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Research paper

Deferasirox in the treatment of iron overload during myeloproliferative neoplasms in fibrotic phase: does ferritin decrement matter?

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ABSTRACT

Few data are available on the treatment with DFX in patients with transfusion dependent Ph- Myeloproliferative Neoplasms in fibrotic phase. Here we report 48MPNpatients and iron overload treated with DFX. Starting DFX dose was 20 mg/Kg in 23 patients, 15 mg/Kg in 20 patientsand 10 mg/Kg in 5 patients. After a median treatment of 27.6 months, 5 patients achieved ferritin < 500 ng/ml, 11 < 1000 ng/ml and 3 a reduction > 50% of basal ferritin with a global response rate of 41%. As to hematological improvement, 9/47 patients (19.1%) showed a persistent rise of Hb > 1.5 g/dl, with disappearance of transfusion requirement in 6 cases. The median OS from DFX initiation in patients with chelation response was 61.0 months compared to 15.8 months in patients without chelation efficacy. Treatment with DFX is feasible and effective in MPN with iron overload and a hematological improvement can occur in a sizeable rate of patients.

1. Introduction

Iron overload is a well-known critical issue in transfusion dependent patients affected by chronic hematological diseases, as thalassemic syndromes (TS) [1] ormyelodisplastic syndromes (MDS) [2]. Excess iron can be extremely toxic may cause organ damage in the absence of iron chelation therapy. Preclinical studies on the role of free iron toxicity on bone marrow function have shown that this condition leads to an accumulation of reactive oxygen species, interfers with the expression of genes encoding for hematopoiesis regulating proteins, and inhibits hematopoiesis. These effects could be partially attenuated by iron-chelation with deferasirox (DFX), suggesting iron toxicity may have a negative impact on the hematopoietic microenvironment.Although the mechanisms through which deferasirox exerts this action are currently unknown, several controlled clinical trials showed the efficacy and safety of deferasirox in these conditions and DFX at present is widely used in current clinical practice in both TS and MDS [3–7].

However, anemia requiring chronic transfusion support and consequent iron overload is one of the major concern also in Ph-negative myeloproliferative neoplasms in fibrotic phase (FP-MPN), as primary myelofibrosis (PMF) or myelofibrosis secondary to polycythemia vera (PPV-MF) and essential thrombocythemia (PET-MF).

At present, very few data are available on the role of iron chelation therapy with DFX in the treatment of patients with FP-MPN and transfusion dependence [8–13]. Our regional cooperative group

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previously reported preliminary results from the largest retrospective real-life analysis currently available in the literature of FP-MPN patients and iron overload secondary to transfusion dependence treated with DFX. We demonstrated that treatment with DFX was effective in reducing iron overload in a substantial rate of patients without severe toxicities; moreover, an erythroid response was reported in more than 20% of patients [14].

In the setting of FP-MPN treated with DFX, the identification of clinical and biological parameters able to predict response to iron chelation therapy at baseline or during treatment is still lacking. In addition, a possible prognostic role of a good response to iron chelation treatment in term of ferritin reduction remains an open issue to debate.

To address these questions, a larger cohort of FP-MPN patients with iron overload treated with DFX and collected in the database of our regional MPN cooperative group with a longer follow-up was analyzed.

2. Materials and methods

Forty-eight patients (M/F 35/13) with FP-MPN and iron overload enrolled in the database of our regional cooperative group, received a treatment with DFX and were considered in the present analysis.All patients had a confirmed diagnosis of PMF, PPV-MF or PET-MF according to the current WHO criterion available at the time of diagnosis.

The main features of the patients at diagnosis are reported in the Table 1.International Prognostic Score System (IPSS) [15] was applied at diagnosis for all patients.

