Efficacy and safety of deferasirox in myelodysplastic syndromes

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Abstract Transfusion dependence in myelodysplastic syndrome (MDS) patients may lead to organ damage due to accumulation of non-transferrin-bound iron with consequent increased oxidative stress. Iron chelation has been reported in retrospective studies to improve overall survival in low-risk MDS patients, but this information needs to be validated in prospective trials. The oral iron chelator, deferasirox, has been shown to reduce serum ferritin levels in chelation naïve and pre-treated patients and to reduce labile plasma iron, independently from the efficacy on iron overload. Deferasirox is a potent NF-kB inhibitor, tested in vivo and on acute myeloid leukemia and MDS cell lines, and this effect may explain in part the phenomenon of hematological improvements reported in case reports and in different clinical trials. The drug has an acceptable safety profile, with the most common side effects reported being non-progressive change in serum creatinine level, gastrointestinal disturbances, and skin rash. In this review, we report the results of different studies testing safety and efficacy of deferasirox in MDS patients, side effects associated with the drug, and suggested management of iron overload.

Keywords Deferasirox · MDS · Efficacy · Safety

Introduction

Myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic stem cells, characterized by ineffective hematopoiesis resulting in blood cytopenias and high risk of progression to acute myeloid leukemia (AML) [1, 2]. MDS may be triggered by previous chemotherapy (especially use of alkylating agents), radiotherapy, or by exposure to benzene derivatives, but are mainly age-related. Frequency of MDS is about four cases per 100,000 individuals and is one of the most frequent hematological malignancies after non-Hodgkin lymphoma and multiple myeloma [3]. Up to the last decade, due to the lack of effective therapies and to the advanced age of many affected patients, supportive care was the only therapeutic option proposed for this condition. Prognosis of MDS is routinely assessed by an international prognostic scoring system (IPSS) proposed in 1997 and based on the number of blood cytopenias, percentage of marrow blasts, and karyotype [4]. This system distinguishes four subgroups of patients with MDS, namely as low, intermediate-1, intermediate-2, and high-risk. Patients with low and intermediate-1 IPSS risk are often grouped into the category of “lower risk MDS”, and typically show a relatively low risk of progression to AML and a prolonged survival, characterized by high transfusion requirement and consequently iron overload. Patients with intermediate-2 and high-IPSS risk are generally grouped as “higher risk MDS”, and often progress to AML and have short survival. According to the depth of cytopenia and refined cytogenetic subgroups, a revised IPSS, called IPSS-R, has been recently proposed [5], which adds further categories such as those at very low and very high risk. Based on prognostic stratification, treatment may vary: patients with lower risk MDS are usually treated for correction of cytopenias, using erythropoiesis-stimulating agents (ESAs) or, in the case of patients with chromosome 5q deletion (del 5q), lenalidomide. In patients with higher risk MDS, treatments aimed at modifying the disease are generally proposed, especially the hypomethylating agents azacitidine or decitabine, which have been recently shown to improve survival for this category of patients [6]. Allogeneic hematopoietic stem cell transplant (HSCT) remains the only potential curative approach for this disease, but it is limited to younger patients with an HLA-identical donor [7].
Iron overload in MDS and role of chelation therapy on survival

