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RESEARCH PAPER

Deferasirox in the management of iron overload in patients with myelofibrosis treated with ruxolitinib: The multicentre retrospective RUX-IOL study

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Abbreviations: AEs, adverse events; DFX, deferasirox; ER, erythroid response; ICR, iron chelation response; ICT, iron chelation therapy; IOL, iron overload; IR, interquartile range; LT, leukaemic transformation; MF, myelofibrosis; MMB, Momelotinib; RBC, red blood cell; RUX, ruxolitinib.

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Summary

Deferasirox (DFX) is used for the management of iron overload (IOL) in many haematological malignancies including myelofibrosis (MF). The 'RUX-IOL' study retrospectively collected 69 MF patients treated with ruxolitinib (RUX) and DFX for IOL to assess: safety, efficacy in term of iron chelation response (ICR) and erythroid response (ER), and impact on overall survival of the combination therapy. The RUX–DFX therapy was administered for a median time of 12.4 months (interquartile range 3.1–71.2). During treatment, 36 (52.2%) and 34 (49.3%) patients required RUX and DFX dose reductions, while eight (11.6%) and nine (13.1%) patients discontinued due to RUX- or DFX-related adverse events; no unexpected toxicity was reported. ICR and ER were achieved by 33 (47.8%) and 32 patients (46.4%) respectively. Thirteen (18.9%) patients became transfusion-independent. Median time to ICR and ER was 6.2 and 2 months respectively. Patients achieving an ER were more likely to obtain an ICR also ($p = 0.04$). In multivariable analysis, the absence of leukocytosis at baseline ($p = 0.02$) and achievement of an ICR at any time ($p = 0.02$) predicted improved survival. In many MF patients, the RUX–DFX combination provided ICR and ER responses that correlated with improved outcome in the absence of unexpected toxicities. This strategy deserves further clinical investigation.

KEYWORDS
cancer, deferasirox, iron overload, myelofibrosis, ruxolitinib

INTRODUCTION

Myelofibrosis is a clonal haematopoietic stem-cell disorder characterized by pathological myeloproliferation and aberrant cytokine production resulting in progressive fibrosis, inflammation and functional disruption of the marrow erythropoietic niche causing marrow failure.[1]

Anaemia is a hallmark of MF, at diagnosis as well as during the course of disease, and is associated with inferior quality-of-life and worse prognosis in all MF prognostic models, such as the International Prognostic Score System (IPSS), the Dynamic-IPSS (DIPSS), the Mutation-enhanced IPSS (MIPSS70) and the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM).[2–7] A red blood cell (RBC) transfusion dependency at or within 1 year of diagnosis may predict shortened survival independently from IPSS and DIPSS category.[8,9]

Anaemia in MF is mostly secondary to the reduction of marrow reserves, ineffective erythropoiesis, chronic inflammation with elevated levels of hepcidin and splenic sequestration.[10–12] Iron overload (IOL) associated with RBC transfusions may further increase marrow toxicity through direct iron deposition, increased oxidative stress due to non-transferrin-bound circulating iron with formation of reactive oxygen species (ROS),[13] and excess iron in the endothelium, macrophages and small bowel, with reduced iron availability.[10–12] Furthermore, MF patients present a significant activation of the NF-kB pathway, which induces a 'cytokine storm' responsible for persistent oxidative stress. The excess of ROS is harmful for haematopoietic stem cells (HCS) and stromal cells inducing increased apoptosis, genotoxic damage and genomic instability, thereby hastening clonal evolution towards leukaemia.[14–16]

Finally, anaemia can be exacerbated by specific MF treatment including the Janus kinase (JAK) inhibitors. In particular, ruxolitinib (RUX) is the first *JAK1/JAK2* inhibitor approved by the US Food and Drug Administration (FDA) in intermediate/high risk MF. RUX is effective in decreasing splenomegaly and improving patients' symptoms but may induce anaemia by hindering the JAK–STAT signalling. In the pivotal COMFORT-1 and -2 trials, 26.4% and 22.5% of RUX-treated patients developed grade 3–4 anaemia respectively.[17–18] This figure was confirmed in the expanded-access JUMP trial, that showed grade 3–4 anaemia in 33% of the over 2000 MF patients included in the study.[19]

Deferasirox (DFX) is the most used iron chelation therapy (ICT) for the management of IOL in thalassemia and myelodysplastic syndromes[20–22] but specific guidelines regarding the use of ICT in MF setting were not available. Recently, a few retrospective independent studies showed that DFX is also effective and safe in MF patients, leading to a haematological improvement in a significant fraction of patients.[23–28]

To date, no data are available in the literature regarding the use of DFX in patients treated with RUX and the possible combined action of these drugs, except for one case report.[29] To address this issue, we have therefore performed a subanalysis of the 'RUX-MF' retrospective study, focusing on the patients who received the combined therapy of RUX and DFX because

of IOL, with the aim to describe safety profile, responses and impact on outcome of this combination in a real-world context.

MATERIAL AND METHODS

Patients and study design

The 'RUX-IOL' study was prompted by the Division of Haematology, San Gerardo University Hospital, Monza, and represents a subanalysis of the 'RUX-MF' observational retrospective study, that involves consecutive MF patients treated with RUX in 22 academic haematology centres that are dedicated to the treatment of MF.[30,31] The list of the participating centres is available in the Appendix. All centres were asked to report, in an electronic case report form (e-CRF), their consecutive MF patients who received RUX according to standard clinical practice. The total number of medical files was reported by each centre by data input into an electronic database developed to record all study data after de-identification of the patients with an alphanumeric code to protect personal privacy. Data collected in this subanalysis included patient demographics, comorbidities, medications, clinical/laboratory tests at diagnosis and during follow-up, date of RUX and DFX start and stop, starting dose of both drugs and requirement for dose reductions over time, and AEs related to both therapies. Also, serum ferritin levels were collected at diagnosis, at DFX start, and at six-month intervals thereafter. Details of ongoing RBC units transfused were recorded throughout the study.