2.1. Response evaluation

The following criteria, based on ferritin reduction, were used in the evaluation of response to iron chelation:

- Complete response: ferritin levels < 500 ng/ml
- Partial response: ferritin levels < 1000 ng/ml
- Ferritin improvement: in patients with basal ferritin levels > 2000 ng/ml, ferritin reduction ≥50% of initial value;
- No response: any other ferritin modification.

Table 1
Main patient features at diagnosis.

M/F, n° (%)	35/13 (72.9/27.1)
Median age, years	70.0
[interquartile range (IQR)]	(64.0–74.7)
Median Hb, g/dl	8.5
(IQR)	(7.2–9.7)
Median WBC, x 10^9/l	6.1
(IQR)	(4.3–11.1)
Median PLTS, x 10^9/l	234
(IQR)	(134 – 453)
IPSS score, n° (%):	1 (2.1)
Low	8 (17.0)
Int-1	18 (38.3)
Int-2	20 (42.6)
High	
DIPSS score, n° (%):	4 (8.3)
Low	12 (25.0)
Int-1	30 (62.5)
Int-2	2 (4.2)
High	
Spleen enlargement, n° (%):	6 (12.5)
No	14 (29.2)
< 5 cm below costal margin	28 (58.3)
> 5 cm below costal margin	
Median ferritin, ng/ml	452
(IQR)	(138–1037)

M = male, F = female, IQR = interquartile range, Hb = hemoglobin, WBC = white blood cells, PLTS = platelets, IPSS = International Prognostic Scoring System.

Hematological improvement was defined in a manner consistent with IWG response criteria used in MDS [16]: a rise in Hb values ≥ 1.5 g/dl and/or a reduction in the transfusion requirement ≥50%, lasting at least 3 months.·

WHO classification was applied to evaluate hematologic and extra-haematological toxicities.

2.2. Statistical analysis

Values reported were expressed as mean ± SD for normally distributed data, as median and interquartile range (IR) for not-normally distributed data, or as percentage frequencies; comparisons between groups of patients were made by paired t test, χ^2 test and Fisher exact test, as appropriate, at significance levels of $p < 0.05$.

The Kaplan-Meier product-limit method was used to estimate univariate survival curves, and the log-rank test was adopted to compare the survival curves. Event-free Survival (EFS) was calculated from the date of DFX therapy start to any of the following events: permanent DFX discontinuation due to toxicity or any other unrelated cause, death due to any cause. Overall Survival (OS) was calculated from the date of DFX start to death due to any cause.

All calculations were made using a standard statistical package (SPSS for Windows Version 15.0; Chicago, IL).

3. Results

Treatment with DFX was started after a median interval from diagnosis of 13.3 months [interquartile range (IQR) 7.2 – 37.6.1] and from start of transfusion dependence of 12.5 months (IQR 5.8–17.5), with a median of 27 packed red cells units received (IQR 20–40).

The main features of patients at DFX treatment baseline are reported in the Table 2. At baseline, 18 patients (37.5%) did not receive any cytotoxic treatment, 24 (50.0%) were receiving cytotoxic treatment with hydroxyurea (21 patients) or other cytotoxic agents (3 patient) and 6 (12.5%) were receiving ruxolitinib since at least 3 months. The starting DFX dose was 20 mg/Kg in 23 patients (47.1%), 15 mg/Kg in 20 patients (41.6%) and 10 mg/Kg in 5 patients (11.3%), according to physician choice based on transfusional requirement, clinical conditions and renal function of each patient.

Extra-hematological toxicity of all WHO grades was reported in 24 patients (50.0%) after a median interval from DFX start of 3.3 months (IQR 1.0–7.1) and consisted of gastrointestinal symptoms in 8 patients, renal toxicity (increase of creatinine serum levels) in 10 patients and skin reactions in 4 patients; in addition, 2 patients had a combined gastrointestinal and renal toxicity. On the whole, 8 patients needed a drug reduction due to toxicity (16.6%). A temporary drug discontinuation due to toxicity was needed in 10 patients (20.8%) while 5 patients (10.4%) needed a permanent discontinuation (gastrointestinal toxicity in 3 patients, renal insufficiency and skin toxicity in 1 patient,

Table 2
Main patient features at baseline of DFX treatment.

