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Iron status and treatment modalities in transfusion-dependent patients with myelodysplastic syndromes

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ABSTRACT

1
2 Transfusion-dependency and iron overload are common among patients with
3
4 myelodysplastic syndromes (MDS) treated with red blood cell (RBC) transfusions.
5
6 Transfusion-dependency is associated with leukemic progression and shorter survival.
7
8 Guidelines recommend iron chelation therapy to manage iron overload, however little
9
10 is known about the chelation patterns in daily clinical practice. The objective of this
11
12 multicenter, retrospective, cross-sectional, observational study was to evaluate iron
13
14 status and its management in transfusion-dependent MDS patients. A total of 193
15
16 patient records from 29 centers were eligible for inclusion. Median patient age was 76
17
18 and median age at diagnosis of MDS was 74. Patients had received an average of
19
20 13.4±7.6 RBC units in the past four months; 44% had received more than 50 units since
21
22 their MDS diagnosis. Medium serum ferritin was 1550µg/L. Ninety patients (46.6%)
23
24 received iron chelation therapy with either deferoxamine (41%), deferasirox (36%), and
25
26 deferoxamine followed by deferasirox (23%). There were no statistically significant
27
28 differences between chelated and nonchelated patients in terms of IPSS, FAB, and/or
29
30 WHO status, though chelated patients had received more RBC transfusions (p=0.014).
31
32 Iron chelation therapy may be underutilized in transfusion-dependent patients.
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34 Undertreatment can be reduced by complementing sound clinical judgment with the
35
36 generally accepted guidelines of a serum ferritin level >1000µg/L and/or 2 or more RBC
37
38 transfusions per month for the past year; considering patients on the basis of their IPSS,
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40 FAB, and/or WHO status; and individually tailored treatment regimens. Prospective
41
42 randomized trials are necessary to establish causally the efficacy of iron chelation
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44 therapy in MDS.
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INTRODUCTION

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4 Myelodysplastic syndromes (MDS) are a heterogeneous group of bone marrow
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6 disorders characterized by cytopenias due to ineffective production of normal mature
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8 blood cells, with course of disease and prognosis dependent on subtype
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10 [1,2,3,4,5,6,7,8,9]. Up to 30% of patients progress to acute myelogenous leukemia
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12 (AML); while up to 65% of nonprogressing MDS patients will develop progressive
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14 cytopenia(s) [5]. As cancer registries seldom include MDS and epidemiological studies
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16 have varied in methodological quality, reliable estimates are scant [5]. The Düsseldorf
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18 (Germany) registry reported an incidence rate of 4.9 per 100,000 population for the
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20 period 1991-2001 (5.5 for men vs. 4.4 for women) [10]. Using 2002-2006 data, the US
21
22 National Cancer Institute (NCI) estimated the annual age-adjusted incidence rate at 4.0
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24 per 100,000 population (5.4 for men vs. 3.1 for women) or 14,324 new cases per year
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26 [11]. Though MDS may occur at any age, it is mainly a disease of old age, with men at
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28 greater risk. The Düsseldorf age-adjusted incidence rates per 100,000 population were
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30 24.5 in the 70-80 age group (38.8 for men vs. 17.8 for women) and 31.3 in the 80-90 age
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32 group (53.6 for men vs. 23.64 for women) [11]. In the NCI analysis, age-adjusted
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34 incidence rates were 24.8 per 100,000 in the 70-79 age group (33.9 for men vs. 17.9 for
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36 women) and 43.9 in the age 80 and older group (65.6 for men vs. 32.2 for women).
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45 From 80% to well over 90% of MDS patients develop anemia, with over half presenting
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47 with hemoglobin levels below 10 g/dL [12,13,14]. Almost all MDS patients are likely to
48
49 require red blood cell (RBC) transfusions at some point, and for 40% of patients this will
50
51 be the sole therapeutic option to manage their anemia, prevent anemia-related
52
53 comorbidity and decline in physical performance, and enhance quality of life [1]. Despite
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55 these potential benefits, transfusion-dependence in MDS patients is associated with
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57 increased risk of disease progression [4,13,15,16] and shorter survival [4,13,15,17]. The
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increased mortality risk is a function of disease severity, and the increased risk of leukemic progression; severity of anemia; and iron overload and the associated risk for end organ damage.

As one unit of blood contains between 100 and 250 mg of iron [3,18] transfusion-dependent patients with MDS invariably develop iron overload at a rate of approximately 0.5mg per kg of body weight per day [19] and typically after 10-20 transfusions [2,20]. The circulating non-transferrin-bound iron produces hydroxyl and oxygen radicals that cause lipid peroxidation and damage to cell membranes, protein, and DNA [2,21], especially in target organs such as heart, liver, and endocrine glands [1,22]. Iron overload is associated with reduced survival: adjusting for transfusion burden, hazard rates increase by 30% for every 500 µg/L increase in serum ferritin above the threshold of 1000 µg/L [4].

Recognizing that blood transfusions are therapeutically beneficial to manage anemia in MDS patients but that transfusional iron overload must be monitored and managed, several guidelines recommend iron chelation therapy [13,14,18,23,24,25,26], especially for patients with a good prognosis and a high transfusion requirement [26,27]. As these guidelines were published between 2002 [14] and 2010 [26], there are some historical differences, however there is growing consensus that iron chelation therapy should be initiated when a patient's serum ferritin reaches 1,000µg/L, and/or after the patient has received two units of RBCs a month for at least one year [27]. A recent review argued that the benefits of iron chelation therapy go beyond the reduction of cardiac and other end organ damage and also include reduced infection risk, improved survival after allogeneic hematopoietic stem cell transplantation, and delay of leukemic progression [28]. As a caveat, though, the evidence to date in support of iron chelation in MDS is from observational studies, not from randomized controlled trials.