Any treatment decision was at the physician's discretion, independent from participation in this study. After the first data entry, the follow-up information was validated when clinical data were revised, and specific queries were addressed to the participating centre in case of inconsistent data.

At data cut-off (1 December 2020), 703 patients were enrolled in the RUX-MF study, and 245 of them (34.8%) presented transfusion-dependent anaemia at the start of RUX treatment. This subanalysis included 69 consecutive MF patients who received combined treatment with RUX and DFX for at least three months for the management of IOL secondary to transfusion-dependent anaemia. These patients were considered eligible for ICT by their treating haematologist in a real-life setting. All patients satisfied at least one of these two criteria, as suggested in the management of anaemia from other haematological disorders[32,33]: serum ferritin levels ≥1000 μg/l secondary to transfusion dependency; ≥10 RBC units transfused before DFX start. Exclusion criteria for initiating ICT were an estimated life expectancy of less than six months and concomitant therapy with stimulant erythropoietic agents (recombinant erythropoietin, steroids, immunosuppressive therapy). All patients were followed until death or to data cut-off.

Definitions

Diagnoses of primary MF (PMF) and post-polycythaemia vera (PPV)/post-essential thrombocythaemia (PET) MF were made according to 2016 World Health Organization criteria (WHO) or International Working Group on Myelofibrosis Research and Treatment (IWG-MRT) criteria respectively.[34–35] All patients who received treatment with RUX in the current analysis were in the chronic phase (peripheral and marrow blast cells <10%).

Risk category was assessed at diagnosis, according to the IPSS,[2] and at start of RUX and DFX treatment, according to the DIPSS.[3] Histologic examination was performed at local institutions; fibrosis was graded according to the European Consensus Grading System.[36] Unfavourable karyotype was categorized as previously described.[37] Diagnosis of LT was made according to WHO, with a 20% bone-marrow or peripheral blood blast threshold for diagnosis.[35] Transfusion dependency was defined as the need of ≥2 RBC transfusions/month for at least three months.

Treatment response

An ICR was defined as the achievement of a stable (≥3 months) ferritin level <1000 μg/l or of a stable (≥3 months) reduction ≥50% of ferritin level compared to that at the start of DFX at any time during DFX therapy.

According to the revised Cheson criteria IWG 2006, an ER was defined as the achievement of transfusion independency [absence of RBC transfusion, capped by haemoglobin (Hb) values ≥85 g/l], a rise in Hb values ≥15 g/l, and/or a reduction in the transfusion requirement ≥50% for at least eight weeks at any time during DFX therapy.[38] According to ER, defined as complete response (CR: transfusion-independent patients), partial response (PR: reduction in the transfusion requirement and/or increase in Hb levels) or absence of response (NR), the patients were divided in two subgroups: haematological responder (CR + PR) and non-responder patients.

Toxicity and long-term outcome

All AEs that occurred during the combined RUX–DFX treatment were retrieved by the evaluation of medical charts through the report of routine laboratory parameters and type/grade of AEs. AEs were categorized as DFX-related or RUX-related. Temporary and permanent drug discontinuations at any time, as well as median dose of DFX and RUX, were also recorded. All AEs were defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0. Specifically, events graded ≥2 required active systemic treatment and those graded 4 were life-threatening.

Outcome measures included death and LT.

Ethical aspects

The RUX-MF study was performed in accordance with the guidelines of the Institutional Review Boards of the

participating centres and the standards of the Helsinki Declaration. The promoter of this study was the Institute of Haematology 'L. and A. Seràgnoli', Azienda Ospedaliera S. Orsola-Malpighi, Bologna. The study (protocol – MF-2014-01) was approved by the Ethics Committee of Area Vasta Emilia Centro of the Emilia-Romagna Region (CE-AVEC) on 10 June 2014 (code assigned by the promoter's Committee: 068/2014/U) and by the local Ethics Committee of all participating centres and has no commercial support.

Statistical analysis

Statistical analysis was carried out at the biostatistics laboratory of the MPN Unit at the Institute of Haematology 'L. and A. Seràgnoli', IRCCS Azienda Ospedaliero-Universitaria, Bologna. Continuous variables have been summarized by their median and IR, and categorical variables by count and relative frequency (%) of each category. Comparisons of quantitative variables between groups of patients were carried out by the Wilcoxon-Mann–Whitney rank-sum test or Student's *t*-test, and association between categorical variables (two-way tables) was tested by the Fisher exact test or chi-squared test, as appropriate. ICR and ER were treated as time-dependent variables. Overall survival (OS) was calculated from start of DFX to death or last contact, using Kaplan–Meier analysis. Prognostic factors for survival and for ICR were identified using the Cox proportional-hazards regression model. The proportional-hazards assumption was assessed with log–log plots. Covariates with a *p*-values ≤0.10 in univariate analyses were considered for multivariable analysis, which was carried out using a backward stepwise approach. The variables included in the multivariable model were selected evaluating the performance of the model in terms of goodness of fit. Given that ICR is a time-dependent covariate, its impact on survival was represented with survival curves obtained with the Simon–Makuch technique, in order to consider the change in an individual's covariate status over time. For all tested hypotheses, two-tailed *p*-values <0.05 were considered significant. Statistical analyses were performed using STATA Software, 15.1 (StataCorp LP, College Station TX, USA).

RESULTS

Population on study

A total of 69 consecutive patients with PMF (50) or PPV-MF (10) and PET-MF (9), fulfilled the inclusion criteria and were included in the analysis. In particular, 67 (97%) patients had serum ferritin levels ≥1000 μg/l and 63 (91%) patients received ≥10 RBC units transfused before DFX start. Main clinical and laboratory features at diagnosis and at start of RUX and DFX treatment are shown in Table 1.

RUX treatment was introduced after a median time from MF diagnosis of 26.4 months [IR 0.1–229.8]. At the time of RUX start, 45 (66.2%) patients were transfusion-dependent, while 24 patients (34.8%) acquired transfusion dependency after a median time of 1.6 months (IR 0.3–9.4) from RUX start. Median RUX starting dose was 30 mg/day (IR 10–40).

