Hematologic responses with deferasirox therapy in transfusion-dependent myelodysplastic syndromes patients

by Norbert Gattermann, Carlo Finelli, Matteo Della Porta, Pierre Fenaux, Michael Stadler, Agnes Guerci-Bresler, Matthias Schmid, Kerry Taylor, Dominique Vassilieff, Dany Habr, Andrea Marcellari, Bernard Roubert, and Christian Rose

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Hematologic responses with deferasirox therapy in transfusion-dependent myelodysplastic syndromes patients

Running title: Hematologic response in myelodysplastic syndromes

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Key words: myelodysplastic syndromes, deferasirox, iron overload, iron chelation therapy, hematologic response.
Abstract

Background: Reductions in transfusion requirements/improvements in hematologic parameters have been associated with iron chelation therapy in transfusion-dependent patients, including those with myelodysplastic syndromes; these data have been limited to case reports and small studies.

Design and methods: To explore this observation in a large patient population, we report a post-hoc analysis evaluating hematologic response to deferasirox in a cohort of iron-overloaded myelodysplastic syndromes patients enrolled in the Evaluation of Patients’ Iron Chelation with Exjade® (EPIC) study using International Working Group 2006 criteria.

Results: 247, 100 and 50 patients without concomitant myelodysplastic syndromes medication were eligible for erythroid, platelet and neutrophil response analyses. Erythroid, platelet and neutrophil responses were observed in 21.5% (53/247), 13.0% (13/100) and 22.0% (11/50) of patients after a median of 109, 169 and 226 days, respectively. Median serum ferritin reductions were greater in hematologic responders compared with non-responders at end of study, although these differences were not statistically significant. Reduction in labile plasma iron to <0.4 μmol/L was observed from week 12 onwards; this change did not differ between hematologic responders and non-responders.

Conclusions: This analysis suggests that deferasirox treatment for up to 1 year could lead to improvement in hematologic parameters in some patients with myelodysplastic syndromes.

Word count: 201
Introduction

Myelodysplastic syndromes (MDS) comprise a heterogeneous range of hematopoietic diseases in which bone marrow dysfunction frequently leads to anemia, neutropenia and/or thrombocytopenia with a propensity to evolve to acute myeloid leukemia.\(^1\) As a result, key goals for MDS therapy include the improvement of hematological parameters and transfusion independence.\(^2\)

Red blood cell transfusions remain an essential therapy to treat the anemia associated with MDS, but transfusion dependency has been identified as an independent factor associated with decreased survival.\(^1,3,4\) Furthermore, chronic transfusion therapy can lead to iron overload and subsequent toxicity, to which patients with MDS may be particularly vulnerable as a result of co-morbidities associated with their typically advanced age.\(^5\) Various clinical practice guidelines recommend the use of iron chelation therapy in lower-risk MDS patients.\(^6-15\)

In addition to reports of reduction in iron burden with deferasirox,\(^16,17\) a number of recently published case reports and small studies have reported improvements in hematologic parameters and transfusion requirements during iron chelation therapy with deferasirox.\(^17-26\) Limited evidence of hematologic improvement in patients with MDS also exists with deferoxamine (DFO) treatment,\(^27,28\) although the exact mechanism of hematological response with iron chelators is unknown.

The assessment of transfusion requirements and pre-transfusion blood counts throughout the EPIC (Evaluation of Patients’ Iron Chelation with Exjade\(^\text®\)) study,\(^29\) which included 341 patients with MDS,\(^16\) has enabled post-hoc analysis of hematologic parameters in a large cohort of patients with MDS. Here, we report the change in transfusion requirements, hemoglobin level and platelet and neutrophil counts in patients with MDS treated with deferasirox in the EPIC study, using the hematologic response criteria outlined by the International Working Group (IWG) 2006.\(^30\)
Design and Methods