Most MDS patients develop red blood cell (RBC) transfusion dependence, and transfusions are the only therapeutic intervention in some patients, such as those at low risk [8]. Anemia related to ineffective hematopoiesis may have a worse impact on quality of life, and chronic anemia is associated with possible cardiac concomitant comorbidities [9]: cardiac remodeling was reported at higher frequency in transfusion-dependent patients with mean hemoglobin (Hb) level of 8.7±1.4 g/dL, compared to patients with mean Hb of 11.3±2.4 g/dL [10]. A US Medicare-based analysis showed that a cardiac event was recorded in 74 % of MDS patients followed over a 3-year period (48 % of events were congestive heart failure) and occurred overall in 79 % of the transfused patients compared to 54 % of the non-transfused subjects [3]. Anemia in MDS patients’ leads to ventricular hypertrophy exacerbates coronary syndromes, and coexistence of renal insufficiency with decreased erythropoietin (EPO) production may further exacerbate anemia [9, 10]. It has been reported that transfusion dependence in MDS patients correlates with overall survival (OS), and one of the first reports was by the Pavia group: in 467 patients, OS and leukemia-free survival (LFS) were inferior in transfusion-dependent patients (requiring ≥1 unit of RBC per 4 weeks), with an HR of 1.91 and 1.84, respectively [11]. Moreover, OS and LFS progressively decreased with increasing transfusion dependence, with an HR of 1.36 and 1.40, respectively, for each additional RBC unit transfused per 4 weeks [11]. The effect on survival was mainly seen in lower-risk patients (P<0.001), and transfusion dependence increased the probability of non-leukemic death [11]. Due to these findings, a modification of IPSS was developed, the so-called WPSS [12], which incorporates transfusion dependence into the calculation of patient risk. OS has also been shown to decrease with increasing ferritin level, with an HR of 1.42 for every 500 ng/mL increase in ferritin over 1,000 ng/mL [13]. This suggests that iron overload itself may worsen survival. Each unit of RBC contains 200 to 250 mg of iron, which the body has no mechanism to excrete. The reticuloendothelial system (RES) clearance capacity is about 10 to 15 g, corresponding to 50 RBC units. When the RES capacity is exceeded, parenchymal deposition and tissue damage occur; in a patient receiving 2 RBC units per month, this will occur in just 2 years. It has been reported that iron has a suppressive effect on erythroid colony: in vitro, in patients with an elevated ferritin level the burst-forming units erythroid (BFU-E) colony were significantly decreased, as compared to patients with a normal ferritin value [14]. Therefore, the excess of iron may have deleterious effects, including the suppression of erythropoiesis, and reducing iron overload may provide benefit, including inhibition of tumor cell proliferation and metastasis, induction of tumor cell differentiation and programmed cell death in preclinical models, and reduction in malignancy in clinical studies. Other clinical studies supported the adverse effect of iron overload on survival. The Japanese group reported the impact of iron overload and of chelation therapy in 152 patients with transfusion-dependent MDS. The ferritin was over 1,000 ng/mL in 37 out of 38 patients who died, being over 5,000 in 24 subjects, suggesting that iron overload may have contributed to mortality [15]. A retrospective US database was analyzed for complications potentially attributable to iron overload in MDS patients, such as cardiomyopathy/congestive heart failure, conduction/rhythm disorders, diabetes, and liver disease, and identified a higher frequency of events in patients who received transfusions than in those who did not [16]. Finally, in an analysis of 2,994 MDS patients, both transfusion dependence and iron overload had a negative impact on OS and on leukemia-free survival (LFS): 835 patients were transfusion dependent at diagnosis, 526 became dependent during follow-up, and 880 were non-dependent. Median OS was 19, 60, and 96 months, respectively. A multivariate analysis of 902 patients from this study showed that iron overload and transfusion dependence added significant prognostic information on OS to the IPSS and WPSS scores and, moreover, on the risk of acute leukemia (AML) transformation [17]. Not all studies were in agreement with the impact of transfusion dependence and iron overload on clinical outcome in MDS patients. A retrospective review of 126 patients with refractory anemia with ringed sideroblasts (RARS) found that while RBC transfusion requirement at diagnosis predicted survival, the number of RBC units transfused and ferritin level did not [18]. Furthermore, the role of iron chelation therapy on survival was examined by two retrospective studies in MDS patients. Leicht et al. reviewed the Vancouver experience and reported on 178 MDS patients [19]: patients received deferoxamine by subcutaneous infusion via portable pump, at least 12 h per day, at least 5 days per week. Sixty-seven percent of patients were transfusion dependent, and only 18 received chelation therapy for a median of 21.6 months. Chelation therapy allowed the change of median ferritin level from 4,215 μg/L to 2,659 μg/L post-therapy. A multivariate analysis showed that predictive factors for OS were the IPSS score and chelation therapy. For patients stratified as low- or intermediate-1 IPSS risk, the 4-year OS was 64 % in patients receiving chelation therapy and 43 % in non-chelated patients. The Groupe Francophone des Myelodysplasies reported in a retrospective study the effect of chelation therapy on survival, which appeared to be dose related [20]. In 170 MDS patients, 59 % were classified as low risk and 115 patients were treated with chelation therapy. Nineteen patients received deferoxamine by intermittent bolus (defined as low chelation), while 57 patients received deferoxamine by infusion ≥3 days per week, or deferiprone, deferasirox, or a combination of agents (defined as standard chelation). The results of this study showed that median OS...
was 115 and 51 months in chelated versus non-chelated patients, respectively. Median OS was 120 and 69 months in the standard and low-chelation groups, respectively. These two studies were limited by the retrospective nature of the analysis, even if in both instances a survival benefit was reported for low-risk patients; due to these reasons, some physicians highlighted the need of controlled and prospective clinical trials to justify the prescription of the drug in this subset of patients.

