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Research paper

Iron chelation therapy in lower IPSS risk myelodysplastic syndromes; which subtypes benefit?

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ABSTRACT

Background: Analyses suggest MDS patients with higher serum ferritin levels (SF) have inferior overall survival (OS), in one study across MDS subtypes. Multiple analyses suggest those with high SF receiving iron chelation therapy (ICT) have superior OS, but which MDS subtypes benefit from ICT remains undefined.
Methods: We performed survival analyses of MDS subtypes by receipt of ICT.
Results: 182 MDS were lower IPSS risk and received red blood cell (RBC) transfusions; 63 received ICT. For the entire cohort, receiving ICT independently predicted superior OS in a multivariate analysis (hazard ratio for death 0.3, $p = 0.01$). Features differing for ICT and non-ICT patients, respectively, were: age; IPSS risk group; number of RBC units transfused; and SF, $p \leq 0.03$ for all. At a median follow up of 76.5 and 28.4 months, 65.1% and 63.0% were alive. Median OS (months) for ICT and non-ICT patients was: RA, 140.9 and 36.3, $p = 0.0008$; RARS/RARS-t, 133.4 and 73.3, $p = 0.02$. For RCMD/RCMD-RS, $p =$ NS, however, 3 (20%) had significant erythroid improvement with ICT; other subtypes had small numbers.
Discussion: In this retrospective analysis, RA and RARS/RARS-t patients receiving ICT had superior OS to non-ICT patients. These findings should be verified and other MDS subtypes examined in larger prospective analyses.

1. Introduction

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by bone marrow failure and ineffective hematopoiesis, leading to peripheral blood cytopenias and an increased risk of progression to acute myelogenous leukemia (AML) [1]. Classification of MDS was formerly based on the French-American-British (FAB) classification and more recently on the World Health Organisation (WHO) classification systems [2,3]. The International Prognostic Scoring System (IPSS) and newer scores are commonly used to asses MDS risk and predict survival and risk of AML transformation [4,5].

Treatment for MDS is largely based on IPSS risk group [6]. Most lower risk MDS patients receive supportive care. Many lower risk MDS patients eventually develop significant anemia requiring transfusion of red blood cells (RBC) and ultimately become transfusion dependant, which in itself adversely affects clinical outcomes and quality of life [7]. As a consequence of transfusions, patients develop iron overload (IOL). Because of the ability of iron to transfer electrons, IOL results in the generation of reactive oxygen species (ROS) or oxygen free radicals, which in pre-clinical models damage lipids, proteins and nucleic acids. Iron overload may affect the major organs and induce apoptosis of hematopoietic progenitor cells via oxidative stress [8,9]. Around 20% of patients have hematologic improvement in the erythroid lineage with ICT [10–13]. Iron chelation therapy (ICT) is recommended by guidelines in patients with lower IPSS risk MDS and transfusional IOL, to reduce IOL and IOL-induced oxidative stress, and to protect the organs [10,14–16]. Beneficial effects of ICT such as erythroid improvement in around 20% of patients are possibly related to a reduction [10–12,16].

Previous analyses suggest patients with MDS and higher serum ferritin levels (SF), a clinically convenient marker of iron load, have inferior overall survival (OS) to patients with lower SF [17,18]. In one analysis, this was true across several MDS subtypes [19]. Multiple analyses suggest lower-risk MDS patients with transfusional IOL receiving ICT have superior OS to non-ICT patients [20–22]. Iron physiology is as yet incompletely understood, however, it is well documented that there are differences in iron physiology between MDS subtypes. For example, hepcidin is a key regulatory hormone important in iron absorption and distribution. Hepcidin levels vary considerably across MDS subtypes, with refractory anemia (RA) and refractory anemia with ring sideroblasts (RARS) having the lowest levels, while