Study design and patients
EPIC was a prospective, 1-year, multicenter, open-label Phase IIIb trial (clinicaltrials.gov identifier: NCT00171821). Hematologic parameters were assessed in all patients enrolled in the study. EPIC study design, including the inclusion and exclusion criteria have been described previously.16,29 In brief, male or female patients with MDS with transfusional iron overload (as shown by serum ferritin levels \( \geq 1000 \text{ ng/mL} \), or \(< 1000 \text{ ng/mL} \) but with a history of multiple transfusions [\( >20 \text{ transfusions} \) or \( >100 \text{ mL/kg of red blood cells} \)] and a liver iron concentration of \( >2 \text{ mg Fe/g dry weight} \) as confirmed by R2 magnetic resonance imaging) and a life expectancy \( \geq 1 \text{ year} \) were enrolled. For this post-hoc analysis, patients were assessed for a hematologic response if they received at least one deferasirox dose during the EPIC study, met the inclusion criteria described in Figure 1 and did not receive concomitant MDS medication.

The study was conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki and was approved by an Institutional Review Board/Independent Ethics Committee.

Deferasirox dosing
Deferasirox dosing for patients with MDS in the EPIC study has been described previously.16 In brief, an initial dose of 20 mg/kg/day was recommended for patients receiving 2–4 units/month (7–14 mL/kg/month) packed red blood cells. Initial doses of 10 or 30 mg/kg/day were considered for patients with lower or higher transfusion frequencies, respectively. Dose adjustments of 5 or 10 mg/kg/d (in the range 0–40 mg/kg/d) were permitted based on 3-monthly serum ferritin trends and safety markers.

Assessments and statistical methods
The IWG 2006 criteria30 (Figure 1) were used to assess erythroid, platelet and neutrophil responses during deferasirox treatment. Time to hematologic response was assessed as the number of days from the first dose of deferasirox to the onset of an erythroid, platelet or neutrophil response.
The definition for erythroid relapse was a reduction in hemoglobin by at least 1.5 g/dL sustained for at least 8 weeks or transfusion dependence after becoming transfusion independent. The IWG definitions for platelet and neutrophil relapse were a decrease of ≥50% from maximum levels in platelets or granulocytes, respectively, for at least 8 weeks. The survival time without relapse was defined as duration between response onset and first significant decrease corresponding to the onset of relapse (as assessed by Kaplan–Meier analysis).

Routine hematology assessments during the EPIC study were performed at a central laboratory at baseline, every 4 weeks and at end of study. Pre-transfusion blood counts were used in this analysis. Details of ongoing transfusions were recorded throughout the study. Serum ferritin levels were assessed every 4 weeks. Labile plasma iron (LPI) levels were evaluated using methods described previously and analyzed at a central laboratory using an assay that measures iron-specific redox cycling capacity in the presence of low ascorbate concentrations. LPI assessments were made pre- and 2 hours post-dose at weeks 12, 28 and 52. Safety and tolerability were evaluated by monitoring the incidence and type of adverse events (AEs). Statistical significance was calculated based on a Wilcoxon rank test.

Results

Patient characteristics
Of the 341 patients with MDS enrolled in the EPIC study, 247 met the erythroid inclusion criteria for response analysis, 100 met the platelet inclusion criterion and 50 met the neutrophil inclusion criterion. Patient demographics and characteristics at baseline are described in Table 1A.

Deferasirox dosing and exposure
The mean deferasirox dose and median deferasirox exposure are summarized for each hematologic response analysis group in Table 1B. The deferasirox dose was similar in each group and in hematologic responders and non-responders. The median deferasirox exposure was also similar across each group, with the exception of platelet non-responders, who had significantly shorter median exposure compared with platelet responders (191 vs 362 days; P=0.016).
Effect of deferasirox on hematologic parameters

Erythroid responses, comprising reductions in transfusion requirements or increases in hemoglobin levels were observed in 21.5% (53/247) of patients with a median time to response of 109 days (range 1–286 days [day on which response started and then lasted for at least 8 weeks]; Figure 2A and B). Twenty-eight patients (11.3%) had a transfusion-only erythroid response and 22 patients (8.9%) had a hemoglobin-only erythroid response. Three patients (1.2%) had both transfusion and hemoglobin erythroid responses (Figure 2A). The overall median time to transfusion response was 100 days (range 1–283). The overall median time to hemoglobin response was 113 days (range 29–286; Figure 2B).