1
2 Two iron chelating agents are approved worldwide, parenteral deferoxamine
3
4 (Desferal®, Novartis) and oral deferasirox (Exjade®, Novartis). A third oral agent,
5
6 deferiprone (Ferriprox®, Apopharma) is approved in some Asian and European
7
8 countries, but not in the USA and Canada due to safety concerns [19,29,30,31].
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11 Deferoxamine is administered through slow continuous infusion over 8 to 12 hours over
12
13 5 to 7 days per week, and the burden of this regimen impacts patient adherence.
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16 Deferiprone dosing is thrice daily p.o., whereas deferasirox is taken p.o. once daily.
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20 The introduction of the orally available iron chelator deferasirox has renewed the
21
22 interest in the management of transfusion-related hemochromatosis in MDS. However,
23
24 little is known about chelation patterns according to transfusion practice and ferritin
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26 levels in daily clinical practice. The objective of the multi-center retrospective
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28 observational study reported here was to evaluate iron status and its management in
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30 transfusion-dependent MDS patients.
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33 34 35 36 **METHODS**

37 38 39 40 41 Study Design

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45 This was a multicenter, retrospective, observational, noninterventional study with a
46
47 cross-sectional descriptive correlational design. Being observational, there were no
48
49 mandatory treatments, tests, and other procedures. Any treatment decisions were per
50
51 the treating physician's best clinical judgment. All data recorded were as available in
52
53 routine clinical practice. The study was conducted in 29 hematology centers throughout
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55 Belgium: 10 university centers and 19 regional medical centers.
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1 The study was approved by the Ethical Committee of each participating center. The
2 study was conducted in accordance with the Helsinki Declaration of the World Medical
3 Association as most recently amended.
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8 Patients

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12 Both male and female adults (age ≥ 18) were eligible, provided they were diagnosed
13 with one of the French-American-British (FAB) and/or World Health Organization
14 (WHO) MDS subtypes and were transfusion dependent. Transfusion dependence was
15 defined as having received at least 1 RBC transfusion every 8 weeks over a period of 4
16 months prior to inclusion in the study [15]. All patients (or their legal guardian)
17 provided written informed consent.
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28 Variables

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32 Data as available from the medical record and used in the statistical analysis included:
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34 patient demographics (age and gender); current medical status and comorbidities
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36 (diabetes, signs of heart failure, other cardiovascular disease, abnormal liver tests, and
37
38 other severe comorbidities with potential impact on survival); history of MDS (date of
39
40 diagnosis, FAB and/or WHO classification at diagnosis, and prognostic classification
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42 [IPSS] at diagnosis); cytogenetic risk group at diagnosis (conventional karyotype or
43
44 fluorescence in situ hybridization [12]); previous MDS treatments (growth factors,
45
46 immunomodulatory agents, chemotherapy, and allogeneic transplantation); most recent
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48 red blood cell hematology (RBC, hemoglobin, hematocrit) and serum ferritin levels;
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50 blood transfusion history (number of RBC units since diagnosis, number of RBC units in
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52 past 4 months); iron chelation therapy (if any, agent and route of administration); and, if
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1 applicable, reason for non-chelation. Iron overload was defined as a serum ferritin level
2 $\geq 1000 \mu\text{g/L}$.
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6 Procedures

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10 Each center identified potential subjects from patient files and current active case load
11 and compared them to the eligibility criteria. To optimize case-finding, centers also
12 queried their associated blood transfusion centers to identify transfusion-dependent
13 MDS patients. The chart reviews were performed between 11 September and 12
14 November 2008.
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24 Statistical Analysis

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29 Descriptive statistics for continuous variables included measures of central tendency
30 and dispersion; for discrete variables, counts, percentages, and proportions were
31 calculated. Tests of significance included Student t-test for independent samples and
32 analysis of variance for resp. 2 and ≥ 3 subgroup comparisons on continuous variables;
33 and χ^2 -based contingency analysis with, as applicable, Yates' correction for 2x2 tables.
34 Bonferonni-class corrections were used to monitor for multiplicity. The statistical
35 significance level was set at $\alpha=0.05$. Statistical analysis was performed using SPSS® v.15
36 (IBM, Chicago, IL).
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RESULTS

Patient Characteristics at Baseline

A total of 193 patient records were eligible for inclusion in this observational study and constituted the evaluable sample. The 29 participating centers contributed between and 1 and 20 patients for a median of 5 patients per center.

Tables 1 and 2 summarize patient characteristics and clinical status at the time of inclusion in the study; including comorbidities, MDS subtypes (FAB and WHO), and cytogenetics (IPSS risk score). The median age was 76 years (range 44-103); the median age at which the MDS diagnosis was made was 74 years (range 39-95); and the median time between diagnosis and start of study was 2 years. For 25% of patients it had been 4 or more years since MDS was diagnosed.

Some centers used the FAB, some the WHO, and some both classification methods. The most common types of MDS were refractory anemia without or with ringed sideroblasts (64.7% per FAB; 38.9% per WHO). Of the 149 patients with known IPSS score at diagnosis, 87.9% were in the low or intermediate 1 category. Similarly, 85 (81.7%) of the 104 patients tested cytogenetically fell in the favorable risk category. Most patients (74.6%) had at least one comorbidity, with cardiovascular disease (51.3%, including signs of heart failure) being the most common.