**Deferasirox in MDS patients: review of clinical trials and single institution experiences**

Phase II prospective and pivotal trial evaluated the efficacy of deferasirox in 184 regularly transfused patients, including 47 MDS patients [21]. Deferasirox was administered once daily as a suspension in water, 30 min before breakfast, for 1 year. A dosing algorithm was used and patients with baseline liver iron concentration (LIC) of 2–3, >3–7, >7–14, and >14 mg Fe/g dry weight were assigned to deferasirox doses of 5, 10, 20, and 30 mg/kg/day, respectively. The primary endpoint of this trial was the binary success criterion defined by maintenance or reduction of LIC based on patients’ baseline value. For patients with baseline LIC of 2 to <10 mg Fe/g dry weight, success was defined as a LIC after 1 year of 1 to <7 mg Fe/g dry weight (failure was <1 or ≥7 mg Fe/g dry weight). For patients with baseline LIC of ≥10 mg Fe/g dry weight, success was defined as a decrease in LIC after 1 year of ≥3 mg Fe/g dry weight (failure as decrease in LIC <3 mg Fe/g dry weight). Secondary endpoints included evaluation of the change in LIC and serum ferritin levels over time. MDS patients enrolled were older than in the other disease groups, and for this subset LIC evaluation at baseline was 46.8 %. The overall success rate was 50.5 % and 78.6 % in MDS patients enrolled, being the higher value. The differences in LIC changes were consistent with mean transfusion iron intake and were least in MDS (0.28±0.14 mg/kg/day). Overall, the results of the trial showed that LIC changes were dependent on dose and transfusion iron intake, with no statistical differences between disease groups, and that the change in serum ferritin in relation to the change in LIC followed a similar trend for all disease groups treated with the drug. In this trial, MDS patients had the lowest transfusion iron intake, but, however, changes in LIC were most pronounced in this subset as compared to Diamond–Blackfan anemia and paralleled the relative change of serum ferritin. Change in serum ferritin over time correlated with changes in LIC across all disease groups in this trial: this fact supported the use of regular serum ferritin assessment for the monitoring of deferasirox efficacy in MDS patients. Serum ferritin may fluctuate in response to abnormal liver function and inflammation and in iron overload conditions; magnetic resonance imaging (MRI) is the most used technique to evaluate LIC estimation. In MDS patients, serum ferritin measurement is widely used and MRI study showed that cardiac function remained normal even with hepatic iron loading [22]. In real-life clinical practice for MDS patients, serum ferritin monitoring is the best tool to assess deferasirox efficacy. Metzgeroth et al. [23] reported a study in which 20 patients with MDS were enrolled to demonstrate the safety and efficacy of the drug in transfusion-dependent patients. The efficacy of deferasirox was monitored by changes in serum ferritin, bone marrow iron, and LIC, as determined by T2*-weighted magnetic resonance imaging. Deferasirox was administered in a once-daily dose of 20–30 mg/kg for 12 months: the drug was effective in reducing median ferritin concentration from 1,515 μg/L to 413 μg/L, but with an increased value in the first 4 weeks of treatment in eight of 12 patients. The median LIC declined from baseline value of 315 to 230 μmol/g at the end of the study. Wimazal et al. [24] reported on 14 MDS patients who were treated with deferasirox (500–1,500 mg daily) for up to 24 months. In these patients, treatment responses were recorded by determining serum ferritin levels before and during therapy. In all patients except one, ferritin levels decreased during therapy. Four patients showed a complete response, one a minor response and five a stable iron overload. In the responding patients, initially elevated liver enzymes decreased substantially.