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refractory cytopenia with multilineage dysplasia (RCMD), refractory anemia with excess blasts (RAEB) and chronic myelomonocytic leukemia (CMML) have the highest [23,24]. Lower hepcidin levels observed in RA and RARS are expected to result in increased absorption of iron from the gastrointestinal tract as well as release of iron from cells of the reticuloendothelial system, adding to risk of IOL. The recent description of the hormone erythroferrone, which regulates hepcidin levels, is another step forward in the understanding of iron physiology, and is an unfolding story [25]. Mitochondrial ferritin is expressed in RARS cells, which may help protect mitochondrial lipids, proteins and nucleic acids from oxidative damage [26,27]. Further, the SF3B1 spliceosome mutation, which leads to abnormal RNA splicing, is associated with the RS phenotype and this could lead to differences in cellular iron processing [28]. Thus, different MDS subtypes might derive more or less clinical benefit from ICT, however, there is little clinical information on this subject. We performed a retrospective analysis of our transfused, lower IPSS risk MDS patients, to try to determine which subtypes of MDS derive clinical benefit from ICT.

2. Methods

The Providence Hematology clinical database, based at St. Paul's Hospital in Vancouver Canada, was searched for patients with MDS. Patients diagnosed with lower IPSS risk MDS confirmed by bone marrow aspirate and biopsy between 1980 and 2017, and who received RBC transfusions were reviewed. Disease specific outcomes and prognostic factors including age, gender, FAB/WHO (according to era) MDS diagnosis, number of cytopenias, marrow blast count, IPSS cytogenetic risk group, IPSS risk group, RBC transfusion requirements, SF, and other MDS treatments received as well as AML progression and cause of death were recorded. For patients receiving ICT, type of chelation agent and duration of chelation were also recorded. Lower risk MDS patients were further subdivided based on MDS subtypes and receipt of ICT.

Iron chelation therapy was initiated and monitored according to standard criteria. Deferoxamine was administered by continuous subcutaneous infusion at a dose of 0.5–3 g, adjusted to SF, over at least 12 h/day, at least five days per week. Deferasirox was administered at a starting dose of 20 mg/kg/day and escalated up to 30 mg/kg/day or down to 10 mg/kg/day according to SF and clinical and biochemical tolerance [14,29].

Erythroid improvement was assessed by International Working Group (IWG) 2006 criteria for patients in whom records on transfusion requirement reduction (> 50%) distant from other treatments expected to influence response were clear [13].

Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) version 24 software. Baseline clinical and laboratory factors were compared using the Chi-square or Fischer's exact test, where appropriate. Kaplan-Meier overall survival (OS) analyses were performed from time of MDS diagnosis, comparing ICT to non-ICT patients. Multivariate analysis was done by Cox regression analysis using SPSS.

3. Results

Of 436 patients in the clinical database with a bone marrow aspirate and biopsy confirmed diagnosis of MDS, 182 were lower IPSS risk and received RBC transfusions. The following patients were excluded for the following reasons: all CMML, t-MDS, (FAB) RAEB and RAEB-2, hypoplastic MDS, RCUD, because there were only 0–1 ICT patients in each group, n = 78; higher risk MDS, n = 90; missing records, n = 4. Sixty three ICT patients received deferasirox (n = 49), deferoxamine (n = 13) or deferiprone (n = 1, intolerant to both deferasirox and deferoxamine) for a median of 17.5 (range 0.1-75) months. Considering the entire cohort, there was no significant difference between the ICT and non-ICT groups in: gender; FAB/WHO MDS diagnosis; marrow blast count; IPSS cytogenetic risk group; other treatments received; or causes of death (p = NS for all, see Table 1). Differing for ICT and non-ICT patients, were: age, p = 0.005; IPSS risk group, p = 0.03; median number of RBC units transfused, p < 0.0001; and median SF, p < 0.0001. Numbers of patients in each subtype were, for ICT and non-ICT patients, respectively: RA, 13 and 24; RARS/RARS-t, 28 and

Table 1
Baseline characteristics of patients with lower IPSS risk MDS receiving red blood cell transfusions by receipt of iron chelation therapy.