Anemia, Transfusion, and Iron Status

RBC count and hemoglobin and hematocrit levels confirmed that patients were severely anemic. On average, they had received 13.4 ± 7.6 RBC units in the past four months;

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2 44.0% had received more than 50 units since being diagnosed with MDS. Medium serum
3 ferritin was 1550µg/L; the 75th percentile was 2502µg/L (Tables 1 and 2).
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6 Iron Chelation Therapy

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11 Ninety patients (46.6%) received iron chelation therapy (Table 3). Treatment flow
12 charts by IPSS, FAB, and WHO classification are presented in Figures 1 through 3. Of the
13 90 chelated patients, 37 (41.1%) received deferoxamine, mainly intravenously (33,
14 84.6%); 32 (35.6%) were treated with deferasirox; and for 21 (23.3%) deferasirox was
15 given after prior deferoxamine therapy (in accordance with the current Belgian
16 reimbursement guidelines, which specify that deferasirox may be initiated if at least 6
17 months of prior deferoxamine therapy did not lead to controlled serum ferritin levels).
18 The time between MDS diagnosis and initiation of chelation therapy ranged from 1
19 month to 31 years ($M \pm SD = 3.6$ years; $Mdn = 2$); 25% of patients had been diagnosed 6 or
20 more years prior to start of chelation therapy. The median duration of treatment with
21 deferoxamine was 2.5 months compared to 16.0 months for deferasirox. There were no
22 statistically significant differences in IPSS, FAB, or WHO classification between chelated
23 and nonchelated patients. The highest ferritin levels were found in patients with
24 refractory anemia and refractory anemia with ringed sideroblasts (FAB and WHO
25 classification) and patients with refractory cytopenia with multilineage dysplasia or
26 unclassified MDS (WHO classification). Mean number of RBC transfusions received was
27 higher for chelated compared to nonchelated patients ($p = 0.014$).
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52 Reasons for non-chelation were provided for 98 of the 103 non-chelated patients (183
53 reasons or an average of 2/patient) and for 53 of the 56 non-chelated patients above the
54 1000µg/L serum ferritin threshold (110 reasons or average of 2/patient) (Table 4). The
55 frequencies of reasons cited were not statistically different between the two groups.
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2 **DISCUSSION**
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7 Chelation therapy is recommended for MDS patients with iron overload secondary to
8 blood transfusion, especially in patients with serum ferritin $\geq 1000\mu\text{g/L}$ and/or at least
9 two RBC transfusions a month over the past year [2,13,14,23,24,26,27]. Chelation may
10 significantly reduce total body iron load and decrease the production of hydroxyl and
11 oxygen radicals, thus lessening cellular and target organ damage and eventually
12 enhancing survival in transfusion-dependent MDS patients [1,2,21,22]. Note, however,
13 that the evidence for the use of chelation therapy in patients with MDS is based, not on
14 randomized controlled trials, but on observational studies; including two recent ones
15 which continue to provide evidence of an beneficial association between chelation
16 therapy and iron status [32,33].
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31 In this observational study of mainly severely anemic patients, the crude iron chelation
32 treatment rate across all patients, regardless of serum ferritin levels, was 46.6% (90 out
33 of 193 patients). This was higher than the 37.7% recently noted in a Spanish study [34],
34 however these percentages are not exactly comparable. In the Spanish study, only
35 patients with Low or Intermediate-1 MDS and with serum ferritin levels $\geq 1000\mu\text{g/L}$
36 were considered for chelation, which moreover was by parenteral deferoxamine as
37 deferasirox was not yet available in Spain. Of the 125 patients in our sample with known
38 recent serum ferritin levels $\geq 1000\mu\text{g/L}$, 69 or 55.2% were chelated – higher than in the
39 Spanish study yet still leaving nontreatment rates of 44.8% and 62.3% in resp. the
40 Belgian and Spanish studies.
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56 Patients with IPSS scores in the Low and Intermediate 1 (Int-1) categories; patients with
57 FAB classification of refractory anemia without (RA) and with ringed sideroblasts
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1 (RARS); and/or patients with WHO classification of RA, RARS or 5q- syndrome (5q-), are
2 considered good candidates for iron chelation therapy. Referring to Figures 1 through 3,
3
4 of particular interest is the branch of 57 non-chelated patients with serum ferritin levels
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6 exceeding the 1000µg/L threshold. Using the IPSS criteria, an additional 41 out of 193
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8 (21.2%) patients may have benefited from chelation therapy; also an 42 (21.8%) when
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10 classifying according to the FAB system; and an additional 29 (15.0%) when applying
11
12 the WHO classification. Arguably, if physicians had applied these criteria, between 119
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14 (61.7%) and 132 (68.4%) of the total patient population would have received iron
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18 chelation.
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22 While endorsing the importance of transfusion dependency (2 RBC units/month for at
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24 least a year; serum ferritin >1000µg/L; Low or Int-1 IPSS; and/or WHO RA, RARS and
25
26 5q-), the Consensus Statement by the MDS Foundation's Working Group on
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28 Transfusional Iron Overload identifies additional factors for evaluating candidates for
29
30 chelation therapy: patients with a projected life expectancy of at least one year, patients
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32 without prognosis-limiting comorbidities, allograft candidates, and patients with a need
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34 to preserve target organ function [13]. Because its serum levels are affected by
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36 inflammation and liver disease, ferritin has been argued to be an inadequate indicator of
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38 body iron content, should not be used for determining the need for iron chelation
39
40 therapy, and should at best be used for monitoring such therapy [26]. Instead, iron
41
42 chelation therapy is recommended in all patients with Int-1 IPSS risk disease who
43
44 receive regular red-cell transfusion therapy after patients have received 20 packed RBC
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46 units (i.e., 4g of iron). Further, iron chelation therapy should be considered for
47