Platelet responses were observed in 13.0% (13/100) of patients with a median time to response of 169 days (range 27–320; Figure 2A and B). Neutrophil responses were observed in 22.0% (11/50) of patients with a median time to response of 226 days (range 57–337; Figure 2A and B).

Time from response onset to hematologic relapse

Time from response onset to relapse in hematologic response is shown as a Kaplan–Meier curve in Figure 2C. Among transfusion responders, only three patients did not receive any transfusions during the study and were considered as transfusion independent. Therefore in accordance with the IWG criteria, relapse in erythroid response was restricted to patients with a hemoglobin response only. Despite this limitation, it is possible to assess transfusion requirements pre-treatment versus those post-response. Although some patients had an increase in transfusion requirement following their transfusion response, the overall mean number of transfusional units in the 8-weeks pre-treatment was 9.1 units, whereas post-transfusion response the overall mean number of transfusional units/8-week period was 4.2 units. Relapse rates were highest for hemoglobin responders (40.0%; n=10), followed by neutrophil responders (18.2%; n=2) and lowest among platelet responders (7.7%; n=1). The median time from response onset to relapse in hemoglobin responders was 83.5 days, ranging from 29 to 204 days. The time from response onset to relapse was 168 days in the one platelet responder who relapsed, and 56 and 252 days (median 154 days) in the two neutrophil responders who relapsed. For those patients with a neutrophil
relapse, it should be noted that from day 248, there was only one patient left at risk of relapse, leading to a drop on day 252 when this patient relapsed.

Changes in markers of iron overload in hematologic responders and non-responders

Serum ferritin

Median baseline serum ferritin levels were comparable in both hematologic responders and non-responders across all analysis groups (Table 1A). By end of study, decreases in median serum ferritin were greater in hematologic responders compared with non-responders (Figure 3A). In the erythroid response analysis group, responders experienced a reduction in serum ferritin of –560 ng/mL (range –5194 to 2064 ng/mL) compared with a reduction of –222 ng/mL (range –7125 to 6124 ng/mL) in erythroid non-responders (P=0.1231). In the platelet response analysis group, responders experienced a reduction in serum ferritin of –976 ng/mL (range –4488 to 6124 ng/mL) compared with a reduction of –115 ng/mL (range –3900 to 5357 ng/mL) in platelet non-responders (P=0.0560). In the neutrophil response analysis group, responders experienced the greatest reduction in serum ferritin overall, with a median decrease of –1316 ng/mL (range –3284 to 6124 ng/mL) compared with a reduction of –583 ng/mL (range –3900 to 1719 ng/mL) in neutrophil non-responders (P=0.3772).

The median absolute change in serum ferritin levels was also evaluated over time during the study. In the erythroid analysis group, the trend in absolute change in serum ferritin was similar for responders and non-responders, both before and after the median time to response (Figure 3B). In the platelet analysis group, absolute change in serum ferritin was greater in the responders than the non-responders from 24 weeks onwards (Figure 3C). In the neutrophil analysis group, the trends in serum ferritin decrease were similar for responders and non-responders before the median time to response, after which the serum ferritin decrease was generally greater in responders than non-responders (Figure 3D).

Labile plasma iron

At baseline, mean pre-dose LPI levels were above the normal threshold of 0.4 μmol/L in all responder and non-responder groups except platelet non-
responders (0.379 ± 0.54 μmol/L). Mean LPI was maintained at less than 0.4 μmol/L at all subsequent pre-dose assessments. During deferasirox treatment, there were no apparent differences in mean LPI levels between responders and non-responders in each analysis group.