Median age, years	71.4
[interquartile range (IQR)]	(66.6–76.2)
Median Hb, g/dl	7.7
(IQR)	(7.1–8.1)
Median Ht, %	24.0
(IQR)	(22.1–26.3
Median ferritin, ng/ml	1544
(IQR)	(1226–2092)
Median creatinine level, mg/ml	1.0
(IQR)	(0.78–1.1)
DIPSS score, n° (%):	6 (12.5)
Int-1	40 (83.3)
Int-2	2 (4.2)
High	

IQR = interquartile range, Hb = hemoglobin, Ht = hematocrit.

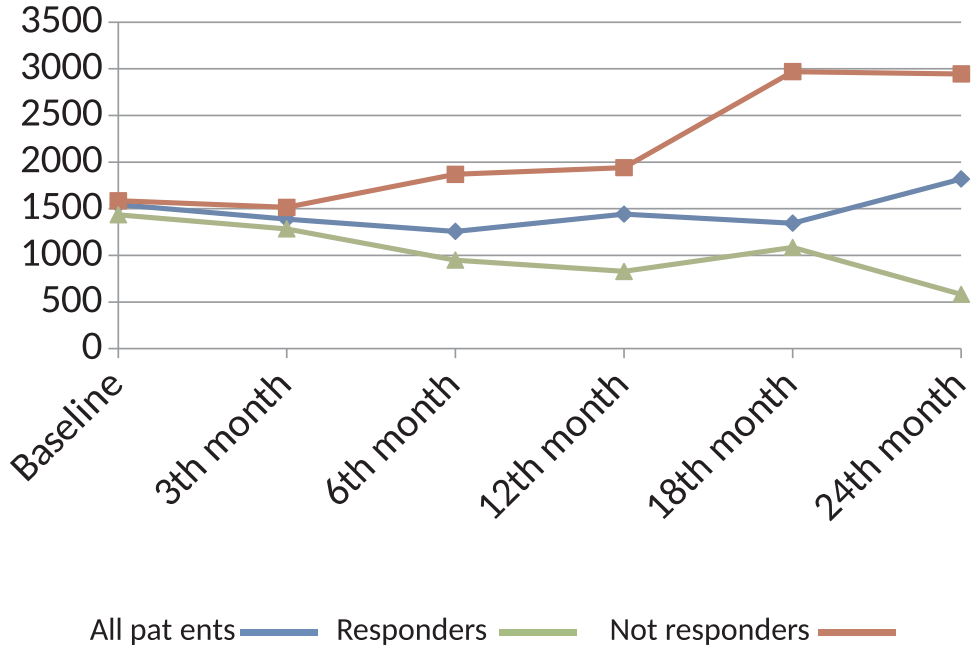

Fig. 1. Median ferritin values at different time-points.

respectively).

All but one patient were evaluable for response (> 6 months of treatment). As to chelation efficacy, after a median treatment period of 27.6 months (IQR 20.1–34.3), 5 patients achieved ferritin levels < 500 ng/ml, 11 patients ferritin levels < 1.000 ng/ml and 3 patients presented a reduction > 50% of basal ferritin but with levels > 1.000 ng/ml, with a global response rate of 41.0%: among the remaining 28 patients, 3 discontinued for early toxicity, 24 did not have any significant ferritin reduction and1 had an early unrelated death (< 6 months of treatment). The median ferritin values at different time-points for the entire cohort of patients and for patients according to chelation response are shown in the Fig. 1.

Baseline characteristics (age, sex, Hb and ferritin levels, WBC and PLTS counts, interval from diagnosis to DFX treatment, DFX starting dosage) were comparedbetween patients who achieved a chelation response and those who did not, to identify factors predicting its achievement. However, none of these factors differed significantly between responders and non-responders (Table 3).