DFX was started before or together with RUX in 14 (20.3%) patients, while 55 patients (79.7%) started DFX after a median duration of RUX therapy of 10.2 months (IR 5.7–19.8). DFX was started after a median value of 20 RBC units/patient (IR 12–168) and after a median of 13 months from start of transfusion dependency (IR 1.5–145.3). The median starting dose of DFX was 1000 mg/day (12.5 mg/kg/day) (IR: 125–2100).

The median RUX and DFX exposure was 34.4 (IR 3.4–92) and 18.4 months (IR 3.3–71.4) respectively. During the observation time, 33 (47.8%) and 39 (56.5%) patients discontinued RUX and DFX, with an incidence rate of permanent discontinuations of 1.4 and 3.6 per 100 patient-months respectively. MF progression, LT and allogeneic stem-cell transplantation were the main causes for both RUX and DFX stop, accounting for 57.5% (19/33) and 41% (16/39) of discontinuations respectively (Table 2).

Safety of the RUX–DFX combination

The combined therapy of RUX and DFX was administered for a median time of 12.4 months (IR 3.1–71.2). In 14 patients, DFX was continued also after RUX discontinuation, for a median time of 7.7 months (IR 3–25.5).

Overall, 36 (52.2%) patients required RUX dose reductions. Of them, eight (11.6%) patients discontinued due to RUX-related AEs during the combined RUX–DFX therapy, specifically: infections (3, 4.3%), anaemia/thrombocytopenia (4, 5.8%) or thrombosis (1, 1.5%). AEs causing RUX discontinuation occurred after a median time of RUX–DFX combined therapy of 9.4 months (IR 3–67.8).

Overall, DFX dose reductions occurred in 34 (49.3%) patients because of renal impairment (22, 31.8%), liver enzymes increase (4, 5.7%), epigastric pain (6, 8.7%), and skin rash (2, 2.9%). Three AEs were grade 3 (two renal impairment and one hepatic disfunction), with no grade-4 event. Of 34 DFX AEs, 29 (85.3%) occurred during DFX–RUX combined therapy, the remaining five (14.7%) post RUX discontinuation. A total of nine patients (13.1%) permanently discontinued DFX due to toxicity, after a median time of 12.4 months (IR 3.2–58.4) of combined RUX–DFX therapy, principally for renal impairment (8, 11.6%), and only one for hepatic disfunction (1, 1.5%). Overall, no unexpected or additional toxicity was reported during concomitant use of DFX and RUX.

Response to treatment

At any time, 33 (47.8%) patients obtained an ICR, with an incidence rate of ICR of 3.9 per 100 patient-months. The median

TABLE 1 Main patients' characteristics

Characteristics	Study cohort (*n* = 69)	No ICR (*n* = 36)	ICR (*n* = 33)	*p* value
Age, years, median (IR)				
at RUX start	68.9 (63.1–75.3)	70 (65.1–75.8)	68.3 (61.2–71.2)	0.14
at DFX start	69.7 (63.9–75.5)	71 (65.9–76.5)	68.7 (61.2–74.9)	0.15
Male sex, no. (%)	43 (62.3%)	24 (66.7%)	19 (57.6%)	0.44
Primary MF, no. (%)	50 (72.5%)	26 (72.2%)	24 (72.7%)	0.96
Intermediate-2/high IPSS risk category at diagnosis, no. (%)	38 (55,1%)	18 (50)	20 (60.6%	0.37
Intermediate-2/high DIPSS risk category at RUX start, no. (%)	55 (79.7%)	30 (83.3%)	25 (75.8%)	0.43
Intermediate-2/high DIPSS risk category at DFX start, no. (%)	58 (84.1%)	30 (83.3%)	28 (84.9%)	0.86
Driver mutation status				
JAK2^{V617F}	47 (68.1%)	25 (69.4%)	22 (66.7%)	0.07
CALR/MPL	15 (21.7%)	10 (27.8%)	5 (15.1%)	
Triple negative	7 (10.2%)	1 (2.8%)	6 (18.2%)	
Haemoglobin at DFX start, median (IR), g/l	83 (77–92)	84 (77–88)	83 (77–94)	0.54
Platelet count at DFX start, median (IR), × 10^9/l	150 (90–224)	149 (88–264)	169 (91–220)	0.88
Leukocytes at DFX start, median (IR), × 10^9/l	7.4 (4.7–13)	9.1 (5.3–13)	6.6 (4.1–10.8)	0.29
No. of RBC units, median (IR)				
at RUX start	5 (0–24)	9 (1.5–28.5)	2 (0–16)	**0.04**
at DFX start	20 (15–31)	20.5 (18–31)	20 (12–30)	0.14
No. of RBC units in a range of 8 weeks around of starting DFX, median (IR)	4.5 (1–14)	5.5 (1–14)	4 (1–8)	0.15
No. of RBC units at start of DFX > 20, no. (%)	40 (58.0%)	23 (63.9%)	17 (51.5%)	0.30
Ferritin, µg/l, median (IR)				
At diagnosis	334 (8–2448)	454 (22–1884)	251 (8–2248)	**0.05**
At start of DFX	1580 (646–6447)	1742 (1132–6447)	1544 (646–4015)	0.11
Ferritin at start of DFX >2000 µg/l, no. (%)	17 (24.6%)	10 (27.8%)	7 (21.2%)	0.53
DFX dose start, median (IR), mg/day	1000 (125–2100)	1000 (500–2100)	1000 (125–2000)	0.15
Adjusted DFX dose, median (IR), mg/day	750 (250–2000)	750 (500–1750)	750 (250–2000)	0.22
Time between diagnosis and DFX start >2 years, no. (%)	40 (58.0%)	17 (47.2%)	23 (69.7%)	0.06

Bold indicate significant *p* values.