48 transfusion-dependent patients with Int-2 and high IPSS risk disease when they are
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50 responding to therapies able to modify their life expectancy or have a hematopoietic
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52 stem cell transplantation in their therapeutic program [26]. Further, it has been argued
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54 that advanced age or severe comorbidities should not preclude iron chelation therapy
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1 [1], though careful evaluation of patients' frailty and consideration of life expectancy are
2 recommended [2]. Other relevant decision factors include patients with elevated serum
3 ferritin levels at the time of MDS diagnosis, in particular those with acquired
4 sideroblastic anemia because of the risk of hematochromatosis [5], and patients on
5 more liberal transfusion strategies where the target hemoglobin is higher than the 8-
6 10g/dL typically maintained in MDS patients [1]. In fact, individually tailoring
7 deferasirox dose to achieve therapeutic targets, with initial dosing based on transfusion
8 requirements and titration per follow-up monitoring data, is recommended [32].
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20 Despite effectiveness data from observational studies, consensus statements, and
21 guidelines, the absence of randomized controlled trials leaves some uncertainty about
22 the efficacy of iron chelation therapy in patients with MDS. However, the position
23 against chelation [35,36,37] is not warranted. It is now well established that adequately
24 designed observational studies, though perhaps unable to provide causal evidence,
25 provide accurate estimates of treatment effects [38,39]
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33 These extant consensus and individual recommendations are helpful in reconciling
34 some of the reasons physicians in our study cited for not chelating patients, including
35 age, life expectancy, and comorbidities (Table 4). Note in this regard that 6 patients with
36 serum ferritin levels $\geq 1000\mu\text{g/L}$ were not chelated because their physician did not
37 consider the threshold for chelation achieved, and 7 because there had not been
38 sufficient prior RBC transfusions. Lastly, there is evidence that, in some patients,
39 effective long-term chelation (1-4 years) may stimulate haemopoiesis resulting in a
40 return to transfusion independence [40] and decrease cardiac iron content [41]. This
41 emphasizes the importance of applying generally accepted guidelines for iron chelation
42 treatment while also considering individual patient factors beyond these guidelines to
43 offer patients individualized treatment plans.
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1 Nonadherence with iron chelation therapy is a known problem [42,43,44], especially
2 with deferoxamine due to the virtually daily, slow, continuous parenteral
3
4 administration. Physician influence should not be excluded: 16 of the 53 patients
5
6 (30.2%) above the serum ferritin threshold of 1000µg/L were not chelated because
7
8 their prescribing physician considered deferoxamine administration too cumbersome.
9
10 Deferasirox's once daily oral dosing coupled with its tolerability [32,45] offers a
11
12 convenient alternative. There is evidence that deferasirox decreases the risk of iron
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14 overload in Low and Int-1 IPSS patients [24], removes cardiac iron more effectively, and
15
16 prevents cardiac iron accumulation [45], and lowers liver iron concentrations and labile
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18 plasma iron levels [33] Clinician education about the importance of patient adherence
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20 should include this information, as well as such essentials as the potential negative
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22 effect of iron overload on heart, liver, and endocrine glands, and the associated increase
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24 in mortality risk.
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31 The results of our study should be considered within the study's limitations and the
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33 directions for future research it provides. This was a retrospective observational study
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35 with a convenience sample and conducted in one European country; not a prospective
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37 population-based cohort study with random subject selection. A center-level bias of
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39 heightened vigilance about iron overload at participating centers cannot be excluded,
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41 certainly not in the eleven out of the 29 centers that have participated in trials of
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43 deferasirox. The study did not examine the effectiveness of iron chelation therapy, in
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45 part because of the availability of two agents with different routes of administration and
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47 the sequential use of both in 23% of patients. A comparative effectiveness study, let
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49 alone a randomized controlled efficacy trial, would be necessary for this. Importantly,
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51 such studies should assess the moderating impact of adherence on iron outcomes. Yet,
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53 unless the aim is to document the superiority of one agent over the other in transfusion-
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55 dependent MDS patients with anemia, the relevance of such studies may be less evident.
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1 The equivalence of deferoxamine and deferasirox has been established in patients with
2 β -thalassemia [46] and sickle cell disease [47], and the pathogenesis of iron overload in
3
4 these anemias is considered generalizable to other anemias requiring transfusion. The
5
6 differential benefit of deferasirox is its convenience of once daily oral intake. Lastly, we
7
8 considered only serum ferritin as marker of iron status, and future studies should
9
10 include established markers like non-transferrin bound iron, labile plasma iron, liver
11
12 iron concentration, and magnetic resonance imaging of target organs. While the current
13
14 guidelines provide general direction for identifying good candidates for iron chelation
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16 therapy, future research is needed to examine expanded patient profiles that may
17
18 benefit from treatment. Being observational, the present study does not address the
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20 need for randomized controlled trials.
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27 **CONCLUSION**