Gattermann et al. [25] reported on the results of the prospective EPIC trial that enrolled 341 MDS patients out of 1,744 patients. Median age was 67.9 years with male and older age prevalence. Although the median iron burden was >2,500 ng/mL, about 50 % of the patients were chelation naïve. Overall, 175 patients completed 1 year of treatment and of 166 patients who discontinued, 44 (12.9 %) discontinued due to adverse events, 33 due to consent withdrawn, and 26 due to death considered not related to the drug. The majority of patients started with 20 mg/kg/day and the dose was adjusted in 200 patients. Increased dose was used in 50 patients, whereas a reduction of the dose was recorded in 71 patients and a temporary interruption in 88 patients, prevalently due to laboratory abnormalities or side effects. The overall mean average actual dose during treatment was 19.2 mg/kg/day. Median baseline serum ferritin levels were 2,730 ng/mL in the overall population, 2,716 ng/mL in chelation-naïve, and 2,764 ng/mL in previously chelated patients. Serum ferritin level decreased significantly from baseline after 1 year of treatment with a median reduction of 606 ng/mL. Patients with lowest mean iron intake were able to achieve significant median reduction of serum ferritin level. Decreased serum ferritin was observed both in pre-treated and chelation naïve patients, with a relative median change of 22 % and 35 %, respectively. The results of the trial showed also a significant change in labile iron plasma level (LPI) at
every time point observed. Gattermann and colleagues [26] reported recently the results of the eXtend and eXjange study, a prospective, non-interventional, observational multicentric trial that investigated the use of deferasirox in chelation naïve and pre-treated patients. One hundred and twenty-three naïve patients were enrolled with a median age of 70 years and with a median serum ferritin level of 2,679 ng/mL; 44 pre-treated patients were also enrolled in the trial, with a median age of 69.6 years and a median serum ferritin level of 2,442 ng/mL. Of this latter subset of patients, 37 previously received deferoxamine and 10 deferiprone. At the end of 1 year of the trial, 62 % of naïve and 70.5 % of pre-treated patients were still receiving the drug, and discontinuations due to side effects were reported in 34 % and 61 % of patients, respectively. A significant reduction of serum ferritin level was observed in naïve patients, whereas in those pre-treated a non-significant median ferritin reduction was detected.

