Changes in parameters of oxidative stress and free iron biomarkers during treatment with deferasirox in iron-overloaded patients with myelodysplastic syndromes

Approximately 60-80% of patients with myelodysplastic syndromes (MDS) present with symptomatic anemia and, of these, 80-90% will require red blood cell (RBC) transfusions as supportive therapy.[1,2] Excess transfusional iron causes accumulation of labile plasma iron (LPI), the pathological form of non-transferrin-bound iron. Labile plasma iron is redox active and is rapidly taken up by cells, leading to a rise in the labile iron pool (LIP)[3,4] and catalyzing generation of reactive oxygen species (ROS).[5] The ensuing oxidative stress[6] and associated decrease in antioxidants such as reduced glutathione (GSH) cause oxidation of lipids, proteins and DNA, cell death and organ damage. Iron overload has thus been shown to affect morbidity and mortality in transfusion-dependent myelodysplastic syndrome patients.[7]

Here we report results from a 3-month, single-arm, open-label trial conducted at five centers in Israel. The effects of deferasirox (Exjade®), a once-daily oral iron chelator, on parameters of oxidative stress, chelatable labile iron pool, labile plasma iron and serum ferritin levels, were assessed in 31 male and female myelodysplastic syndrome patients aged 18 years or over with an International Prognostic Scoring System (IPSS) score of Low or Intermediate-1 risk, who had received 20 units or more of packed red blood cells, and had evidence of iron overload (serum ferritin >1,000 ng/mL). Oxidative stress parameters were measured every 3-4 weeks in red blood cells, platelets and polymorphonuclear leukocytes (PMN) as previously described.[8] Creatinine analysis was performed in all patients weekly for the first month.

Nineteen patients completed the study (Table 1); there were 12 withdrawals due to adverse events (n=4; 36%), death (n=2; 18%), transformation to high-grade MDS (n=1; 9%), eligibility criteria (n=1; 9%), withdrawal of consent (n=1; 9%) and unspecified reasons (n=3; 27%).

The baseline characteristics demonstrate high levels of oxidative stress and iron overload in these transfused patients with myelodysplastic syndromes; levels of reactive oxygen species were higher than the normal range while levels of the antioxidant reduced glutathione were lower than normal. These results confirm our previous study, which also showed increased oxidative stress in patients with myelodysplastic syndromes.[9]

Sixteen patients received daily deferasirox 20 mg/kg/day for three months, while the dose was lowered to 4-6 mg/kg/day after one month in 3 patients in response to adverse events (mainly gastrointestinal, increased creatinine and rash). Sixteen patients were treated for 82-105 days, 2 patients for 112 and 120 days, respectively, and one patient for 38 days. The mean duration of treatment with deferasirox was 91±16 (range 38-120) days. The treatment resulted in significant reductions in cellular markers of oxidative stress (Figure 1) demonstrating the benefits of short-term iron chelation in patients with myelodysplastic syndromes.

Baseline levels of labile iron pool and serum ferritin indicated that these patients were iron overloaded. Treatment with deferasirox for three months significantly reduced the levels of intra- and extra-cellular free iron species. Geometric mean levels of labile iron pool decreased from 19 (95% confidence interval (CI) 17-25) to 14 (12-19) mean fluorescence channel (MFC; P=0.002) in red blood cells, and from 22 (19-31) to 18 (15-27) MFC (P<0.02) in platelets. Deferasirox also significantly decreased mean labile plasma iron ± SD from 0.39±0.43 to 0.11 ± 0.45 μM (n=16; P=0.02; normal levels ≤0.4 μM). A similar decrease in labile plasma iron in deferasirox-treated patients with myelodysplastic syndromes was previously reported by List *et al.*[10] In our study, there were no significant changes in serum ferritin or transferrin saturation from baseline to end of study (geometric means). This may be because treatment duration was not long enough or it may indicate that the dose of deferasirox was not optimal.