Abbreviations: DFX, deferasirox; DIPSS, Dynamic International Prognostic System (Passamonti *et al*., 2010); ICR, iron chelation response; IR, interquartile range; MF, myelofibrosis; RBC, red blood cells; RUX, ruxolitinib.

time to ICR was 6.2 months (IR 3.1–12). Compared to non-responders, patients who achieved an ICR did not present significant differences in principle and biological features at diagnosis and at the start of RUX or DFX, except for significantly lower ferritin levels at diagnosis (median ferritin 251 vs 454 µg/l, $p = 0.05$) and a lower number of RBC units prior to RUX start (median RBC 2 vs 9, $p = 0.04$) (Table 1). As expected, a more significant reduction of ferritin levels at 3, 6, 12 and 18 months from DFX start was observed in ICR patients, compared to non-responders (Figure 1, $p = 0.001$).

During the observation time, 32 patients (46.4%) achieved an ER (haematological responders), with 13 (18.9%) patients who obtained a transfusion independency (CR) and 19 (27.5%) patients who showed haematological improvement (PR). The median time to ER was two months from DFX start (IR 2–9). Conversely, 37 (53.6%) patients never achieved an ER during the observation time.

Patients who achieved an ER were more likely to obtain also an ICR [hazard ratio (HR): 2.21; 95% confidence interval (CI) 1.04–4.72, $p = 0.04$). In particular 12/13 patients (92.3%) who obtained CR, achieved ICR (Figure S1). The duration of ER was longer in ICR *versus* no-ICR patients (26.9 vs 7.8 months, $p = 0.04$).

Notably, RUX starting dose did not influence the probability to achieve an ICR or an ER (log-rank $p = 0.58$ and $p = 0.69$ respectively). RUX dose at baseline, at 3, 6 and 12 months after DFX start was not associated with significant reduction of ferritin levels (Figure S2). Also, RUX dose

TABLE 2 Dose reduction and discontinuation of DFX and RUX

	Study cohort (n = 69)
RUX dose reduction, no of patients (%)	**36 (52.2)**
Causes of RUX discontinuation, no of patients (%)	**33 (47.8)**
RUX-related AEs causing discontinuation, no of patients (%)	**8 (11.6)**
Anaemia/thrombocytopenia	4 (5.8)
Infections	3 (4.3)
Thrombosis	1 (1.5)
RUX-unrelated AEs causing discontinuation, no of patients (%)	**25 (36.2)**
Disease progression/LT	12 (17.4)
Allogeneic stem cell transplantation	7 (10.2)
Death	3 (4.3)
Others	3 (4.3)
DFX dose reduction, no of patients (%)	**34 (49.3)**
Causes of DFX discontinuation, no of patients (%)	**39 (56.5)**
DFX-related AEs causing discontinuation, no of patients (%)	**9 (13.1)**
Renal impairment	8 (11.6)
Liver enzymes increase	1 (1.5)
DFX-unrelated AEs causing discontinuation, no of patients (%)	**30 (43.4)**
Disease progression/LT	9 (13.1)
Allogeneic stem cell transplantation	7 (10.1)
Ferritin <500 μg/l	5 (7.2)
Death	5 (7.2)
Others	4 (5.8)

Bold indicate the total (and relative percentage) of the various AEs.

Abbreviations: AE, adverse event; DFX, deferasirox; LT, leukaemic transformation; RUX, ruxolitinib.

reduction did not correlate with ICR/ER (log-rank p = 0.72 and p = 0.87 respectively). The achievement of ER did not appear to be significantly related to dose reduction of RUX: in fact, of the 33 patients who never reduced the dose of RUX, 14 (42.4%) achieved an ER, similar to the 18/36 (50%) patients who had a RUX dose reduction (p = 0.45).

Finally, six patients (8.7%) stopped DFX permanently because of ferritin levels <500 μg/l and resolution of transfusion dependency.

Outcome

After a median follow-up of 22.3 months (IR 12.3–48.2) from DFX start, 22 patients (31.9%) died, because of: LT (8, 34.8%), MF progression (8, 34.8%), infections (2, 8.7%), bleeding (1), or other (4). The mortality rate was significantly lower in patients achieving an ICR compared to non-responders (21.2% vs 44%, p = 0.04). During follow-up, no long-term IOL-related complications were reported, including liver cirrhosis, pancreatic islet cell damage, diabetes or heart failure.

Among baseline variables tested for association with survival, only the absence of leukocytosis at DFX start (leukocytes <25 × 10^9/l) was significantly associated with improved outcome in multivariable analysis (HR: 0.26, 95% CI 0.08–0.84, p = 0.02) (Figure 2). The achievement of an ICR at any time during combined therapy also remained significantly associated with longer survival (HR: 0.33, 95% CI 0.13–0.83, p = 0.02) (Figure 3). No clinical/laboratory features could predict LT (data not shown).

DISCUSSION

The role of ICT in the setting of MF patients is still largely undefined. To date, clinical indications for ICT are generally derived from thalassaemia and myelodysplastic syndromes,[20–22] in absence of specific guidelines for MF. Recently, two independent retrospective studies[27–28] suggested that DFX was feasible and effective also in MF patients and a haematological improvement can occur in a significant fraction of patients. In the first study, 19 out of 48 (39.6%) patients treated with DFX had a progressive reduction in ferritin levels, with a global ICR rate of 41%. Also, 19.1% of patients achieved a persistent increase of Hb >15 g/l, with disappearance of transfusion requirement in six cases (12.5%).[27] In the IRON-M study[28] after a median DFX exposure of 17.2 months, 12 out of 45 (29.3%) MF patients obtained an ICR with a better survival from DFX initiation in patients with ICR with respect to non-responders. An ER was achieved in 43.9% of the cases and was more frequent in ICR patients. However, in both these studies the vast majority of patients did not receive a concomitant treatment with RUX. The present multicentre retrospective study reports a large cohort of patients that received the combined RUX–DFX therapy, with the aim to increase the proficiency of using ICT in MF and to open a critical debate about the indication for ICT in combination with JAK2 inhibitors.

