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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.