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31 Despite the known efficacy of chelation therapy for transfusion-induced iron overload, it
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33 is underutilized in the management of transfusion-dependent MDS patients in Belgium –
34
35 even though this trend is unlikely to be limited to Belgium. Thus this study provides
36
37 further evidence of the need to optimize treatment strategies and algorithms for
38
39 treating transfusional iron overload in patients with MDS. Undertreatment can be
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41 reduced by complementing sound clinical judgment with the generally accepted
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43 guidelines of a serum ferritin level $>1000\mu\text{g/L}$ and/or 2 or more RBC transfusions per
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45 month for the past year; considering patients on the basis of their IPSS, FAB, and/or
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47 WHO status; and individually tailored treatment regimens.
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Table 1. Patient characteristics and clinical status

Demographics				
Age	(range; M±SD; Mdn)	44-103	75.6±9.2	76
Gender	male (n, %)	110	57.0%	
	female (n, %)	83	43.0%	
Comorbidities				
	(n, %)			
Number	0	49	25.4%	
	1	72	37.3%	
	2	46	23.8%	
	≥ 2	26	13.5%	
Type ¹	Cardiovascular disease	99	51.3%	
	Signs of heart failure	43	22.3%	
	Other severe comorbidities with potential impact on survival	39	20.2%	
	Diabetes	33	17.1%	
	Abnormal liver tests	32	16.6%	
Hematology				
	(range; M±SD; Mdn)			
Red blood cells (x 10 ¹² /L)		1.82-4.58	2.82±0.50	2.78
Hemoglobin (g/dL)		4.9-14.2	8.8±1.4	8.7
Hematocrit (%) (n=192)		16.7-47.5	26.3±4.2	26
Iron status				
	(range; M±SD; Mdn)			
Serum ferritin (µg/dL) (n=176)		7-11035	2298±2142	1550

Unless otherwise noted, all n=193.

¹ Multiple comorbidities possible, hence percentages exceed 100.

Table 2. MDS history, disease status at MDS diagnosis, and prior and current treatments

MDS history				
Age at MDS diagnosis (years)	(range; M+SD; Mdn)	39-95	72.2±9.9	74
Time from MDS diagnosis (years)	(range; M+SD; Mdn)	0-32	3.4±4.0	2
FAB classification at diagnosis		(n, %)		
Refractory anemia		78	40.4%	
Refractory anemia with ringed sideroblasts		47	24.4%	
Refractory anemia with excess of blasts		16	8.3%	
Refractory anemia with excess of blasts in transformation		5	2.6%	
Chronic myelomonocytic leukemia		5	2.6%	
Classification not used		42	21.8%	
WHO classification at diagnosis		(n, %)		
Refractory anemia		41	21.2%	
Refractory anemia with ringed sideroblasts		34	17.6%	
Refractory cytopenia with multilineage dysplasia		20	10.4%	
Refractory sideroblastic cytopenia with multilineage dysplasia		2	1.0%	
Refractory anemia with excess of blasts - I		10	5.2%	
Refractory anemia with excess of blasts - II		5	2.6%	
5q- syndrome		14	7.3%	
Unclassified myelodysplastic syndrome		6	3.1%	
Classification not used		61	31.6%	
Karyotype		(n, %)		
Favorable (normal, isolated 5q-, isolated 20q-, or deletion Y)		85	44.0%	
Poor (any chromosome 7 anomaly or ≥ 3 aberrations)		11	5.7%	
Intermediate (all other anomalies)		8	4.1%	
Unknown		89	46.1%	

MDS severity per IPSS prognostic score at diagnosis	(n, %)			
Low		56	29.0%	
Intermediate 1		75	38.8%	
Intermediate 2		13	6.7%	
High		5	2.6%	
Unknown		44	22.8%	
RBC transfusions in past four months (n=192)	(range; M+SD; Mdn)	2-40	13.4±7.6	12
0-10 transfusions	(n, %)	19	9.9%	
11-20 transfusions		31	16.1%	
21-50 transfusions		58	30.2%	
>50 transfusions		84	43.8%	
Highest recorded serum ferritin level (n=192)	(n, %)			
< 1000 µg/L		48	25.0%	
1000 - 1999 µg/L		64	33.3%	
2000 - 2999 µg/L		23	12.0%	
3000 - 3999 µg/L		13	6.8%	
≥ 4000 µg/L		29	15.1%	
missing		15	7.8%	
Prior treatments				
Growth factors (n=192)		95	49.5%	
Immunomodulatory agents (n=189)		30	15.9%	
Chemotherapy (n=190)		32	16.8%	
Allogeneic transplantation (n=191)		2	1.0%	
Current treatments				
Growth factors (n=188)		50	26.6%	
Immunomodulatory agents (n=186)		5	2.7%	
Chemotherapy (n=188)		25	13.3%	
Allogeneic transplantation candidate (n=187)		1	0.5%	

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6 Unless otherwise noted, all n=193.