Patient Characteristic at MDS diagnosis	ICT Patients n = 63	Non-ICT patients n = 119	p
Age (median [range]), years	67 (32–87)	74 (39–93)	**0.005**
Gender (n [%])			0.7
Male	38 (60.3%)	68 (57.1%)	
Female	24 (38.1%)	51 (42.9%)	
FAB or WHO MDS diagnosis (n [%])			0.07
RA	13 (20.6%)	24 (20.2%)	0.008
RARS, RARS-t	28 (44.4%)	31 (26.1%)	0.02
RCMD, RCMD-RS	15 (23.8%)	37 (31.1%)	0.3
Del(5q)[1]	3 (4.8%)	6 (5.0%)	0.3
RAEB-1	2 (3.2%)	12 (10.1%)	0.7
MDS-U, MDS/MPN-U	2 (3.2%)	10 (9.4%)	0.2
Marrow blast count (median [range])	1 (0–7)	1 (0–9)	0.2
IPSS cytogenetic risk group			0.1
Favorable	44 (69.8%)	75 (63.0%)	
Intermediate	7 (11.1%)	22 (18.5%)	
Poor	1 (1.6%)	5 (4.2%)	
NA	10 (15.9%)	17 (14.3%)	
IPSS Risk Group			**0.03**
Low	30 (47.6%)	46 (38.7%)	
Intermediate-1	27 (42.9%)	69 (58.0%)	
≤ Intermediate-1	6 (9.5%)	4 (3.4%)	
#RBC Units Transfused (median [range])	50 (16–330)	21 (1–200)	< **0.0001**
Serum Ferritin Level (ng/mL; median [range])	687 (49–6447)	260 (31–7783)	< **0.0001**
Iron Chelation Therapy			n/a
deferasirox	49 (77.8%)	n/a	
deferoxamine	13 (20.6%)	n/a	
deferiprone	1 (1.6%)	n/a	
Duration of ICT (median [range]), months	17.5 (0.1–75)	n/a	n/a
Other treatments received			0.2
Supportive care	26 (41.3%)	56 (47.1%)	
ESA	22 (34.9%)	23 (19.3%)	
IST	5 (7.9%)	2 (1.7%)	
Lenalidomide	3 (4.8%)	6 (5.0%)	
AZA	2 (3.2%)	11 (9.2%)	
AML chemotherapy	0 (0%)	1 (0.8%)	
Allogeneic SCT	0 (0%)	8 (6.7%)	
Other[2]	3 (4.8%)	8 (6.7%)	
Cause of death			0.2
MDS progression	2 (3.2%)	8 (6.7%)	
Infection	2 (3.2%)	9 (7.6%)	
AML progression	6 (9.5%)	7 (5.9%)	
Other[3]	7 (11.1%)	6 (5.0%)	
Unknown	4 (6.4%)	11 (9.2%)	

[1]2 with 1 additional cytogenetic abnormality: +8, n = 1; −13q, n = 1 [2]other treatments, ICT: VPA, hydroxyurea, androgen, n = 1 each; non-ICT: hydroxyurea, n = 3; anagrelide, n = 2; androgen, ivig, ruxolitinib, n = 1 each. [3]other causes of death, ICT: CHF from IOL, n = 4; cirrhosis from IOL, intracranial bleeding post-trauma, progressive pulmonary fibrosis, n = 1 each; non-ICT: MI, n = 2; subdural hematoma post-trauma; intracranial metastatic non-hematologic malignancy; CHF, n = 1 each.
#, number; (5q), long arm of chromosome 5; AML, acute myelogenous leukemia; CHF, congestive heart failure; EB, excess blasts; del, deletion; ESA, erythropoiesis stimulating agent; FAB, French-American British; ICT, iron chelation therapy; IOL, iron overload; IPSS, International Prognostic Scoring System; IST, immunosuppressive therapy; ivig, intravenous immunoglobulins; MDS, myelodysplastic syndrome; MI, myocardial infarction; MPN, myeloproliferative neoplasm; n, number; NA, not available; n/a, not applicable; p, probability; RA, refractory anemia; RBC, red blood cell; RCMD, refractory anemia with multilineage dysplasia; RS, ring sideroblasts; SCT, (hematopoietic) stem cell transplantation; t, thrombocytosis; U, unclassified; VPA, valproic acid; WHO, World Health Organization.

31; RCMD/RCMD-RS, 15 and 37; MDSU plus MDS/MPNU, 2 and 10; RAEB-1, 2 and 12; and del(5q)MDS, 3 and 6.