**Safety and tolerability**

*Patient discontinuations*

Overall, 54.7, 38.0 and 54.0% of erythroid, platelet and neutrophil analysis groups, respectively, completed the study (Table 2). Across all groups, completion rates were higher in responders versus non-responders (77.4 vs 48.5% [erythroid response analysis]; 76.9 vs 32.2% [platelet response analysis]; 81.8 vs 46.2% [neutrophil response analysis]). Overall, the most common reasons for discontinuation included AEs, withdrawal of consent and death (Table 2). Adverse events leading to discontinuation were higher in the platelet analysis group (n=26, 26.0%), compared with either the erythroid (n=46, 18.6%), or neutrophil (n=8, 16.0%) analysis groups. In particular, gastrointestinal AEs leading to drug discontinuations were higher in the platelet analysis group (n=15, 15.0%) compared with either the erythroid (n=24, 9.7%) or neutrophil (n=6, 12.0%) analysis groups.

*Adverse events*

Adverse events in patients with MDS enrolled in the EPIC study have been described in detail previously. In patients who met the criterion for hematological response analyses, the frequency of drug-related AEs were similar across erythroid (n=160, 64.8%), platelet (n=63, 63.0%) and neutrophil (n=31, 62.0%) analysis groups; diarrhea was the most frequently reported drug-related AE in all analysis groups.

**Discussion**

This *post-hoc* analysis in a large group of patients with MDS adds to the existing literature from small studies and case reports showing an improvement in hematologic parameters with the iron chelator deferasirox. Here iron-overloaded patients with MDS treated with deferasirox for 1 year experienced improvement in hematologic parameters with an overall erythroid response of 21.5%, platelet response of 13.0% and neutrophil response of 22.0%. Patients with concomitant
MDS medication were removed from the analyses to eliminate any influence of such medication on hematologic responses. However, when previously assessed there was no apparent bias towards either responders or non-responders in the small number of patients who received concomitant medication (data not shown).

Deferasirox dosing and exposure was similar in both responders and non-responders across all analysis groups, with the exception of platelet non-responders, for whom median deferasirox exposure was significantly shorter. This corresponds with the higher rate of discontinuation for patients in the platelet analysis group.

The results are consistent with several case reports and small studies describing hematologic improvements, including transfusion independence, in patients with MDS receiving deferasirox treatment. Interestingly, in one case example, improvements in transfusional requirements and hemoglobin levels observed after 3 months of deferasirox treatment were reversed following deferasirox interruption, but regained when deferasirox was resumed. The IWG 2000 criteria, which classify hematologic responses as major or minor depending on the extent of the improvement, were used in a recent retrospective analysis in eight transfused patients (seven patients with MDS, one patient with myelofibrosis) treated with deferasirox (seven patients) and deferoxamine (one patient). Minor erythroid responses (1–2 g/dL increase in hemoglobin in patients with pretreatment hemoglobin concentrations <11 g/dL or 50% decrease in transfusion requirements in transfusion-dependent patients) were observed in five patients treated with deferasirox. A major platelet response was observed in one patient treated with deferasirox (major platelet response is defined as: an absolute increase in platelet count of ≥30,000/mm³ in patients with a pretreatment platelet count less than 100,000/mm³ or stabilization of platelet counts and platelet transfusion independence in platelet transfusion-dependent patients). The IWG 2000 criteria have also been used to analyze preliminary data from 83 patients with lower-risk MDS treated with deferasirox who entered the extension phase of the large US03 study; hematologic improvements were reported in six (7%) patients. There are limited reports of hematologic improvement in patients with MDS treated with deferoxamine. One study in 11 patients showed a reduction in hemoglobin requirement ≥50% in 7/11 (64%)
patients and five patients (46%) became transfusion independent. Platelet and neutrophil counts increased in 7/11 (64%) and 7/9 (78%) evaluable patients, respectively. There are even fewer published data on hematologic improvements with deferiprone; a case study in a single patient with myelofibrosis noted an increase in hemoglobin levels following deferiprone treatment. Hematologic improvement has also been demonstrated during iron chelation therapy in other diseases including myelofibrosis and aplastic anemia. The latter observation suggests that the effect of iron chelation therapy on hematopoiesis may not be a MDS-specific phenomenon and warrants further investigation in other anemias.