7 Abbreviations: FAB = French-American-British; IPPS = International Prognostic Scoring System; M = Mean; Mdn = Median;
8 MDS = Myelodysplastic Syndrome; n = subsample size; range = minimum and maximum; RBC = Red Blood Cells; SD =
9 Standard Deviation; WHO = World Health Organization
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Table 3. Comparison of patients receiving versus not receiving iron chelation therapy

		Chelated patients		Non-chelated patients (All)		p ¹	Non-chelated patients with most recent serum ferritin >1000µg/L		p ²
n (%)		90	46.6%	103	53.4%	n.s.	57	55.3%	n.s.
Age (years)	(range; M±SD)	46-88	74.0±8.5	44-103	75.9±9.6	n.s.	51-103	77.0±9.5	n.s.
RBC units transfused in past 4 months	(range; M±SD)	4-40	14.9±7.5	2-39	12.2±7.6	0.014	4-38	13.9±7.8	n.s.
FAB classification at diagnosis	(n, %) ³								
Refractory anemia		33	36.7%	45	43.7%		26	45.6%	
Refractory anemia with ringed sideroblasts		25	27.8%	22	21.4%		16	28.1%	
Refractory anemia with excess of blasts		7	7.8%	9	8.7%		3	5.3%	
Refractory anemia with excess of blasts in transformation		2	2.2%	3	2.9%		0	0.0%	
Chronic myelomonocytic leukemia		2	2.2%	3	2.9%		1	1.8%	
Classification not used		21	23.3%	21	20.4%	n.s.	11	19.3%	n.s.
WHO classification at diagnosis	(n, %) ³								
Refractory anemia		20	22.2%	21	20.4%		13	22.8%	
Refractory anemia with ringed sideroblasts		17	18.8%	17	16.5%		12	21.1%	
Refractory cytopenia with multilineage dysplasia		8	8.9%	12	11.7%		8	14.0%	
Refractory sideroblastic cytopenia with multilineage dysplasia		0	0%	2	1.9%		1	1.8%	
Refractory anemia with excess of blasts - I		5	5.6%	5	4.9%		1	1.8%	
Refractory anemia with excess of blasts - II		2	2.2%	3	2.9%		2	3.5%	
5q- syndrome		5	5.6%	9	8.7%		4	7.0%	
Unclassified		4	4.4%	2	1.9%		2	3.5%	
Classification not used		29	32.23%	32	31.1%	n.s.	14	24.6%	n.s.

MDS severity per IPSS prognostic score at diagnosis	(n, %)³								
Low	22	24.4%	34	33.0%		22	38.6%		
Intermediate 1	39	43.3%	36	35.0%		19	33.3%		
Intermediate 2	2	2.2%	11	10.7%		4	7.0%		
High	2	2.2%	3	2.9%		0	0.0%		
Unknown	25	27.7%	19	18.4%	n.s.	12	21.1%	n.s.	

Unless otherwise specified, all n = 193.

Abbreviations: FAB = French-American-British; IPSS = International Prognostic Scoring System; M = Mean; Mdn = Median; MDS = Myelodysplastic syndrome; n = subsample size; n.s.=not significant; range = minimum and maximum; RBC = Red Blood Cells; SD = Standard Deviation; WHO = World Health Organization.

¹ For comparing chelated vs. non-chelated patients.

² For comparing chelated vs. non-chelated patients with most recent serum ferritin >1000µg/L

³ As proportion on the 103 non-chelated patients based on most recent serum ferritin value.

⁴ As percentage of column n (chelated n=90; all non-chelated n=103; non-chelated with serum ferritin >1000µg/L n=57)

Table 4. Reasons for non-chelation

	Non-chelated patients (all) (n=98)		Non-chelated patients with most recent serum ferritin > 1000µg/L (n=53)		p
No serum ferritin values available	2	2.0%	0	0.0%	n.c.
Serum ferritin threshold not reached	22	22.4%	6	11.3%	n.s.
Not enough RBC transfusions received	22	22.4%	7	8.4%	n.s.
Patient age	39	39.8%	28	52.8%	n.s.
Limited life expectancy	35	35.7%	24	45.3%	n.s.
Comorbidities	32	32.7%	21	39.6%	n.s.
Not convinced about iron chelation for MDS	5	5.1%	2	3.8%	n.c.
Deferoxamine administration too cumbersome	18	18.4%	16	30.2%	n.s.
Other	8	8.2%	6	11.3%	n.s.

Abbreviations: n = subsample size; MDS = Myelodysplastic Syndrome; n.c. = not calculable; n.s.= not significant; RBC = red blood cells
omnibus p=n.s.

Figure Legend

Figure 1

Treatment flow of all patients based on iron chelation therapy, serum ferritin values, and IPPS scores. Light shaded boxes in the non-chelated patient arm refer to categories of potential candidates for iron chelation therapy according to international recommendations. Abbreviations: Int-1 = Intermediate 1; Int-2 = Intermediate 2; IPSS = International Prognostic Scoring System; SF = Serum Ferritin.

Figure Legend

Figure 2

Treatment flow of all patients based on iron chelation therapy, serum ferritin values, and FAB classification. Light shaded boxes in the non-chelated patient arm refer to categories of potential candidates for iron chelation therapy according to international recommendations. Abbreviations: CMML = Chronic Myelomonocytic Leukemia; FAB = French-American-British; RA = Refractory Anemia; RAEB = Refractory Anemia with Excess of Blasts; RARS = Refractory Anemia with Ringed Sideroblasts.

Figure Legend

Figure 3

Treatment flow of all patients based on iron chelation therapy, serum ferritin values, and WHO classification. Light shaded boxes in the non-chelated patient arm refer to categories of potential candidates for iron chelation therapy according to international recommendations. Abbreviations: RA = Refractory Anemia; RAEB = Refractory Anemia with Excess of Blasts; RAEB-II = Refractory Anemia with Excess of Blasts II; RARS = Refractory Anemia with Ringed Sideroblasts; RCMD = Refractory Cytopenia with Multilineage Dysplasia; RSCMD = Refractory Sideroblastic Cytopenia with Multilineage Dysplasia; SF = Serum Ferritin; WHO = World Health Organization; 5q = 5q Syndrome.