As to hematological improvement, 9/47 patients (19.1%) showed an unexpected and persistent (> 3 months) rise of Hb levels > 1.5 g/dl, with disappearance of transfusion requirement in 6 cases, after a median time from DFX start of 6.3 months (IQR 4.3–12.1). Haematological improvement was achieved together with a reduction of ferritin levels in 6 patients, while a ferritin-independent haematological response was seen in the remaining 3 patients. As to concomitant treatment of these responding patients, 3 received DFX only, while 6 received concomitant active treatment (4 HU, 1 thalidomide, 1 ruxolitinib) since more than 10 months. The median duration of hematological improvement was 11 months (IQR 5–16). None of the baseline characteristics differed significantly between responders and non-responders(Table 4).

In addition, one other patient with severe thrombocytopenia at baseline (PLTS 11 × 10^9/l), receiving DFX treatment only, showed an increase of PLTS > 30 × 10^9/l, lasted 10 months and uncoupled with improvement in Hb levels or transfusion need.

After a median follow-up of 21.9 months (IQR 12.2–27.7), 26

Table 3
Clinical features at baseline according to chelation response.

	RESPONDERS	NON-RESPONDERS	p
Median age, years (IQR)	68.7 (67.0–76.0)	72.2 (66.1–76.4)	0.635
Gender (M/F)	14/5	21/8	0.865
Baseline median Hb, g/dl (IQR)	7.9 (6.9–8.2)	7.6 (7.4–8.2)	0.475
Baseline median WBC, x 10^9/l (IQR)	6.3 (3.6–10.1)	5.9 (5.0–15.9)	0.904
Baseline median PLT, x 10^9/l (IQR)	247 (155–695)	210 (126–451)	0.879
Baseline median ferritin, ng/ml (IQR)	1435 (1180–2046)	1585 (1214–2280)	0.976
Median time from diagnosis, months (IQR)	30.2 (6.9–49.2)	12.8 (8.0–32.2)	0.401

IQR = interquartile range; M = male, F = female, Hb = hemoglobin, WBC = white blood cells, PLTS = platelets.

Table 4
Clinical features at baseline according to hematological improvement.

	RESPONDERS	NON-RESPONDERS	p
Median age, years (IR)	70.2 (67.3–76.8)	71.5 (66.8–76.4)	0.921
Gender (M/F)	6/3	28/10	0.672
Baseline median Hb, g/dl (IR)	8.0 (7.3–8.4)	7.6 (7.2–8.1)	0.120
Baseline median WBC, x 10^9/l (IR)	5.7 (4.9–8.3)	6.4 (4.1–14.3)	0.502
Baseline median PLT, x 10^9/l (IR)	290 (188–579)	210 (113 – 453)	0.943
Baseline median ferritin, ng/ml (IR)	1504 (1261–1883)	1544 (1177–2291)	0.980
Median time from diagnosis, months (IR)	21.7 (10.4–90.4)	13.2 (6.9–35.8)	0.672
Concomitant MPN treatment, n° (%):	3 (16.6) 4 (19.0)	15 (83.4) 17 (81.0)	0.723
None	1 (16.6)	5 (83.4)	
Hydroxyurea	1 (50.0)	1 (50.0)	
Ruxolitinib			
Other			

IQR = interquartile range; M = male, F = female, Hb = hemoglobin, WBC = white blood cells, PLTS = platelets, MPN = myeloproliferative neoplasm.