First, we observed an acceptable toxicity of the DFX–RUX combination, with a discontinuation rate of DFX during combined therapy of 13.1% for toxicity, principally secondary to mild renal impairment, which is similar to previously published data in patients with myelodysplastic syndromes.[39] Importantly, the great majority of RUX (88.4%) and DFX (77%) discontinuations occurred for no drug-related AEs. Also, no unexpected toxicity was reported during the combination therapy.

Also, almost 50% of patients achieved an ICR and a significant proportion of these obtained an ER, with about 20% of patients becoming transfusion-independent. These data are comparable to those achieved in patients with myelodisplastic syndromes who received DFX treatment.[21] Neither initial RUX dosing nor subsequent dose reductions were found to be associated with ER. This finding could suggest a specific role of DFX in eliciting responses. It also reinforces the recommendation to use the maximum tolerated dose of RUX in patients with anaemia.

Finally, our data also seem to suggest a possible positive role of efficient ICT on survival: the achievement of an ICR at any time during combined therapy of RUX and DFX was significantly predictive for longer survival. This result could correspond to the biological observation of a possible

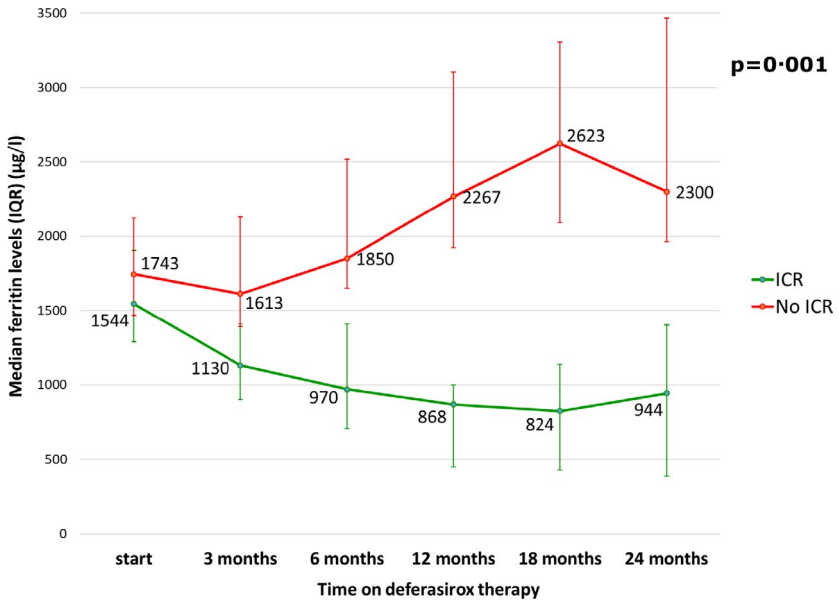

FIGURE 1 Ferritin levels during combined therapy with RUX and DFX. Median ferritin levels (and respective interquartile ranges) are illustrated according to achievement or lack of iron chelation response (ICR) at any time. DFX, deferasirox; RUX, ruxolitinib [Colour figure can be viewed at wileyonlinelibrary.com]

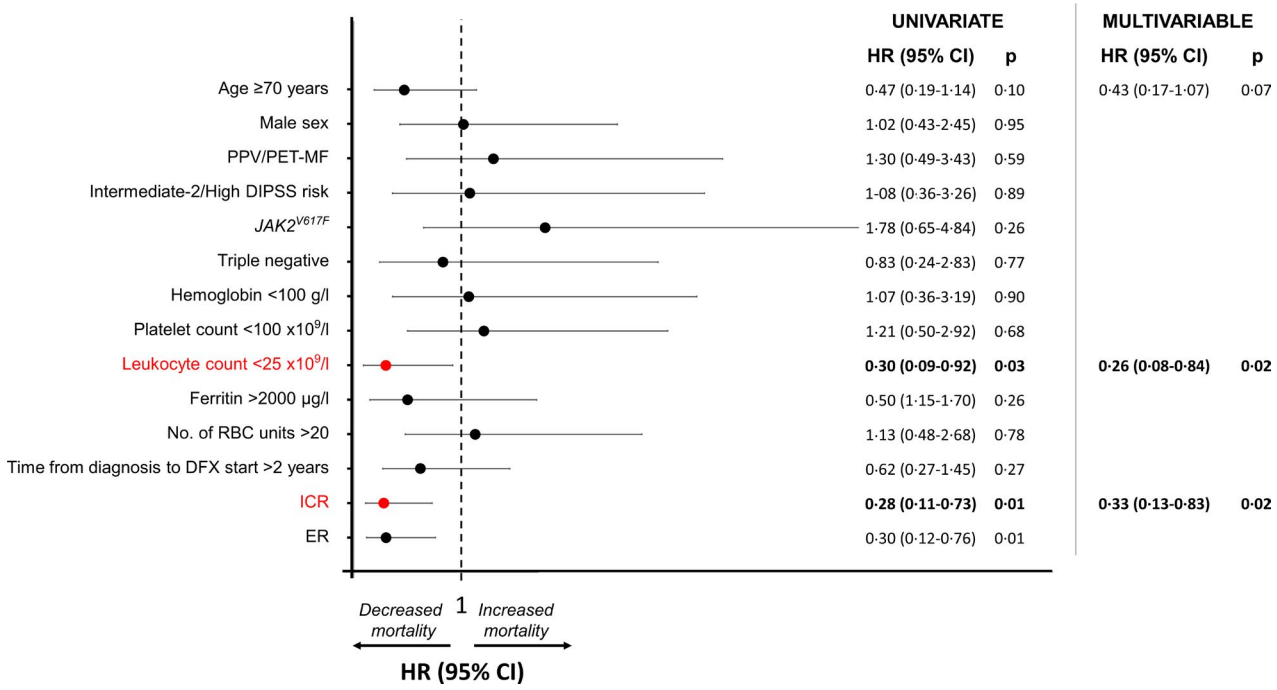

FIGURE 2 Prognostic factors for survival. Prognostic factors were identified with a Cox proportional-hazards model. The forest plot represents the results of the univariate analyses. Single Covariates with a $p \leq 0.10$ in univariate analyses were considered for multivariable analysis and the variables included in the multivariable model were selected evaluating the performance of the model in terms of goodness of fit. Baseline parameters were evaluated at the time of deferasirox (DFX) start, erythroid response (ER) and achievement of Iron Chelation Response (ICR), occurring at any time during combined therapy of ruxolitinib (RUX) and DFX, were considered as a time-dependent covariate. PPV/PET-MF: post-polycythemia vera/post-essential thrombocythemia myelofibrosis; CI, confidence interval; DIPSS, Dynamic International Prognostic System) (Passamonti et al, 2010); HR, hazard ratio; RBC, red blood cells [Colour figure can be viewed at wileyonlinelibrary.com]