Disclosures

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Study design: I. Abraham, M. Delforge, K. MacDonald, C. Ravoet, D. Selleslag

Study implementation: W. Pluymers

Essential investigators: G. Bries, M. Delforge, C. Graux, P. Mineur, C. Ravoet, D. Selleslag, A.

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Figure 1

Figure 1

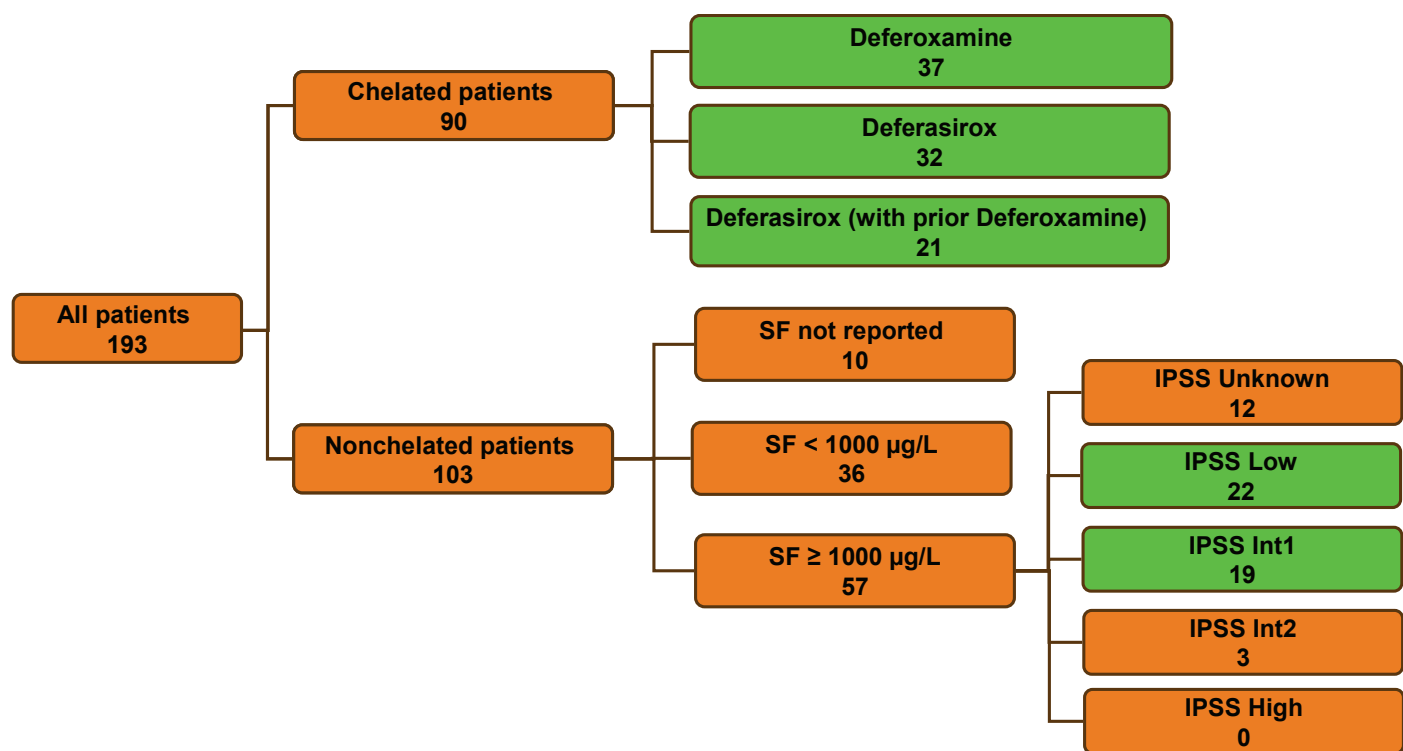


Figure 2

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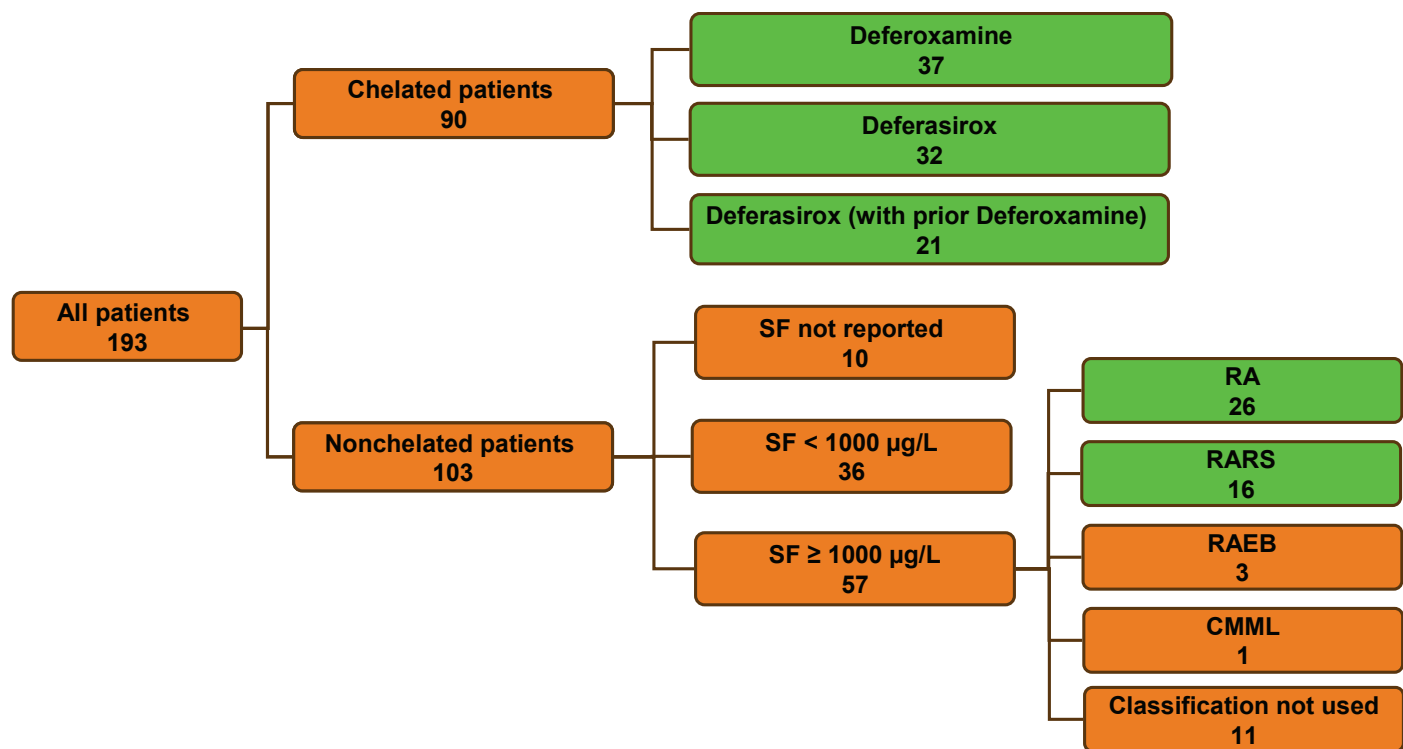
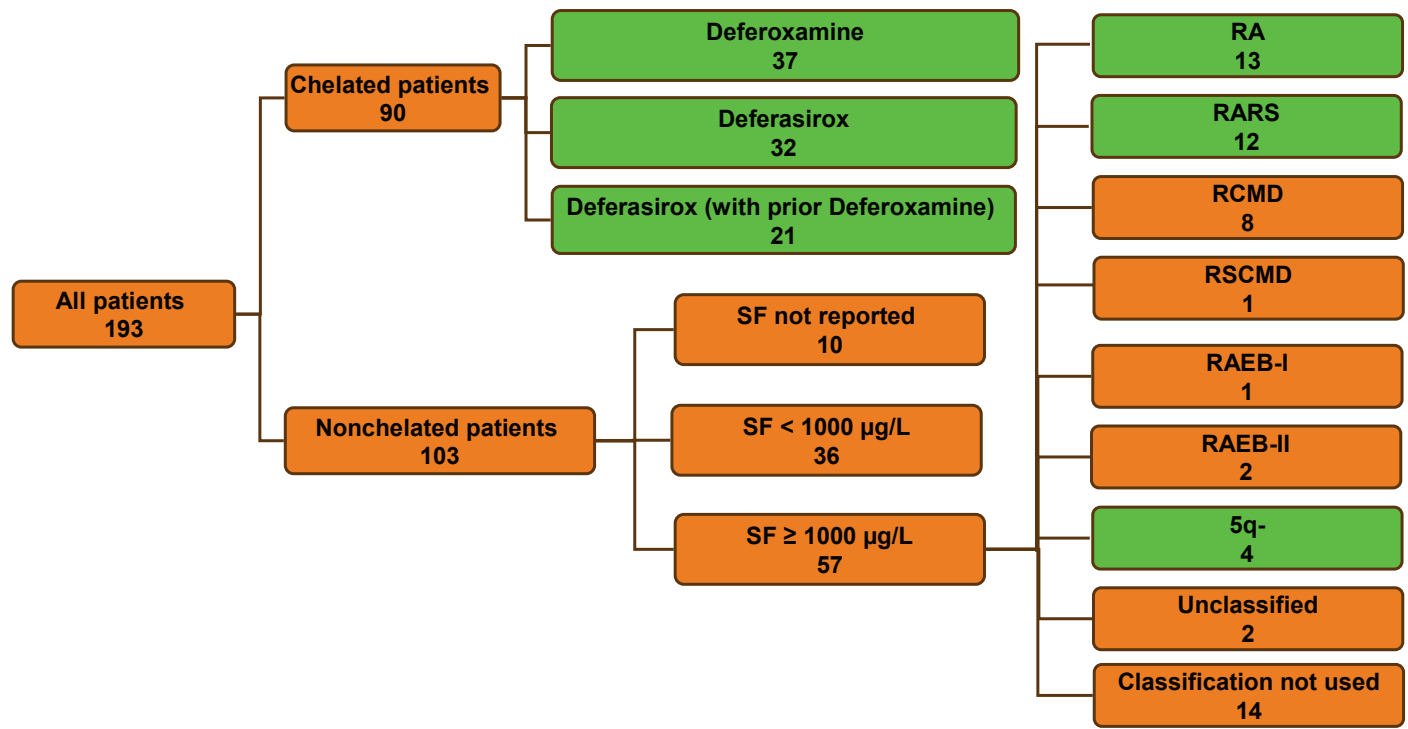


Figure 3



***Conflict of interest**

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