Examining baseline clinical features in the RA group more closely, there was no significant difference between groups in blast count, IPSS score or cause of death. However, IPSS cytogenetic category was favourable in all 9 (100%) patients who had informative cytogenetics analysis in the ICT group and in 10 of 17 (59%) non-ICT patients, while cytogenetic risk was intermediate in 7 (29%, p = 0.02). IPSS-R scores could be calculated in 7 of 13 (54%) patients in the ICT group and 14 of 24 (58%) in the non-ICT group, and were not significantly different (p = 0.1).

At a median follow up for all included patients, for ICT and non-ICT patients, of 76.5 (12.8-258.1) and 28.4 (0.03-187.4) months, 41 (65.1%) and 75 (63.0%) were alive (p < 0.0001). The median (range) follow up for RA, RARS/RARS-t and RCMD/RCMD-RS, respectively, was 38.5 (1.5-256.3), 51.6 (0.1-193.0) and 29.0 (4.1-189.7) months (RA vs. RCMD/RCMD-RS, p = 0.03; RARS/RARS-t vs. RCMD/RCMD-RS, p = 0.001). In a multivariate analysis of the entire cohort, age and receiving ICT remained significant for OS age: hazard ratio [HR] (95% confidence intervals [CI]) for death 1.04 (1.004-1.08), p = 0.03; and receiving ICT: HR 0.3 (0.1-0.8), p = 0.01], see Table 2. There were age differences favoring ICT patients in: the entire cohort, the RARS/RARS-t group, p = 0.004; and RAEB-1 patients, p = 0.0006; see Table 3. Median OS for ICT and non-ICT patients in MDS subtypes was significantly superior in ICT patients for the entire cohort, and in the subtypes RA and RARS/RARS-t, and is shown in Table 4 and Fig. 1a–c. For RCMD/RCMD-RS (Fig. 1d), RAEB-1, MDS-U plus MDS/MPN-U and del(5q)MDS, there was no significant difference in OS between ICT and non-ICT patients (p = NS for all). Interestingly, however, when looking at clinical features within subtypes, for RCMD/RCMD-RS, 16 of 38 (42%) non-ICT patients received lenalidomide, azacitidine or allogeneic stem cell transplantation (SCT) over their course, compared to none of 15 (0%) ICT patients, with a trend toward significance (p = 0.05; specific MDS treatments received in MDS subtypes comparing ICT to non-ICT patients are shown in Supplementary Table 1). Neither removing these patients from the analysis nor doing a multivariate analysis of RCMD/RCMD-RS patients only, including other treatments received, revealed a statistically significant OS difference between groups, however. Hazard ratios for death in RA, RARS/RARS-t, RARS/RARS-t adjusted for age, and RCMD patients were 0.2 (p = 0.01), 0.4 (p = 0.02), 0.4 (p = 0.04) and 0.5 (p = 0.4), respectively, for patients receiving ICT (see Table 5). There were no identifiable difference in causes of death between ICT and non-ICT groups in the whole cohort (Table 1) or in the MDS subtypes. However, although the numbers of AML deaths were equivalent between groups, the time from MDS diagnosis to AML transformation for ICT and non-ICT patients, respectively, was 32.0 and 13.7 months (p = 0.02).

Clear hematologic-improvement in the erythroid lineage, remote from other medications that could have influenced transfusion requirements, and consisting of a 50% or greater reduction in RBC transfusion requirements, occurred in 8 (12.7%) ICT patients in the entire cohort (RA, n = 1; RARS/RARS-t, n = 4; RCMD/RCMD-RS, n = 3), with 3 (4.8%) patients becoming transfusion independent (the first within 17 months of starting deferasirox, maintained for 4 months after which deferasirox was stopped, the second within 5 months of starting deferasirox, maintained for 40 months, including 33 months after stopping deferasirox; the third within 6 weeks of starting deferasirox, maintained for 65 months on decreasing doses of deferasirox until death from unrelated causes in the patient's late 80's) [13,30,31]. Comparing these patients to ICT patients with RA, RARS/RARS-t and RCMD/RCMD-RS without clear erythroid improvement, there was no significant difference in OS between groups (p = NS).