correlation between an efficient chelation and a reduction in oxidative stress and genetic instability in haematopoietic stem cells (HSC) and myeloid progenitors. Indeed, both RUX and DFX reduce the bone-marrow oxidative damage, with interaction with NF-KB and JAK–STAT signalling, and could operate a potential therapeutic synergy.[14–16,40]

The main constraint of this study is its retrospective nature which accounts for some limitations of the work.

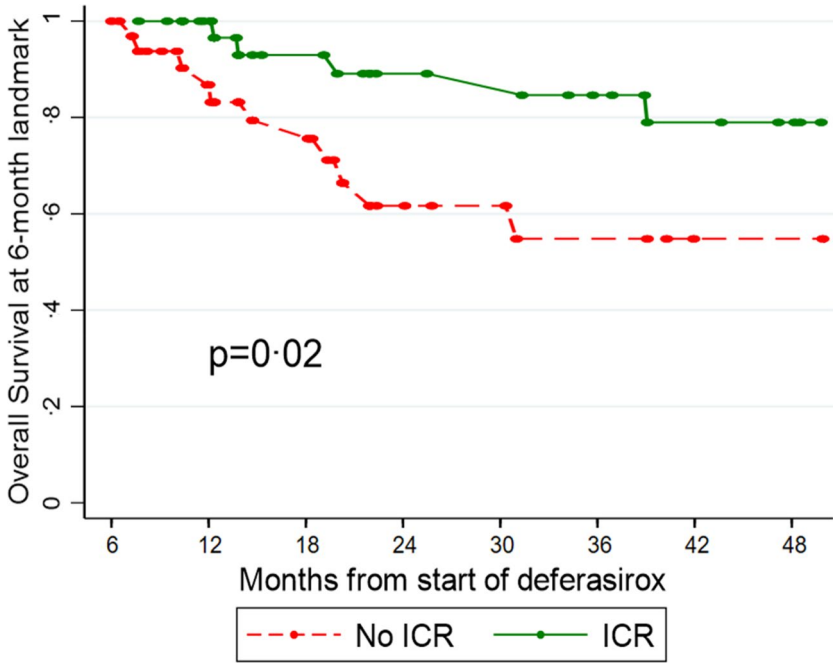

FIGURE 3 Survival according to Iron Chelation Response (ICR) at a 6-month landmark. The survival curves were obtained with the Simon–Makuch technique. The landmark time point was set at 6 months from deferasirox (DFX) start, which is the approximated median time from DFX start to achievement of an ICR. The *p*-value refers to the overall significant association to survival after a Cox proportional-hazards multivariable model [Colour figure can be viewed at wileyonlinelibrary.com]

First, we do not have a 'planned' control arm of the RUX-IOL population: therefore, the possibility of a positive selection of patients undergoing combined therapy with ICT and RUX cannot be completely excluded. However, the selection bias, if present, was involuntary. The decision whether or not to combine ICT with RUX was made by the treating haematologist regardless of subsequent participation in this retrospective data collection and was based on multiple factors including the haematologist's clinical experience with the use of ICT in transfusion-dependent anaemia. An indirect comparator to our clinical experience can be derived from the results of the COMFORT trials, whose inclusion criteria did not allow ICT. Notably, RUX is effective in controlling splenomegaly and symptoms related to MF but does not aim to achieve an ER; conversely, its use is associated with decreased haemoglobin values and increased transfusion need, particularly during the first weeks of therapy. The pooled analyses of these studies[41] showed that OS in the RUX group was similar between patients who were transfusion-dependent or not at week 24.

To further explore this issue, we have also compared principal end-points of efficacy and outcome of RUX-IOL patients with those derived from historical patients of the RUX-MF global cohort (245 patients) that experienced transfusion-dependent anaemia during RUX treatment; of them, 139 (56.7%), did not receive ICT or other anaemia-directed drugs. In these non-chelated patients, serum ferritin levels were not available, because, in the absence of ICT, monitoring of serum ferritin was not performed in routine clinical practice. However, we observed that an ER during the first six months of RUX therapy was achieved by 29/139 (20.8%) patients in the historical arm *versus* 26/69 (37.7%) RUX-IOL patients in the same period ($p = 0.01$), in the absence of a significant difference also in terms of RUX starting dose in the two groups (57% vs 60.9% of patients with RUX starting dose ≥30 mg/day respectively, $p = 0.62$). Finally, the median OS of RUX historical patients was significantly worse than in the RUX-IOL cohort (median survival 2.9 vs 5.6 years respectively, log-rank $p < 0.001$) (data not shown). However, we believe that only a planned prospective randomized study can correctly answer this question.

Second, we had no information about IOL-related complications. An underreport of events cannot be ruled out, due to not only the retrospective nature of this study but also the pandemic period. Nevertheless, the median follow-up of our study (22.3 months from DFX start) was too short to detect such complications, that are usually long-term events, mostly occurring after 24 months of observation. We acknowledge that a long-term update of the present cohort may be useful and we have planned a further analysis with a prolonged follow-up. Finally, inadequate recognition of degree and causality of AEs and poor assessment of drug compliance cannot be entirely ruled out. Nonetheless, despite these limitations, the substantial number of included patients, the cooperation of haematology centres with a particular focus on MF, and the accurate revision of each case history may have partially compensated these intrinsic shortcomings in our study. We acknowledge that this limitation can hardly be avoided when dealing with a rare condition, such as MF, and a specific subpopulation, such as transfusion-dependent patients receiving RUX and DFX. Nevertheless, retrospective studies are at present the only and valuable source of comprehensive data in this setting, and lead to personalized therapy.

