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Comparison of 24-month outcomes in chelated and non-chelated lower-risk patients with myelodysplastic syndromes in a prospective registry☆

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ABSTRACT

This 5-year, prospective registry enrolled 600 lower-risk MDS patients (pts) with transfusional iron overload. Clinical outcomes were compared between chelated and nonchelated pts. At baseline, cardiovascular comorbidities were more common in non-chelated pts, and MDS therapy was more common in chelated pts. At 24 months, chelation was associated with longer median overall survival (52.2 months vs. 104.4 months; $p < .0001$) and a trend toward longer leukemia-free survival and fewer cardiac events. No differences in safety were apparent between groups. Limitations of this analysis included, varying time from diagnosis and duration of chelation, and the fact that the decision to chelate may have been influenced by pt clinical status.

1. Introduction

Myelodysplastic syndromes (MDS) are clonal stem cell disorders characterized by impaired hematopoiesis and increased risk of acute myeloid leukemia (AML). Approximately half of patients with MDS will develop severe anemia (hemoglobin level less than 10 mg/dL) and will require periodic or regular red blood cell transfusions [1,2]. Transfusion requirement may lead to iron overload and has been associated with increased risk of death and shorter leukemia-free survival [3,4]. Retrospective and observational studies have shown that iron overload is associated with an increased risk of cardiac, hepatic, and endocrine damage [5]. Malcovati et al. have shown a stepwise increase in risk of death associated with increased serum ferritin in patients with MDS. Each 500 ng/mL increase in serum ferritin above 1000 ng/mL was associated with a 40% increased risk of death [3]. Similarly, a multicenter, observational study by Groupe Francophone des Myélodysplasies (GFM) sought independent prognostic factors for survival in patients who are iron-overloaded with lower-risk MDS [6]. Multivariate analysis showed that transfusion requirement of more than 3 units/month and increased International Prognostic Scoring System (IPSS) risk status were associated with increased risk of death, whereas adequate iron chelation (40 mg/kg/day deferoxamine 3 or more times/week) was associated with 70% lower risk of death. Adequate chelation was the strongest predictor of overall survival in the French study, in which patients had a mean of 1.7 comorbidities.

Recently, prospective evidence for the benefits of iron chelation on hematologic parameters has been published for the oral iron chelator deferasirox. The large evaluation of patients' iron chelation with Exjade® trial assessed iron-overload parameters in transfusion-dependent patients with MDS and showed reductions

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Table 1
Baseline demographics and MDS risk status[a].

Variable	Non-chelated $n = 337$	Chelated $n = 263$	Chelated ≥6 months $n = 191$
Median age (range), y	77 (47–99)	75 (21–94)	74 (21–94)
Male: female ratio	1.42:1	1.31:1	1.20:1
MDS risk status, *n* (%)			
World Health Organization	112 (33.2)	78 (29.7)	57 (29.8)
Refractory anemia	38 (33.9)	13 (16.7)	8 (14.0)
Refractory anemia with ring sideroblasts	34 (30.4)	40 (51.3)	32 (56.1)
Refractory cytopenia with multilineage dysplasia	20 (17.9)	12 (15.4)	8 (14.0)
Refractory cytopenia with multilineage dysplasia and ring sideroblasts	8 (7.1)	7 (9.0)	5 (8.8)
MDS associated with isolated del (5q)	12 (10.7)	6 (7.7)	4 (7.0)
French-American-British	59 (17.5)	58 (22.1)	39 (20.4)
Refractory anemia	23 (39.0)	22 (37.9)	13 (33.3)
Refractory anemia with ring sideroblasts	17 (28.8)	28 (48.3)	21 (53.8)
Refractory anemia with excess blasts (< 11%)	19 (32.2)	8 (13.8)	5 (12.8)
International Prognostic Scoring System	166 (49.3)	127 (48.3)	95 (49.7)
Low	56 (33.7)	56 (44.1)	38 (40.0)
Intermediate-1	110 (66.3)	71 (55.9)	57 (60.0)

[a] Criteria used for risk classification was determined by accepted practice at the time of initial diagnosis. MDS, myelodysplastic syndromes.

in serum ferritin, labile plasma iron, and alanine aminotransferase (ALT) levels after 1 year of chelation therapy [7]. List et al. showed similar results over 3 years of follow-up in heavily transfused, lower-risk patients with MDS [8]. At study end, serum ferritin was reduced by 37%, labile plasma iron was normalized in patients with elevated baseline levels, and transferrin saturation was reduced to 67% from a baseline of 91%. Improved ALT levels were significantly correlated with reduced serum ferritin in the study by List et al.