The median (range) duration of ICT for RA was 12 (1–64) months, for RARS/RARS-t 20.5 (1–69) months, and for RCMD/RCMD-RS 17 (1–58) months (p = NS for both RA versus RCMD/RCMD-RS and RARS/RARS-t versus RCMD/RCMD-RS). For all patients, the median overall survival for receiving iron chelation therapy for < 6 months was 110 months; for 6–24 months, 75 months; and for > 24 months, 161 months (p = 0.04 but p = NS for < 6 versus 6–24 months). Of the 19 patients receiving ICT for > 24 months, 4 (21%) were RA, 10 (53%) were RARS/RARS-t, and 3 (16%) were RCMD/RCMD-RS [MDS-U and del(5q), n = 1 (5.2%) each]. Eighteen patients discontinued DFX and 4 discontinued DFO. Reasons for discontinuation were: MDS progression, n = 8, including 7 progressions to AML and 1 to higher risk MDS; renal insufficiency, n = 4; gastrointestinal side effects, went to stem cell transplantation, became transfusion independent on specific MDS medications, and unclear, n = 2 each; side effects not otherwise specified and recurrent infections at injection sites, n = 1 each. Of the 4 patients discontinuing DFO, reasons were: stem cell transplantation,

Table 2
Multivariate analysis, entire cohort of transfused lower IPSS risk MDS patients included in the subtypes analysis, overall survival from MDS diagnosis.

	Coefficient	SE	p-value	HR	95.0% CI of HR	
					Lower	Upper
Age at MDS Dx	0.04	0.02	**0.03**	1.04	1.004	1.1
IPSS score	0.2	0.5	0.7	1.2	0.4	3.3
Serum Ferritin	0.0	0.0	0.7	1.0	1.0	1.0
MDS Dx	−0.2	0.2	0.2	0.8	0.6	1.1
Iron Chelation (Yes vs. No)	−1.1	0.5	**0.01**	0.3	0.1	0.8

CI, confidence interval; Dx, diagnosis; HR, hazard ratio; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; p, probability; SE, standard error.

Table 3
Age at MDS diagnosis in different MDS subtypes by receipt of iron chelation therapy.

	Age [median (range)] years		
	ICT	Non-ICT	p
Entire cohort	67 (32–87)	74 (39–93)	0.0005
RA	64 (32–87)	74 (39–90)	0.1
RARS/RARS-t	67 (35–83)	76 (40–88)	0.004
RCMD/RCMD-RS	72 (51–86)	74.5 (44–88)	0.9
RAEB-1	52 (51–53)	68 (48–82)	**0.0006**
MDS-U + MDS/MPN-U	78.5 (72–85)	77.5 (52–89)	0.7
Del(5q)MDS	67 (66–70)	67.5 (46–72)	0.9

Del(5q), deletion of the long arm of chromosome 5; EB, excess blasts; ICT, iron chelation therapy; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; p, probability; RA, refractory anemia; RS, ring sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; t, thrombocytosis; U, unclassifiable.

Table 4
Median overall survival in the entire cohort of transfused lower IPSS risk MDS patients and in MDS subtypes by receipt of iron chelation therapy.

FAB or WHO MDS diagnosis	Median OS (months)		p
	ICT	Non-ICT	
Entire cohort	133.8	66.7	< 0.0001
RA	140.9	36.3	0.008
RARS, RARS-t	133.4	73.3	**0.02**
RCMD, RCMD-RS	41.9	63.9	0.3
RAEB1	28.5	17.3	0.7
MDS-U, MDS/MPN-U	28.1	NR @ 77.4	0.2
Del (5q)*	63.9	NR @ 121.2	0.3

*2 with 1 additional cytogenetic abnormality: +8, n = 1; −13q, n = 1.
(5q), long arm of chromosome 5; EB, excess blasts; del, deletion; EB, excess blasts; FAB, French-American British; ICT, iron chelation therapy; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; p, probability; RA, refractory anemia; RCMD, refractory anemia with multilineage dysplasia; RS, ring sideroblasts; t, thrombocytosis; U, unclassified; WHO, World Health Organization.