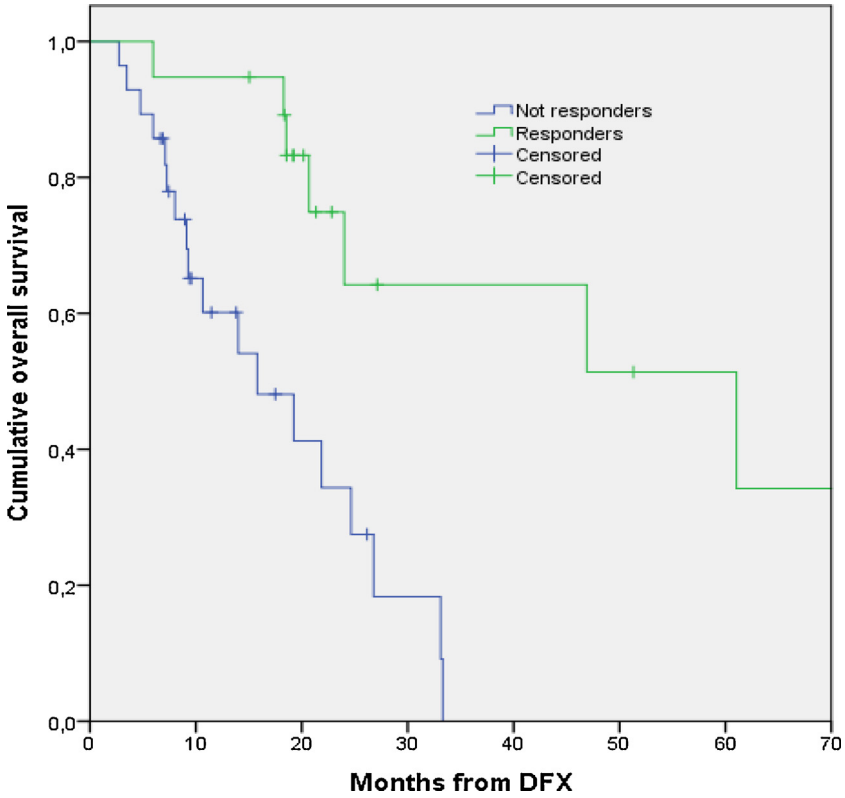

Fig. 2. Cumulative overall survival from DFX start according to chelation response.

patients died (23 from disease progression and 3 from unrelated causes) and 3 were lost to follow-up, while the remaining 19 patients were alive. Of the surviving patients, 5 discontinued DFX therapy due to toxicity and 12 were still receiving DFX therapy.

The median OS of the whole cohort from DFX initiation was 24.0 months (95%CI 18.5–29.4): the median OS from DFX initiation in patients with chelation response was 61.0 months (95%CI 18.4–103.6) compared to 15.8 months (95%CI 5.9–25.6) in patients without chelation response ($p = 0.001$) (Fig. 2).Together with chelation response, only IPSS intermediate-1 score had a favourable predictive role for OS since DFX treatment at univariate analysis. In a Cox multivariate model, both these variables retained their independent protective role (HR 0.224, 95%CI 0.079–0.623; $p = 0.005$ for chelation response and HR 0.183, 95%CI 0.040–0.848; $p = 0.030$ for IPSS intermediate-1, respectively).

4. Discussion

Transfusion dependence and iron overload are still unresolved issues in MPN patients evolving to fibrotic phase. Tissue damages from iron overload are consequences not only of iron burden, but depend also from the rate of iron accumulation and the duration of exposure of parenchymal cells to iron overload [17]: thus, iron chelation therapy should be always considered in transfusion-dependent FP-MPN patients to prevent heart failure and other organ damages.

Serum ferritin, despite the well-known limitations of its measurement, is commonly used as the reference parameter of iron overload in transfusion dependent patients and is worldwide used to evaluate response to chelation therapy, as surrogate of more sensitive parameters, which use is not easily feasible in a real-life setting. Although the safety threshold for serum ferritin has yet to be established, it has been shown that values steadily < 1000 mg/l are associated with a very low rate of complications [18].

The clinical use of DFX and its benefit are consolidated in hematological diseases as MDS or genetic disorders in the hemoglobin synthesis, but not in FP-MPN. Recently, two different Italian retrospective studies reported preliminary data on the safety and efficacy of DFX in terms of ferritin reduction, coupled with a possible hematological improvement related to DFX treatment in Ph-negative MPN patient [13,14].