However, prospective data on the relationship between chelation, morbidity, and mortality are lacking. The goal of this registry is to evaluate the association between chelation and clinical outcomes in lower-risk MDS patients. We report 24-month data from an ongoing, 5-year registry of lower-risk patients with MDS in the United States. This registry provides prospectively collected data on clinical and safety parameters in chelated versus non-chelated, iron-overloaded, transfusion-dependent, lower-risk patients with MDS.

2. Patients and methods

This study is a prospective, 5-year, observational registry of 600 lower-risk patients with MDS and iron overload from 118 centers in the United States (9 academic sites; 109 community cancer centers) that enrolled patients over a 2-year period. The first patient first visit was completed on December 20, 2010. The current analysis presents 24-month data from the registry; this represents a composite of data from patients who have completed up to 24 months on the registry. Patient baseline characteristics and study outcomes were analyzed according to their chelation status (non-chelated, chelated, and chelated ≥6 months cumulatively). Chelated patients were defined as those patients who received chelation at any point. In addition, a planned subanalysis was performed for patients who received ≥6 months of cumulative chelation because this duration was thought to provide an adequate treatment period. The chelated ≥6 months group was included in the overall chelated group. Follow-up occurred every 6 months for up to 60 months or death. Assessments included demographics, survival, causes of death, leukemic transformation, serum ferritin, concomitant illnesses, MDS therapy, ongoing transfusion requirements, and safety.

Patients were aged 18 years or older with transfusional iron overload (serum ferritin more than 1000 ng/mL, 20 or more packed red blood cell units, or ongoing transfusion requirement of 6 or more units every 12 weeks) and lower-risk MDS by IPSS, World Health Organization (WHO), and/or French-American-British (FAB) criteria. Approved and experimental MDS therapies were permitted. Adverse events were documented occurring on study and during the 4 weeks after stopping chelation therapy. This study was conducted in accordance with the declaration of Helsinki. All enrolled patients gave written informed consent.

Data are summarized according to demographic and baseline characteristics, safety observations, and outcome measurements. Summary statistics were calculated for continuous variables, and descriptive statistics were calculated for discrete variables and laboratory tests.

3. Results

3.1. Baseline characteristics

Median age was similar across patient groups (non-chelated, 77 years [range, 47–99]; chelated, 75 years [range, 21–94]; chelated ≥6 months, 74 years [range, 21–94]; Table 1). All groups had a larger percentage of men than of women, although the difference was noted less in the chelated groups. Overall, 86.7% of patients were Caucasian, 6.2% were Hispanic, 5.5% were African American, 1.0% were Asian, and 0.3% each were Native American or other. In all, 82% of patients were enrolled at community cancer centers.

Approximately half of patients were classified lower-risk MDS by IPSS criteria, approximately 30% were classified lower-risk by WHO, and approximately 20% were classified lower-risk by FAB. The MDS risk status profiles were similar across groups except that a larger percentage of non-chelated patients were classified as intermediate-1 risk by IPSS criteria (non-chelated, 66.3%; chelated, 55.9%; and chelated ≥6 months, 60.0%), having refractory anemia by WHO criteria (non-chelated, 33.9%; chelated, 16.7%; and chelated ≥6 months, 14.0%), and having refractory anemia with excess blasts by FAB criteria (non-chelated, 32.2%; chelated, 13.8%; and chelated ≥6 months, 12.8%).

Baseline cardiac and vascular comorbidities were more common in the non-chelated group (Table 2). Cardiac conditions included coronary artery disease, cardiomyopathy, rhythm abnormalities, structural abnormalities, and infectious/inflammatory conditions. Use of MDS therapies was more common in chelated patients. Overall, 287 (85.2%), 243 (92.4%), and 175 patients (91.6%) in the non-chelated, chelated, and chelated ≥6 months groups, respectively, had received MDS therapy prior to or at enrollment. Growth factor use trended higher among chelated patients. Erythropoietin was used by 65.3% of non-chelated, 76.8% of chelated, and 80.1% of chelated ≥6 months groups; granulocyte colony-stimulating factor (GCSF) was used by 18.1% of non-chelated, 24.0% of chelated, and 25.7% of chelated ≥6 months groups. Low-dose chemotherapy/immunomodulator use, with the exception of hydroxyurea, trended higher in chelated patients. Azacitidine use in non-chelated, chelated, and chelated ≥6 months groups was 40.1%, 51.7%, and 55.0%; decitabine use was 26.1%, 31.2%, and 30.9%; lenalidomide use was 16.3%, 36.5%, and 39.8%; thalidomide use was 3.6%, 7.2%, and 7.9%; and hydroxyurea use was 3.6%, 2.3%, and 2.6%, respectively. Units transfused trended higher in the chelated group. Median (range) lifetime units transfused before the study were 20