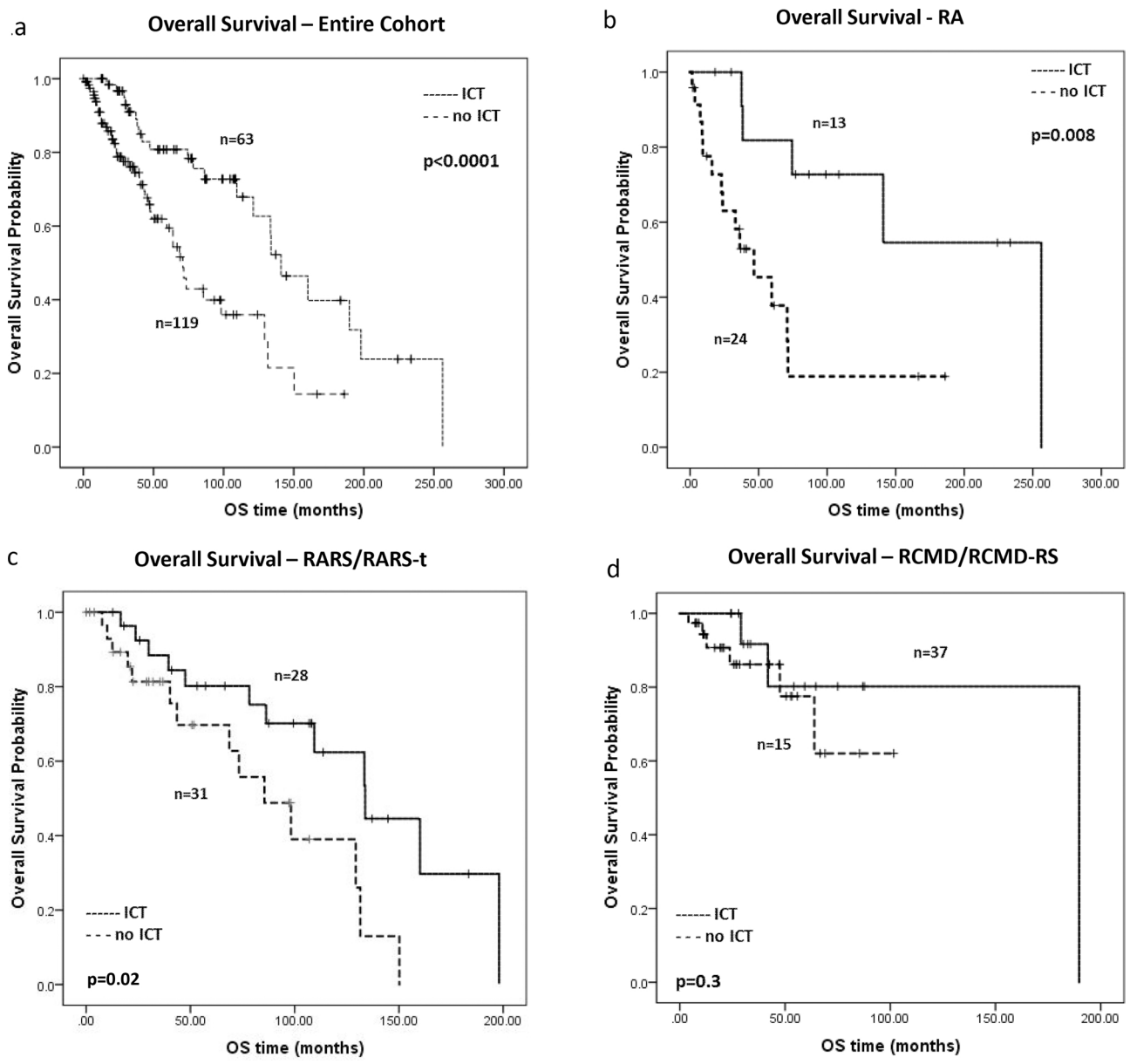

Fig. 1. Overall survival in patients with lower IPSS risk MDS receiving red blood cell transfusions by receipt of iron chelation therapy: a) the entire cohort b) RA c) RARS/RARS-t d) RCMD/RCMD-RS.

Table 5
Hazard ratio for death with iron chelation therapy in different lower IPSS risk MDS subtypes.