Given that hematologic response with deferasirox was not observed in all treated patients, it was of interest to determine factors that may be associated with this response. Of note, reductions in serum ferritin at end of study were generally greater in hematologic responders than non-responders. Although these differences were not statistically significant, the observation suggests that hematologic response might be at least partially dependent on serum ferritin reductions. On assessment of LPI levels, no differences were noted with respect to reduction in LPI between hematologic responders and non-responders. We therefore speculate that serum ferritin reduction may not be sensitive enough or perhaps too slow to be used as an early discriminator between responders and non-responders. LPI assessment on the other hand may be too sensitive as it is indeed suppressed in all chelated patients (both hematologic responders and non-responders). It may be that other parameters such as labile cellular iron could discriminate between responders and non-responders and warrant further investigation. Of course, a connection between responders and deferasirox exposure may also exist, in that responders may have better compliance to their medication than non-responders.

The mechanism behind improvements in hematologic response with deferasirox has yet to be elucidated. Reduction in oxidative stress, a state which has a variety of inhibitory effects on erythroid and hematopoietic function, has been proposed as a possible explanation for the observed hematologic improvement. This hypothesis is supported by the ability of deferasirox to provide 24-hour sustained suppression of LPI and to significantly reduce
reactive oxygen species.\textsuperscript{37} In vitro and in vivo data in leukemia cell lines and peripheral mononuclear cells collected from patients with MDS have demonstrated the inhibitory effects of deferasirox on nuclear factor-κB (NF-κB) activity.\textsuperscript{38} This protein has been shown to be constitutively activated in bone marrow samples from patients with MDS,\textsuperscript{39} and is involved in several cellular processes including cell proliferation and differentiation and suppression of apoptosis.\textsuperscript{40} This inhibition was not observed with either DFO or deferiprone, and analyses have suggested the observed inhibitory effects may be independent of the iron chelation effect.\textsuperscript{38} As hematological responses have been reported with DFO as well as with deferiprone, albeit in a small patient population,\textsuperscript{28,32} the importance of NF-κB in the hematologic response is uncertain. NF-κB levels were not assessed in this study, but the greater reduction in serum ferritin levels observed for hematologic responders in this study are more supportive of a role for iron reduction in the response mechanism. Alternative mechanisms may include other pharmacological effects of deferasirox on hematopoiesis, redistribution of iron from storage sites to hematopoietic tissue\textsuperscript{41} or an effect on the neoplastic clone or bone marrow microenvironment.\textsuperscript{18}

This study does have a number of limitations including the lack of a control arm comparing deferasirox to best supportive care. Other treatments including the hypomethylating drug azacitidine and lenalidomide have been shown to improve hematologic parameters in patients with MDS\textsuperscript{42-44} and are approved for that purpose; azacitidine for all five French-American-British (FAB) subtypes of MDS\textsuperscript{45} and lenalidomide in del 5q syndrome.\textsuperscript{46,47} Deferasirox, on the other hand, is approved for the treatment of iron overload in patients with MDS, hence the implications of the observed hematologic improvements with regard to MDS patient outcomes remain to be further elucidated in future trials. This is especially true given that transfusion dependency is associated with a negative effect on overall survival\textsuperscript{48} likely due to the fact that a transfusion-dependent state reflects severe bone marrow disease as well as causing iron overload. Hence, the ability of agents such as deferasirox to reduce transfusion requirements may have a potential impact on patient survival. However, this can only be confirmed in prospective randomized trials.