In conclusion, the DFX and RUX combination may be effective and well tolerated in MF patients, with a safety profile that is clinically manageable with regular patient monitoring. Significant ICR and ER responses have been observed and an efficient ICT appears to correlate with improved survival. Therefore, the suggestion not to procrastinate the start of ICT in patients with MF during RUX treatment, although worthy of confirmation in larger cohorts, seems to find support in our data. Possibly, an earlier start of the combined therapy might result in longer treatment durations and better results. Unfortunately, this study cannot adequately answer the question because of the too short median period of observation for DFX–RUX combination therapy (12 months).

The efficacy and a sustainable cost of the RUX–DFX combination will also have to evaluated in the panorama of new drugs that will soon be approved for the treatment of MF. In particular, in the contest of investigational JAK inhibitors, the selective inhibitor of JAK1, JAK2, and ACVR1 momelotinib (MMB) has demonstrated significant benefit in improving anaemia in patients with MF, increasing rates of transfusion independence. This as yet experimental drug is endowed with low haematological toxicity, possibly allowing therapy over a prolonged period of time. The anaemia benefits were observed in conjunction with decreased plasma hepcidin and improved iron homeostasis likely contributing to increased erythropoiesis, consistent with the action mechanism of the drug. However, MMB did not appear to be superior to RUX with regards to improving splenomegaly and constitutional symptoms and hence the drug remains unlicensed at present.[42–44] Therefore, we may hypothesize that RUX will continue to be widely used in patients with significant splenomegaly or systemic symptoms, regardless of the presence of anaemia. In this context, the implementation of strategies that can mitigate anaemia is of paramount importance. The combination of RUX and DFX represents a potential treatment strategy to treat anaemia in this setting.

Further and possibly prospective studies will better confirm whether this combination strategy may improve the management of RUX-associated anaemia in MF and have a positive impact on outcome, as well as identify a subset of patients for whom alternative drugs (i.e. MMB) may be preferable.

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AUTHOR CONTRIBUTIONS

Elena M. Elli, Roberto Latagliata, and Francesca Palandri designed research; all authors performed research and collected data; Daniela Bartoletti, Elena M. Elli, Francesca Palandri and Roberto Latagliata analysed and interpreted data; Daniela Bartoletti, Francesca Palandri and Elena M. Elli performed statistical analysis; Elena M. Elli, Francesca Palandri, Roberto Latagliata and Daniela Bartoletti wrote the manuscript.

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REFERENCES

1. Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2021;96:145–62.
2. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009;113:2895–901.
3. Passamonti F, Cervantes F, Vannucchi AM, Morra E, Rumi E, Pereira A, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010;115:1703–8.
4. Guglielmelli P, Lasho TL, Rotunno G, Mudireddy M, Mannarelli C, Nicolosi M, et al. MIPSS70: mutation-enhanced international prognostic score system for transplantation-age patients with primary myelofibrosis. J Clin Oncol. 2018;36:310–8.
5. Passamonti F, Giorgino T, Mora B, Guglielmelli P, Rumi E, Maffioli M, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukaemia. 2017;31:2726–31.
6. Tefferi A, Lasho TL, Jimma T, Finke CM, Gangat N, Rakhee V, et al. One thousand patients with primary myelofibrosis: the mayo clinic experience. Mayo Clin Proc. 2012;87:25–33.
7. Porter JB. Practical management of iron overload. Br J Haematol. 2001;115:239–52.
8. Elena C, Passamonti F, Rumi E, Malcovati L, Arcaini L, Boveri B, et at. Red blood cell transfusion-dependency implies a poor survival in primary myelofibrosis irrespective of IPSS and DIPSS. Haematologica 2011;96:167–70.
9. Tefferi A, Siragusa S, Hussein K, Schwager SM, Hanson CA, Pardanani A, et al. Transfusion-dependency at presentation and its acquisition in the first year of diagnosis are both equally detrimental for survival in primary myelofibrosis–prognostic relevance is independent of IPSS or karyotype. Am J Hematol. 2010;85:14–7.
10. Mesa RA, Barosi G, Cervantes F, Reilly JT, Tefferi A. Myelofibrosis with myeloid metaplasia: disease overview and non-transplant treatment options. Best Pract Res Clin Haematol. 2006;19:495–517.
11. Ganz T. Hepcidin and its role in regulating systemic iron metabolism. Haematology Am Soc Hematol Educ Program. 2006;29–35:507.
12. Pardanani A, Finke C, Abdelrahman RA, Lasho TL, Tefferi A. Associations and prognostic interactions between circulating levels of hepcidin, ferritin and inflammatory cytokines in primary myelofibrosis. Am J Hematol. 2013;88:312–6.
13. Isidori A, Borin L, Elli E, Latagliata R, Martino B, Palumbo G, et al. Iron toxicity - Its effect on the bone marrow. Blood Rev. 2018;32:473–9.
14. Ghoti H, Amer J, Winder A, Rachmilewitz E, Fibach E. Oxidative stress in red blood cells, platelets and polymorphonuclear leukocytes from patients with myelodysplastic syndrome. Eur J Hematol. 2007;79:463–7.