MDS subtype	HR	95% CI	P
RA	**0.2**	**0.07 – 0.7**	**0.01**
RARS/RARS-t	**0.4**	**0.2 – 0.9**	**0.02**
RARS/RARS-t adjusted for age	**0.4**	**0.2 – 0.9**	**0.04**
RCMD	0.5	0.1–2.6	0.7
RAEB–1	0.5	0.03 – 9.8	0.7
MDSU + MDS/MPN-U	0.03	NS	0.5
Del(5q)MDS	0.02	NS	0.6

CI, confidence interval; HR, hazard ratio; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; NS, not significant; p, probability; RA, refractory anemia; RCMD, refractory cytopenia with multilineage dysplasia; RS, ring sideroblasts; t, thrombocytosis; U, unclassified.

n = 2; AML progression and injection site infections, n = 1 each. One additional patient discontinued both DFX and then DFO for renal insufficiency, and biopsy-proven eosinophilic nephritis, respectively, and is currently receiving deferiprone.

Ferritin levels for ICT patients in the entire cohort were (median [range]): initial, 687 (49–6447); most recent, 2333 (349–10,329; $p < 0.0001$) and for non-ICT patients were: initial, 260 (12–7783); most recent, 998 (31–7783; $p < 0.0001$) ng/mL. The median (range) time between baseline and most recent ferritin measurements for ICT patients was 50.8 (1–144) months and for non-ICT patients 14.2 (1–130) months. Ferritin levels at most recent follow up compared to initial levels in the subtypes RA, RARS, and RCMD were stable to increased for both ICT and non-ICT patients and did not decrease significantly for any group.

4. Discussion

In this retrospective analysis, patients with lower IPSS risk RA and RARS/RARS-t receiving ICT had superior OS to non-ICT patients, while RCMD/RCMD-RS, RAEB-1, MDS-U plus MDS/MPN-U and del(5q)MDS patients did not. Numbers in the latter three groups were limited, however, so these results do not rule out an OS difference between ICT

and non-ICT patients in these subtypes, and this point should be clarified in larger analyses, preferably prospectively, and examining other MDS subtypes for which our numbers were too limited to attempt a meaningful analysis. In addition, in the RCMD/RCMD-RS group, 42% of non-ICT patients received the active MDS therapies lenalidomide, azacitidine or SCT, compared to no patients in the ICT group, with a trend toward statistical significance favouring non-ICT patients ($p = 0.05$), which could have obscured a potential survival benefit to receiving ICT. Further, follow-up was shorter for RCMD/RCMD-RS patients; median was 29 months versus 38.5 months for RA and 51.6 months for RARS/RARS-t ($p \leq 0.03$).

Moreover, in all patients, although causes of death including deaths from AML did not differ significantly between ICT and non-ICT patients, the time from MDS diagnosis to AML transformation, respectively, was 32.0 and 13.7 months ($p = 0.02$). While it is possible that this may be a reflection of differences in MDS risk groups between ICT and non-ICT patients not captured by the IPSS score, previous pre-clinical and clinical analyses suggest that iron overload may accelerate AML progression, and this could have contributed to the OS difference seen between groups [19,32,33]. This analysis, however, was non-controlled and there could have been factors affecting the results that were not taken into consideration. For example, there were differences in patient age favoring ICT patients in RARS/RARS-t, however, ages were not significantly different between ICT and non-ICT patients in RA, which also showed superior OS for ICT patients. In both groups, the superior OS for ICT patients was maintained in a multivariate analysis. We were not able to rigorously take into account retrospectively factors such as patient frailty, comorbidity and disability, which could have affected the findings. However, that 42% of non-ICT patients in the RCMD/RCMD-RS group received the active MDS therapies lenalidomide, azacitidine or SCT, compared to no patients in the ICT group, suggests that at least in this MDS subgroup, non-ICT patients were considered by the treating physicians to be at least as robust as ICT patients, so as to be offered these therapies. In addition to the non-controlled and retrospective nature of this analysis, factors such as transfusion intensity and time to transfusion dependence were not controlled, nor was IPSS-R score. For these reasons, as well as because of limited patient numbers, these findings should be considered exploratory and verified in larger studies. The randomized, placebo controlled trial of deferasirox in MDS is unlikely to give clarity on the relative benefits of ICT in MDS subtypes due to the reduction of its sample size by two thirds to 210 patients; in contrast, we had 346 lower IPSS risk MDS patients before several subtypes were excluded due to small numbers of patients receiving chelation [34].