Recently, we reported our single institution experience on 40 patients with MDS consecutively treated with deferasirox at the dose of 10–30 mg/kg/day outside clinical trials [27]. Serum ferritin was measured monthly, and safety assessment included monitoring of adverse events during treatment and of liver and renal parameters. Median serum ferritin at baseline was 2,878 ng/mL. Median dose of deferasirox was 1,125 mg/day. At a median follow-up of 12 months of treatment, there was a significant reduction in serum ferritin from baseline, the median value being 1,400 ng/mL (p=0.001). Serum ferritin decrease from baseline at 12 months was observed in both chelation naïve and pre-treated patients, with similar efficacy in median value reduction from 2,670 ng/mL to 1,540 ng/mL (p=0.001) in 15 naïve patients and from 2,460 ng/mL to 1,350 ng/mL in 25 pre-treated patients (p=0.001). Thirty-three patients with starting dose of 20 mg/kg/day were able to achieve a significant reduction of serum ferritin (from a median of 2,700 ng/mL to a median of 1,950 ng/mL, p=0.002); of these, three patients permanently discontinued therapy due to evolution to acute leukemia (two patients) and relapse of another neoplasm (one patient). Four patients (three RA and one RAEB-1) had a reduction of transfusion requirement (from a median of 5 units/month to 1 unit/month) according to IWG 2006 criteria, with mean Hb value increasing from 8.5 g/dL to 10.5 g/dL, and mean Hb improvement being 2 g/dL (p=0.02). No increased toxicity was noted when deferasirox was used concomitantly with azacitidine (eight patients who were intermediate-2 IPSS risk) or lenalidomide (two patients with del(5q)).

List and colleagues [28] described the results of open-label, single-arm, phase III trial conducted at 45 centers throughout the USA and Canada. One hundred and seventy-three out of 176 patients enrolled, received the drug and 53 % completed 1 year of treatment. In these patients, serum ferritin decreased 23 % and 36.5 % in patients who completed 3 years. Results showed that reduction in serum ferritin significantly correlated with ALT improvement. Sixty-eight patients had elevated level of labile plasma iron at baseline, and at week 13 all patients had normalized value. Reasons for discontinuation were adverse events or progression in 43 patients and laboratory abnormal values in 23 patients. Twenty-eight patients died, but none of the deaths were considered related to the drug. The German group reported on the use of deferasirox (mean daily dose 19 mg/kg) in 50 low- or intermediate-1 IPSS risk patients: a significant reduction of ferritin (31 %) and mean LIC was reported after 1 year of treatment. Fifty-two percent of patients did not complete 12 months of treatment due to the onset of adverse events (28 %) or abnormal laboratory values (7 %). Hematological improvement was reported in six patients (11 %) [29].

Both EPIC and US03 trial, the largest studies testing deferasirox in MDS, showed that about 50 % of patients enrolled discontinued the treatment within 1 year of treatment. This may reflect ordinary evolution of MDS (evolution in acute leukemia or more severe dysplasia) or concomitant presence of other diseases in the majority of MDS patients who were aged more than 60 years. Although analyses reported were evaluated in about 50 % of patients, the results were confirmed in other studies reported, even if referred to small series of patients. Not all elderly MDS patients can be candidate to deferasirox treatment at 20 mg/kg as stated in the trials: in our experience, older patients with severe comorbidities started at 10 mg/kg and then if no side effects were recorded, the dose was increased to 20 mg/kg. Patients with severe renal impairment and with creatinine clearance less than 40 mL/min should not be treated with the drug. In our clinical practice, we monitored creatinine value every week during the first month of treatment and adjust the dose of the drug accordingly (Table 1).