A number of issues arose concerning the analysis and interpretation of the findings of this study, regarding the IWG 2006 criteria.\textsuperscript{2} Within these criteria, the
hemoglobin response (defined as an increase in hemoglobin of at least 1.5g/dL) does not distinguish between patients that are not transfused or constantly transfused. In the present study, all patients underwent measurement of hemoglobin prior to each transfusion. Although no change in transfusion requirement was observed in these hemoglobin responders, the increase in hemoglobin reported is clinically important even in patients requiring regular transfusions, as this is associated with better outcomes such as improved quality of life and a reduction in complications. In addition, when considering transfusion relapse following initial response, adhering strictly to the IWG 2006 criteria\textsuperscript{2} (achievement of transfusion independence followed by a return to transfusion dependence) meant that those patients with an erythroid response based on their transfusion requirements could not be analyzed for subsequent relapse. Despite this, it is important to note that overall the mean number of transfusional units over an 8-week period following transfusion response was lower than in the pre-treatment 8-week period.

In conclusion, given the large number of patients included in this analysis, these results provide additional evidence supporting previous observations that deferasirox treatment over 1 year may improve hematologic parameters in patients with MDS. Further prospective, controlled studies are required to confirm the hematologic improvements observed in this study. Additional studies into the mechanisms involved in this response and whether any factors can predict response are also warranted to enhance understanding of this additional benefit of deferasirox.
Acknowledgments

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Author contributions and disclosure of conflicts of interest

Norbert Gattermann, Carlo Finelli, Matteo Della Porta, Pierre Fenaux, Michael Stadler, Agnes Guerci-Bresler, Mathias Schmid, Kerry Taylor, Dominique Vassilieff and Christian Rose served as investigators on this trial, enrolling patients and contributing to data interpretation. Dany Habr and Andrea Marcellari coordinated the execution of the trial and contributed to the analysis, interpretation and reporting of the trial data. Bernard Roubert served as the trial statistician. All authors reviewed and provided their comments on this manuscript and approved the final version.