However, due to the relatively small number of MPN patients and the short follow-up of those studies, there are still 2 major open questions to address: which clinical features are predictive of better response to DFX therapy? Is ferritin reduction a good indicator of response, with a correlation to improved survival in patients responding to chelation therapy?

In the present report, we have expanded and updated our cohort of patients, to give an answer to both these open questions. To date, our cohort of 48 patients is the largest reported in literature at our knowledge. A rate of about 40% of global responses in terms of ferritin reduction was observed, comparable to that reported in the previous studies.

It is questionable whether patients with stable ferritin levels in presence of persistent transfusion need, who were considered with our current criteria among not responders, should more correctly evaluated as “minor responders”: the observation of a shorter OS in this latter group compared to patients achieving ferritin reduction allows us to leave them among not responders.

As to the identification of factors predictive for better response to DFX, none of the clinical characteristics evaluated in the present report showed a statistical significance: thus, the first open question still remains unresolved and further studies with different (biological?) features and/or larger cohorts are warranted.

On the contrary, the prognostic role of ferritin reduction was clearly appreciable: FP-MPN patients reaching a reduction of ferritin levels had a significant longer OS compared to patients who failed to achieve ferritin reduction. The favorable prognostic role for OS of ferritin reduction during chelation treatment in MPN patients is consistent with data already reported in other subsets, like MDS and aplastic anemias [19]: it is worth of note, however, that at present all these data are from

retrospective studies and they need to be confirmed in prospective randomized trials.

Moreover, we have observed an erythroid improvement in about 20% of patients,in many cases (but not always) coupled with reduction of ferritin levels. As suggested in MDS, reduction in non-transferrin bound iron (NTBI) and reactive oxygen species (ROS) induced by DFX could improve bone marrow function [20,21] also in FP-MPN patients independently by ferritin reduction, leading to a recovery of peripheral values. It is worth of note that in our experience an improvement of platelets value can occur, even if very rarely. However, the small number of patients does not allow us to draw any firm conclusion on this issue.

Based on our present data, DFX should be considered not only as a supportive therapy, but could acquire the role of "active" treatment for chronic anemia in FP-MPN patients. In this sense, it will be of increasing interest to explore interactions between DFX and current targeted therapies of FP-MPN and their impact on clinical response.

In conclusion, treatment with DFX is feasible and relatively effective in FP-MPN with iron overload, as patients achieving any chelation response had a longer OS. Clinical prospective trials are warranted to address open issues, in particular the identification of factors predictive for response to DFX and the role of a combined treatment with DFX and JAK-2 inhibitors.

Disclosure of interest

The authors report no conflict of interest.

References

[1] A.T. Taher, A.N. Saliba, Ironoverload in thalassemia: different organs at different rates, Hematology 8 (2017) 265–271.

[2] N. Gattermann, Iron overload in myelodysplastic syndromes, Int. J. Hematol. 107 (2018) 55–63.

[3] G.M. Brittenham, Iron-chelating therapy for transfusion iron overload, N. Engl. J. Med. 364 (2011) 146–156.

[4] N. Gattermann, C. Finelli, M. Della Porta, et al., Deferasirox in iron-overloaded patients with transfusion-dependent myelodysplastic syndromes: results from the large 1-year EPIC study, Leuk. Res. 34 (2010) 1143–1150.

[5] E. Angelucci, V. Santini, A.A. Di Tucci, et al., Deferasirox for transfusion-dependentpatients with myelodysplasticsyndromes: safety, efficacy, and beyond (GIMEMA MDS0306 Trial), Eur. J. Hematol. 92 (2014) 527–536.

[6] F. Nolte, B. Höchsmann, A. Giagounidis, et al., Results from a 1-year, open-label, single arm, multi-center trial evaluating the efficacy and safety of oral deferasirox in patients diagnosed with low and int-1 risk myelodysplastic syndrome (MDS) and transfusion-dependent iron overload, Ann. Hematol. 92 (2013) 191–198.