### Safety of deferasirox in MDS patients

In a phase II trial enrolling 47 MDS patients, dose was temporarily interrupted in 24 patients (51 %) and adjusted in 28 (59.6 %) due to side effects. Four MDS patients died, but in none of the cases was this considered related to the drug and 14.9 % discontinued due to safety. In the whole series of patients, the most common adverse events with a reported relationship to study drug were transient gastrointestinal events which occurred in 45.6 % of patients, and included abdominal pain, nausea, vomiting, diarrhea, and constipation, as well as skin rash recorded in 8.7 % of patients, whereas a non-progressive increase in serum creatinine was observed in 73 patients [21]. In the report by Metezegeroth et al., the most common adverse events were mild and transient gastrointestinal side effects, skin rash, non-progressive transient increases in serum creatinine and
urine beta2-microglobulin, and a temporary reduction of the creatinine clearance. The renal parameters normalized after end of treatment. No hematologic toxicities were observed [23]. In the EPIC study [25], adverse events were reported in 327 patients (95.9 %), being drug-related in 66 % with the most common being diarrhea, other gastrointestinal symptoms, and skin rash. The majority of events were recorded in patients who took <20 mg/kg/day of drug. Most drug-related side effects were mild to moderate and did not lead to discontinuation, without differences between chelated and naïve patients. Nineteen serious drug-related adverse events were reported in 14 patients, among them a case of pancytopenia considered not related to the drug due to persistence of the event after discontinuation of the drug, and a case of acute renal failure occurred in a patient with other severe comorbidities and concomitant administration of other drugs. Hearing loss and lens opacities were reported uncommonly. Eighty-five patients (48 chelation naïve and 37 previously chelated) had two consecutive serum creatinine increase >33 % above baseline; 34 patients required a dose reduction which led to a normalization in 65 % of the patients. Nine patients had treatment temporarily interrupted and one chelation naïve patient discontinued following a creatinine increase. Three cases of acute renal failure were reported, but only one was considered related to the drug.

Deferasirox treatment was associated to a significant decrease in ALT value after 12 months of treatment, directly correlated to dose administered. A direct correlation was reported between decreased serum ferritin level and improved ALT value in iron-overloaded patients: every decrease of 500 ng/mL of serum ferritin level was associated to a decrease in 21.6 U/L of ALT value [24].

In the eXtend and eXjange study [26], drug-related side effects were reported in 42 naïve patients and 18 pre-chelated MDS patients. The most common adverse events reported were diarrhea, nausea, increased serum creatinine, and rash. Five naïve and two pre-chelated MDS patients experienced a serious adverse event, which included gastrointestinal hemorrhage, myocardial infarction, neutropenia, lens opacity, increased serum creatinine, and acute renal failure. Only one pre-chelated patient experienced an increase of ALT value during treatment. In our experience, interruptions due to toxicity were recorded in 40 % of patients: most common adverse events were diarrhea (five patients, 12.5 %) and skin rash (four patients, 10 %). Seven patients had increased serum creatinine values >33 % above baseline, but there were no progressive increases. In the US trial reported by List et al. [28], the most common side effects described were gastrointestinal (diarrhea, nausea, and vomiting), dyspnea, fatigue, and creatinine increases, and the rate of discontinuation due to side effects was 24.8 %. The rates of renal adverse events were higher in patients with abnormal baseline creatinine value (42 %) than in patients with normal baseline serum creatinine value (31.5 %). Serious adverse events were reported in the same frequency of that reported in other trials that used deferasirox, the most common being pneumonia in 20 patients, followed by febrile neutropenia and pyrexia.

### Management of side effects

A panel of expert suggested practical recommendations in July 2010 to avoid or manage gastrointestinal disturbances, more commonly observed in MDS patients and not related to different dose categories or different age [30]. The exact pathogenetic mechanisms are not fully understood and seem to be not different between naïve and pre-treated patients, but a trend was reported for higher rate of diarrhea and abdominal pain in pre-treated patients. Recommendations to avoid gastrointestinal disturbances include to clearly explain to patients at start of therapy that gastrointestinal side effects could occur, to advise patients to sip water rather than juice together with the drug, to assume drug in the evening (30 min before dinner or 2 h after) rather than in the morning, and that a high-fat food could double the drug exposure. Splitting in two the dose in naïve patients is not recommended due to the pharmacological and compliance concerns. Three algorithms were generated for the management of diarrhea according to the frequency of bowel movements, mild, moderate, and severe. For mild diarrhea, only supportive care was suggested, but physicians were advised to...