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### Table 1A. Characteristics of patients eligible for hematologic analyses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Erythroid response analysis</th>
<th>Platelet response analysis</th>
<th>Neutrophil response analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Responders (n=53)</td>
<td>Responders (n=13)</td>
<td>Responders (n=11)</td>
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<tr>
<td></td>
<td>Non-responders (n=194)</td>
<td>Non-responders (n=87)</td>
<td>Non-responders (n=39)</td>
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<tr>
<td>Mean age, years (range)</td>
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<td>63.8 (38–82)</td>
<td>68.9 (38–85)</td>
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<td></td>
<td>68.9 (33–89)</td>
<td>67.3 (18–87)</td>
<td>65.9 (18–83)</td>
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<tr>
<td>Male:female, n</td>
<td>29:24</td>
<td>10:3</td>
<td>7:4</td>
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<tr>
<td></td>
<td>112:82</td>
<td>58:29</td>
<td>23:16</td>
</tr>
<tr>
<td>Race (Caucasian:Oriental:other), n</td>
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<td>11:2:0</td>
<td>8:3:0</td>
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<tr>
<td></td>
<td>179:14:1</td>
<td>75:11:1</td>
<td>32:7:0</td>
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<tr>
<td>History of hepatitis B and/or C, n (%)</td>
<td>2 (3.8)</td>
<td>1 (7.7)</td>
<td>1 (9.1)</td>
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<tr>
<td></td>
<td>6 (3.1)</td>
<td>4 (4.6)</td>
<td>2 (5.1)</td>
</tr>
<tr>
<td>History of splenectomy, n (%)</td>
<td>2 (3.8)</td>
<td>0 (0)</td>
<td>3 (3.5)</td>
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<tr>
<td></td>
<td>4 (2.1)</td>
<td>3 (3.5)</td>
<td>1 (2.6)</td>
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<td>Prior chelation therapy, n (%)</td>
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<tr>
<td>None</td>
<td>27 (50.9)</td>
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<td></td>
<td>87 (44.8)</td>
<td>44 (50.6)</td>
<td>22 (56.4)</td>
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<td>DFO</td>
<td>19 (35.8)</td>
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<td></td>
<td>85 (43.8)</td>
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<td>Deferiprone</td>
<td>3 (5.7)</td>
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<td>5 (2.6)</td>
<td>5 (5.7)</td>
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<td>DFO and deferiprone*</td>
<td>4 (7.5)</td>
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<td>1 (9.1)</td>
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<tr>
<td></td>
<td>16 (8.2)</td>
<td>3 (3.4)</td>
<td>0 (0)</td>
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<tr>
<td>Other</td>
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<tr>
<td>Mean duration of previous iron chelation</td>
<td>2.4</td>
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<td>1.7</td>
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<td>therapy, years (range) [n=26]</td>
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<td>(0.1–1.6)</td>
<td>(1.6–8.8)</td>
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<tr>
<td></td>
<td>(n=105)</td>
<td>(n=42)</td>
<td>(n=17)</td>
</tr>
<tr>
<td>Mean number of transfusion sessions in the</td>
<td>24.4±14.4</td>
<td>24.2±20.7</td>
<td>17.6±14.5</td>
</tr>
<tr>
<td>year prior to study entry ± SD, n</td>
<td>25.4±18.5</td>
<td>28.3±23.7</td>
<td>22.6±13.3</td>
</tr>
<tr>
<td>Mean transfusion history duration ± SD, years</td>
<td>3.7±3.1</td>
<td>1.9±1.1</td>
<td>3.8±6.3</td>
</tr>
<tr>
<td></td>
<td>3.6±4.8</td>
<td>3.2±2.6</td>
<td>3.2±2.4</td>
</tr>
</tbody>
</table>
### Table 1B. Deferasirox dosing and exposure

<table>
<thead>
<tr>
<th></th>
<th>Erythroid response analysis</th>
<th>Platelet response analysis</th>
<th>Neutrophil response analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders (n=53)</td>
<td>Non-responders (n=194)</td>
<td>Responders (n=13)</td>
</tr>
<tr>
<td>Mean actual deferasirox dose ± SD, mg/kg/d</td>
<td>19.2±4.4</td>
<td>19.3±5.8</td>
<td>18.3±4.6</td>
</tr>
</tbody>
</table>

SD, standard deviation; DFO, deferoxamine; SD, standard deviation; MDS, myelodysplastic syndromes; *Both DFO and deferiprone received either as monotherapy or in combination.
Table 2. Patient discontinuations

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Erythroid response analysis</th>
<th>Platelet response analysis</th>
<th>Neutrophil response analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders (n=53)</td>
<td>Non-responders (n=194)</td>
<td>Responders (n=13)</td>
</tr>
<tr>
<td>Total discontinuations, n (%)</td>
<td>12 (22.6)</td>
<td>100 (51.5)</td>
<td>3 (23.1)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 (3.8)</td>
<td>44 (22.7)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Subject withdrew consent</td>
<td>5 (9.4)</td>
<td>22 (11.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (3.8)</td>
<td>14 (7.2)</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Subject no longer requires treatment</td>
<td>2 (3.8)</td>
<td>4 (2.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unsatisfactory therapeutic effect</td>
<td>0 (0)</td>
<td>6 (3.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Administrative problems</td>
<td>1 (1.9)</td>
<td>4 (2.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>0 (0)</td>
<td>3 (1.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abnormal laboratory value(s)</td>
<td>0 (0)</td>
<td>2 (1.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
Figure legends

Figure 1. Analyses inclusion criteria and definitions of hematologic responses\textsuperscript{30}
Hb, hemoglobin; RBC, red blood cell

