Research. [Evaluation Studies Research Support, Non-U.S. Gov't]. 36 (8) (2012) 1067–1070. Aug.