### Table 1 Summary of advantages and disadvantages of deferasirox in MDS

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<th>Advantages</th>
<th>Disadvantages</th>
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<td>Reduction of serum ferritin</td>
<td>Gastrointestinal toxicity</td>
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<td>Reduction of LPI and ROS</td>
<td>Renal impairment (limited use in elderly patients with low creatinine clearance)</td>
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<td>Reduction of organ damage</td>
<td>Limited use only in low-risk MDS</td>
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<td>Potential activity on NF-κB</td>
<td>No clear data on the impact of the drug on overall survival</td>
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<td>Hematological improvement</td>
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<td>Improvement of hepatic parameters due to iron overload</td>
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to transfer to the next level of severity if diarrhea was stable or worse after 1 week. In case of moderate event, a reduction of dose to 10 mg/kg/day was suggested together with supportive care, and for severe case it was recommended to discontinue the therapy and to investigate other etiologies and to re-introduce the drug at lower dose with gradual dose escalation after the resolution of the event. The management suggested for abdominal pain and nausea/vomiting included time administration (considering evening dose rather than in the morning), use of concomitant drugs (anti-acidic drugs or anti-emetics), reduction of the dose in case of mild-to-moderate events, or discontinuation in case of severe events, with reintroduction at lower dose after the resolution and gradual dose escalation. The panel agreed not to give prophylactic anti-acidic drugs since this might decrease the absorption of the drug.

Skin rashes could occur in 5 % of patients during treatment, but less than 1 % was reported as severe; etiologies are still unknown. In case of mild-to-moderate rash, it was suggested to continue treatment without dose adjustment, whereas in case of moderate or more severe rash, it was suggested to discontinue treatment and to reintroduce the drug at a lower dose with gradual dose escalation after the resolution. In case of severe rash, the drug should be reintroduced concomitantly with oral steroids [31].

Management of increases of non-progressive serum creatinine level required discontinuation of treatment if the increase is above >33 % of normal value in two consecutive visits and reintroducing the drug at a lower dose with gradual dose escalation. Among several trials, only 10 % of patients required discontinuation of treatment due to increased creatinine level, but more than 70 % of patients resolved spontaneously. A pooled renal analysis was presented in MDS patients, including patients enrolled in different clinical trials, and the results showed that patients with creatinine clearance at baseline less than 60 mL/min did not experience a greater decline in creatinine clearance during follow-up: patients with creatinine clearance 40–60 mL/min could receive the drug with close monitoring. Intermittent proteinuria did not require discontinuation of treatment but monthly monitoring was suggested; renal function tests should be tested in duplicate at baseline and monthly thereafter [31].

Elevations in liver transaminases were reported in 6 % of patients enrolled in different trials, but only 2 % of cases were considered related to the drug. In the EPIC study [25], only 1 % of patients had increased ALT value greater than 10 times the upper limit of normal, but all patients had high ALT value at baseline due to iron overload. Other causes of altered liver function should be considered and liver function tests should be monitored every 2 weeks for the first month and then every month. In case of severe increase, a discontinuation of treatment has been suggested with reintroduction of the drug at lower dose and gradual dose escalation after the resolution or after the causes of increase have been elucidated [25, 31].

Discontinuation of treatment has also been suggested for the occurrence of lens opacity and hearing loss: auditory and ophthalmic tests are needed before the start of treatment and then annually, even if the rates of these events were uncommonly reported and comparable with that reported during deferoxamine treatment [31].