Figure 2. (A) Percentage of patients experiencing hematologic responses, (B) median time to hematologic responses during deferasirox treatment and (C) time from response onset to relapse in patients with hemoglobin, platelet and neutrophil hematologic responses

Trans, transfusion reduction-only response; Hb, hemoglobin improvement-only response; Hb+Trans, both transfusion reduction and hemoglobin response
On the neutrophil curve, from day 248, there is only one patient left a risk, leading to a drop on day 252 when he relapsed

Figure 3. Median decrease in serum ferritin from (A) baseline to end of study and over the course of the study in (B) erythroid, (C) platelet and (D) neutrophil analysis groups
FIGURES

Figure 1. Patients not receiving concomitant MDS medication

Inclusion criteria for erythroid response analysis
- Pretreatment Hb levels <11 g/dL
- OR RBC transfusion requirements >4 units/8 weeks

Inclusion criterion for platelet response analysis
- Pretreatment platelet counts <100 x 10^9/L

Inclusion criterion for neutrophil response analysis
- Pretreatment absolute neutrophil counts <1.0 x 10^9/L

Erythroid response definition
Hb response
- Hb increase ≥1.5 g/dL OR
Transfusion response
- Reduction of ≤4 RBC transfusions/8 weeks compared with pretreatment transfusion number on the previous 8 weeks. Only RBC transfusions given for a Hb of ≤9.0 g/dL

Platelet response definition
- Increase ≥30 x 10^9/L for patients with >20 x 10^9/L platelets OR
- Increase from <20 x 10^9/L to >20 x 10^9/L and by ≥100%

Neutrophil response definition
- ≥100% increase
- AND an absolute increase >0.5 x 10^9/L

All responses to last ≥0 weeks

Figure 2.

A

<table>
<thead>
<tr>
<th>Hematologic response</th>
<th>Patients with response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid</td>
<td>5</td>
</tr>
<tr>
<td>Platelet</td>
<td>20</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>25</td>
</tr>
</tbody>
</table>

Trans

Hb

Trans+Hb
B

Erythroid response (n=53)
Hemoglobin only response (n=22)
Transfusion only response (n=28)
Platelet response (n=13)
Neutrophil response (n=11)

Days (median)

C

Survival without relapse

Time from response onset to relapse (days)

Patients at risk of relapse

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin responders</th>
<th>Platelet responders</th>
<th>Neutrophil responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin responders</td>
<td>25 24 22 21 20 19 18 16</td>
<td>15 14 13 12 10 9 8 7</td>
<td>6 5 4 3</td>
</tr>
<tr>
<td>Platelet responders</td>
<td>13 13 12 11 10 9 8 7 6 5 4 3</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>Neutrophil responders</td>
<td>11 11 10 9 8 7 6 5 4</td>
<td>3 2 1</td>
<td></td>
</tr>
</tbody>
</table>
Figure 3.

A

Absolute change in median serum ferritin from baseline (ng/mL)

Responders (N=53)
Non-responders (N=194)

B

Median time to erythroid response
109 days (15.6 weeks)

Responders, n 50 51 50 48 46 44 47 40 42 39 40 40 40
Non-responders, n 173 160 138 135 130 126 111 106 103 101 97 92 92
**C**

![Graph showing absolute change in median serum ferritin from baseline (ng/mL) over time (weeks) for responders and non-responders.]

**Time (weeks)**

- Median time to platelet response: 169 days (24.1 weeks)
- Responders: N=13
- Non-responders: N=87

**D**

![Graph showing absolute change in median serum ferritin from baseline (ng/mL) over time (weeks) for responders and non-responders.]

**Time (weeks)**

- Median time to neutrophil response: 226 days (32.3 weeks)
- Responders: N=11
- Non-responders: N=39

Table:

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Responders, n</th>
<th>Non-responders, n</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>11</td>
<td>36</td>
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<tr>
<td>4</td>
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