[7] J.J. Meerpohl, G. Antes, G. Rucker, et al., Deferasirox for managing iron overload in people with thalassaemia, Cochrane Database Syst. Rev. (2012) CD007476, , https://doi.org/10.1002/14651858.CD007476.pub2.

[8] E. Messa, D. Cilloni, F. Messa, et al., Deferasirox treatment improved the hemoglobin level and decreased transfusion requirements in four patients with the myelodysplastic syndrome and primary myelofibrosis, Acta Hematol. 120 (2008) 70–74.

[9] L. Del Corso, E. Balleari, E. Arboscello, et al., Mayor erythropoietic response after deferasirox treatment in a transfusion-dependent anemic patient with primary myelofibrosis, Case Rep. Hematol. 2013 (2013), https://doi.org/10.1155/2013/520712 Article ID 520712.

[10] H. Tesch, C. Ihling, Loss of transfusion dependency following deferasirox treatment of iron overload in a woman with myelofibrosis and spherocytosis-a case report, Onkologie 36 (2013) 205–208.

[11] E. Matsuki, K. Matsumoto, A. Nakaya, et al., Marked improvement of anemia during treatment with deferasirox in patients with primary myelofibrosis and acute myeloid leukemia with myelodysplastic-related changes, Rinsho Ketsueki 53 (2012) 78–82.

[12] A.A. Di Tucci, R. Murru, D. Alberti, et al., Correction of anemia in a transfusion-dependent patient with primary myelofibrosis receiving iron chelation therapy with deferasirox (Exjade, ICL670), Eur. J. Hematol. 78 (2007) 540–542.

[13] E.M. Elli, A. Belotti, A. Aroldi, et al., Iron chelation therapy with deferasirox in the management of iron overload in primary myelofibrosis, Mediterr. J. Hematol. Infect. Dis. 6 (2014) e2014042.

[14] R. Latagliata, C. Montagna, R. Porrini, et al., Chelation efficacy and erythroid response during deferasirox treatment in patients with myeloproliferative neoplasms in fibrotic phase, Eur. J. Haematol. 96 (2016) 643–649.

[15] F. Cervantes, B. Dupriez, A. Pereira, et al., New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment, Blood 113 (2009) 2895–2901.

[16] B.D. Cheson, P.L. Greenberg, J.M. Bennett, et al., Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia, Blood 108 (2006) 419–425.

[17] A.T. Taher, K.M. Musallam, A. Inati, Iron overload: consequences, assessment, and monitoring, Hemoglobin 33 (Suppl. 1) (2009) S46–57.

[18] H.R. Bruch, Y. Dencausse, J. Heßling, et al., CONIFER - non-interventional study to evaluate therapy monitoring during deferasirox treatment of iron toxicity in myelodysplastic syndrome patients with transfusion Iron overload, Oncol. Res. Treat. 39 (2016) 424–431.

[19] I.H. Kim, J.H. Moon, S.N. Lim, et al., Efficacy and safety of deferasiroxestimated by serumferritin and labile plasma ironlevels in patients with aplastic anemia, myelodysplasticsyndrome, or acute myeloidleukemia with transfusionalironoverload, Transfusion 55 (2015) 1613–1620.

[20] M. Meunier, S. Ancelet, C. Lefebvre, et al., Reactive oxygen species levels control NF-kBactivation by low dose deferasirox in erythroid progenitors of low risk myelodysplastic syndromes, Oncotarget 8 (2017) 105510–105524.

[21] R. Guariglia, M.C. Martorelli, O. Villani, et al., Positive effects on hematopoiesis in patients with myelodysplastic syndrome receivingdeferasirox as oral iron chelation therapy: a brief review, Leuk. Res. 35 (2011) 566–570.