### Hematological improvement due to deferasirox treatment

Some evidences that iron chelation therapy could be correlated with improved hematopoiesis have been reported in the majority of instances in low-risk MDS patients. Impact on transfusion dependence has been reported also in some cases of myelofibrosis and aplastic anemia [32–38]. Jensen et al. [39] first described a reduction of transfusion requirement and improvement of platelet or neutrophil counts that occurred in seven out of 11 patients treated with deferoxamine. In the US03 trial [28], a post hoc analysis was performed to evaluate hematologic response after 1 year according to IWG criteria. Erythroid response was observed in 26 out of 173 enrolled patients (15 %), but three patients were treated concomitantly with other drugs (erythropoietin and lenalidomide). Twenty-two percent of patients achieved platelet response, whereas neutrophil response was observed in 15 % of patients and multilineage response in eight patients. Median time to improvement was reported to be 169 days, without clear differences in terms of LPI modifications between hematologic responders and non-responders. Messa et al. [40] reported four hematologic improvements (three major and one minor) in three MDS patients receiving the drug, one of which was classified as having a high-risk MDS. Some other isolated cases were also reported; one of this, observed by our group as a low-risk patient treated with deferasirox who obtained an erythroid response, lost after the discontinuation of the drug and re-obtained after its reintroduction. Finally, Gattermann and colleagues [41] reported the results of a post hoc analysis evaluating hematologic response in patients enrolled in the EPIC study. Erythroid responses were observed in 21.5 % of patients (53 out of 247 evaluable patients), neutrophil responses in 22 %, and platelet responses in 13 %. As described in the US experience [28], median serum ferritin reductions were greater in patients with hematologic improvements as compared to patients without, whereas no statistical differences were detected in terms of LPI level.
Changes in biological parameters during deferasirox treatment

Excess of iron due to transfusions can cause accumulation of LPI, a toxic form of non-transferrin-bound iron. LPI is absorbed into cells leading to increased labile iron pool (LIP) with rapid creation of reactive oxygen species (ROS). Oxidative stress leads to oxidation of proteins, lipids, and DNA, with increased apoptosis and organ damage. Ghoti and colleagues [42] reported the effects of deferasirox on oxidative parameters in 31 MDS patients. At baseline, all patients showed high levels of ROS and reduced levels of glutathione (GSH). Treatment with deferasirox significantly reduced LIP from 19 to 14 (mean fluorescence channel) in red blood cells, LPI from 0.39 to 0.11, without significant changes in serum ferritin level from baseline to end of study. The same group reported modifications of hepcidin level during deferasirox treatment: 19 MDS patients were studied and the results showed that 17/19 patients had higher hepcidin value at baseline (mean 545 ng/mL) [43]. During treatment with the drug, the mean hepcidin level increased gradually with time and reached 811 ng/mL. The authors suggested that deferasirox could reduce parenchymal iron overload not only directly but also indirectly through elevation of hepcidin level, which leads to inhibition of intestinal iron absorption and iron mobilization from the reticuloendothelial system to the parenchymal cells. It has also been reported that deferasirox is a powerful NF-kB inhibitor, both in MDS and AML cell lines, independently from the efficacy on iron chelation therapy: 40 MDS peripheral blood samples and two leukemia cell lines (HL60 and K562) were evaluated after incubation with deferasirox and other iron chelator and subsequently tested for NF-kB activity and p65 localization. Only deferasirox was able to reduce NF-kB activity as compared to other drugs, independently from the presence or absence of iron overload. This latter data was tested by the addition of ferric hydroxyquinoline that did not increase the activity of deferasirox, suggesting that the mechanism of action is independent from iron deprivation by chelation. NF-kB inhibition should be the pathogenic mechanism responsible for hematologic improvements observed with the drug [44]. No data were published about the use of deferasirox in high-risk MDS: the potential mechanisms of action of the drug (activity on NF-kB) and the strong reduction of LPI and ROS should be of benefit in this subset of patients (Table 1). Specific trials with deferasirox in this contest, as single agent or in association, are needed.

Conclusions

Supportive care for MDS patients includes transfusion administration, but physicians less frequently recognize management of iron overload associated with this treatment as a part of therapy. In recent years, understanding of biological consequences of iron overload in MDS patients has indicated that iron chelation therapy should be promptly started as essential treatment. Retrospective analyses indicated an impact by iron overload on outcome of MDS patients and suggested that iron chelation therapy could improve overall survival. Deferasirox, with its manageable safety profile and its confirmed efficacy, is a valid option for MDS patients with iron overload. Further prospective trials are needed to definitely ascertain if the drug, as a single agent, has an impact on survival.

Conflict of interest The authors declare that they have no conflict of interest.

References