15. Zhang Y, Zhai W, Zhao M, Li D, Chai X, Cao X, et al. Effects of iron overload on the bone marrow microenvironment in mice. PloS one. 2015;10:e0120219.
16. Bjørn ME, Hasselbalch HC. The role of reactive oxygen species in myelofibrosis and related neoplasms. Mediators Inflamm. 2015;648090:1–11.
17. Verstovsek S, Mesa RA, Gotlib J, Gupta V, DiPersio JF, Catalano JV, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol. 2017;10:55.
18. Cervantes F, Vannucchi AM, Kiladjian J-J, Al-Ali HK, Sirulnik A, Stalbovskaya V, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood. 2013;122:4047–53.
19. Al-Ali HK, Griesshammer M, Foltz L, Palumbo GA, Martino B, Palandri F, et al. Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts. Br J Haematol. 2020;189:888–903.
20. Bollig C, Schell LK, Rücker G, Allert R, Motschall E, Niemeyer CM, et al. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database Syst Rev 2017;8:Cd007476.
21. Molteni A, Riva M, Pellizzari A, Borin L, Freyrie A, Greco R, et al. Haematological improvement during iron-chelation therapy in myelodysplastic syndromes: the experience of the "Rete Ematologica Lombarda". Leuk Res. 2013;37:1233–40.
22. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines). Myelodisplastic Syndromes, version 2.2014 rev.
23. Leitch HA, Chase JM, Goodman TA, Ezzat H, Rollins MD, Wong DHC, et al. Improved survival in red blood cell transfusion dependent patients with primary myelofibrosis (PMF) receiving iron chelation therapy. Hematol Oncol. 2010;28:40–8.
24. Di Tucci AA, Murru R, Alberti D, Rabault B, Deplano S, Angelucci E. Correction of anaemia in a transfusion-dependent patient with primary myelofibrosis receiving iron chelation therapy with deferasirox (Exjade, ICL670). Eur J Haematol. 2007;78:540–2.
25. Elli EM, Belotti A, Aroldi A, Parma M, Pioltelli P, Pogliani EM. Iron chelation therapy with deferasirox in the management of iron overload in primary myelofibrosis. Med J Hematol Infect Dis. 2014;6:e2014042.
26. Latagliata R, Montagna C, Porrini R, Di Veroli A, Crescenzi Leonetti S, Niscola P, et al. Chelation efficacy and erythroid response during deferasirox treatment in patients with myeloproliferative neoplasms in fibrotic phase. Eur J Haematol 2016;96:643–9.
27. Di Veroli A, Campagna A, De Muro M, Maurillo L, Trawinska MM, Leonetti Crescenzi S, et al. Deferasirox in the treatment of iron overload during myeloproliferative neoplasms in fibrotic phase: does ferritin decrement matter? Leuk Res. 2019;76:65–9.
28. Elli EM, Iurlo A, Aroldi A, Caramella M, Malato S, Casartelli E, et al. Deferasirox in the management of iron-overload in patients with myelofibrosis: a multicentre study from the Rete Ematologica Lombarda (IRON-M study). Br J Haematol. 2019;186:e123–6.
29. Piro E, Lentini M, Levato L, Russo A, Molica S. Sustained erythroid response in a patient with myelofibrosis receiving concomitant treatment with ruxolitinib and deferasirox. Chemotherapy. 2018;63:107–10.
30. Palandri F, Palumbo G.A, Bonifacio M, Tiribelli M, Benevolo G, Martino B, et al. Baseline factors associated with response to ruxolitinib: an independent study on 408 patients with myelofibrosis Oncotarget 2017; 8:79073–86.
31. Palandri F, Tiribelli M, Breccia M, Bartoletti D, Elli EM, Benevolo G, et al. Ruxolitinib rechallenge in resistant or intolerant patients with myelofibrosis: frequency, therapeutic effects, and impact on outcome. Cancer 2021;1;127(15):2657–65.
32. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. Chapter 3 - IRON OVERLOAD AND CHELATION. In: Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT). 3rd ed.; Nicosia (CY): Thalassaemia International Federation; 2014.
33. Hoeks M, Yu G, Langemeijer S, Crouch S, de Swart L, Fenaux P, et al. Impact of treatment with iron chelation therapy in patients with lower-risk myelodysplastic syndromes participating in the European MDS registry. Hematologica. 2020;105(3):640–51.
34. Barosi G, Mesa RA, Thiele J, Cervantes F, Campbell PJ, Verstovsek S, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. Leukaemia. 2008;22:437–8.
35. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukaemia. Blood. 2016;127:2391–405.
36. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128–32.
37. Gangat N, Caramazza D, Vaidya R, George G, Begna K, Schwager S, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol. 2011;29:392–7.
38. Cheson BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108:419–25.
39. Musto P, Maurillo K, Simeoni V, Poloni A, Finelli C, Balleari E, et al. Iron-chelating therapy with deferasirox in transfusion-dependent, higher risk myelodysplastic syndromes: a retrospective, multicentre study. Br J Haematol. 2017;177:741–50.
40. Carreau N, Tremblay D, Savona M, Kremyanskaya M, Mascarenhas J. Ironing out the details of iron overload in myelofibrosis: Lessons from myelodysplastic syndromes. Blood Rev. 2016;30:349–56.
41. Verstovsek S, Gotlib J, Mesa RA, Vannucchi AM, Kiladjian JJ, Cervantes F, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. J Hematol Oncol. 2017;10(1):156.
42. Sureau L, Orvain C, Ianotto JC, Ugo V, Kiladjian JJ, Paz DL, et al. Efficacy and tolerability of Janus Kinase inhibitors in myelofibrosis: a systematic review and network meta-analysis. BCJ. 2021;11(7):135.
43. Bassiony S, Harrison CN, DP ML. Evaluating the safety, efficacy and therapeutic potential of Momelotinib in the treatment of intermediate/high-risk myelofibrosis: evidence to date. Ther Clin Risk Manag. 2020;16:889–901.
44. Oh Stephen T, Talpaz M, Gerds AT, Gupta V, Verstovsek S, Mesa R, et al. ACVR1/JAK1/JAK2 inhibitor momelotinib reverses transfusion dependency and suppresses hepcidin in myelofibrosis phase 2 trial. Blood Adv. 2020;4(18):4282–91.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Abbreviations: AEs, adverse events; DFX, deferasirox; LT, leukaemic transformation; RUX, ruxolitinib. These events occurred during the entire follow-up.