Patients in the RA subtype receiving ICT had an OS of 140.9 vs. 36.3 months in non-ICT patients, which might suggest a selection bias in favour of the ICT patients. Looking more closely at baseline clinical features, the IPSS cytogenetic category was favourable in 9 (100%) patients who had informative cytogenetic analysis in the ICT group and in 10 of 17 (59%) non-ICT patients, while cytogenetic risk was intermediate in 7 (29%, $p = 0.02$), and it is possible that this may have influenced outcomes, accentuating a survival difference between ICT and non-ICT patients.

It is perhaps notable that both patient groups (RA and RARS/RARS-t) showing a significant difference in OS between ICT and non-ICT patients were those with the lowest hepcidin levels. Conversely, RCMD/RCMD-RS, despite reasonable numbers of patients for analysis, did not show a difference in OS between groups, and this is one of the MDS subtypes with high hepcidin levels. This raises the intriguing question whether there are significant differences in iron processing by different MDS subtypes which may influence clinical outcome. As iron physiology and pathophysiology is better defined in the future, this point may become more clear.

Erythroid improvement occurred in 8 (12.7%) ICT patients in the entire cohort, with 3 (4.8%) patients becoming transfusion independent for a period of 4, 40 and 65 months. Although the rate of erythroid improvement in this series is lower than reported in several other studies, transfusion records were often incomplete, and we only considered patients to have erythroid improvement for whom we had complete records and could determine that the timing of erythroid improvement was not related to other medications [10–12,16]. Also of note, although there was no OS difference in our analyses between ICT patients with erythroid improvement and ICT patients in the same MDS subtypes without erythroid improvement, some patients we considered to be without erythroid improvement could have had subtle improvements in transfusion requirements which were not captured in this analysis but could have obscured differences in clinical outcomes between groups. Moreover, significant improvements in quality of life were observed in patients with erythroid improvement, particularly in the patients who became transfusion independent. Three of the patients with erythroid improvement, including the patient with the longest transfusion independence, were in the RCMD/RCMD-RS group (20% of this subtype), which might be a reason to consider a trial of ICT in this subtype of MDS patients despite the apparent lack of difference in OS between ICT and non-ICT patients. There are as yet no clinical predictors as to which patients will have an erythroid improvement with ICT that have been identified, including in this series of patients, but identifying such predictive factors would be helpful in identifying patients more or less likely to benefit from ICT in future. The lack of OS benefit in ICT patients with erythroid improvement compared to those without erythroid improvement could imply that the superior OS seen with ICT in lower IPSS risk MDS may not be entirely attributable to erythroid improvement, however, as the numbers of patients with clear erythroid improvement were small, this point requires future clarification.

In summary, in this retrospective analysis, patients with lower IPSS risk RA and RARS/RARS-t receiving ICT had superior OS to non-ICT patients, while other MDS subtypes did not, though patients with erythroid improvement and transfusion independence following ICT were identified in the RCMD/RCMD-RS subtype, and a survival difference in this subtype may have been obscured by more non-ICT patients having received active MDS treatments. This analysis expands on an earlier study examining RARS versus non-RARS subtypes of MDS and survival in ICT versus non-ICT patients [35]. The current study includes 40% more chelation patients, excludes non-ICT patients for comparison in subtypes for which no to few patients received chelation, and restricts the analysis to transfused patients only; in the previous analysis 23% of patients comprised 3 subtypes with 0–1 ICT patients, and 29% of patients were not transfused. Though the current analysis of transfused patients only is perhaps a more appropriate comparison and the results perhaps more robust, the findings nonetheless should be verified in larger, and if possible, prospective analyses, and other lower IPSS risk MDS subtypes examined for a possible difference in clinical outcomes between ICT and non-ICT patients.

Conflicts of interest

SAW – none

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the

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