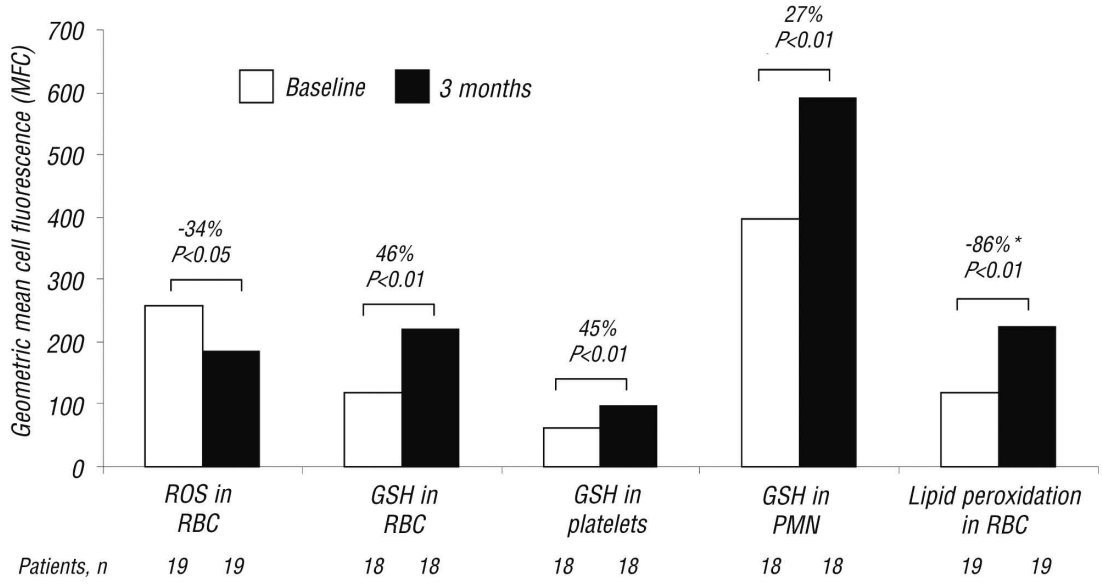
Ten of 19 (53%) patients who completed the study experienced an adverse event, all in the first month of treatment; 7 patients (37%) reported more than one adverse event. A total of 22 adverse events were reported: 6 (27%) infections (n=4 Grade 1, n=2 Grade 2); 7 (32%) gastrointestinal (n=6 Grade 1, n=1 Grade 2); 3 (14%) bone pain (one Grade 1, one Grade 2, and one unknown); 5 (23%) skin rash and dyspnea (n=3 Grade 1, one Grade 2 and one unknown); and one (5%) impaired kidney function (Grade 1).

In conclusion, these data highlight the potential of short-term iron chelation therapy to act as an antioxidant by decreasing intra- and extra-cellular toxic iron species and consequently oxidative stress. In the absence

Table 1. Baseline characteristics.

Patients who underwent full evaluation, n	19
Mean age (95% CI), years	68 (62-75)
Male:female, n	7:12
IPSS risk group, n	
Low	8 (42)
Intermediate-1	11 (58)
Mean interval from diagnosis to initiation of treatment ± SD (range), years	4±2 (3.3-5.5)
Geometric mean RBC transfusions (95% CI), n	45.6 (32-87)
Oxidative stress parameters	
Geometric mean ROS in RBC (95% CI), MFC	256 (234-434)
*Geometric mean GSH in RBC (95% CI), MFC	116 (95-183)
*Geometric mean GSH in platelets (95% CI), MFC	61 (54-71)
*Geometric mean GSH in PMN (95% CI), MFC	397 (344-549)
Geometric mean lipid peroxidation in RBC (95% CI), MFC	117 (90-221)
Iron overload parameters	
Geometric mean LIP in RBC (95% CI), MFC	19 (17-25)
Geometric mean LIP in platelets (95% CI), MFC	22 (19-31)
†Geometric mean LPI (95% CI), μM	0.39 (0.15-0.62)
Geometric mean serum ferritin level (95% CI), ng/mL	1,558 (1,972-3,574)
Geometric mean serum transferrin saturation, (95% CI) %	70 (64-109)

n=18; †n=16; CI: confidence interval; MFC: mean fluorescence channel.



*Cell fluorescence is proportional to ROS and GSH but inversely proportional to lipid peroxidation

Figure 1. Dynamic changes in oxidative stress parameters in RBC, platelets and PMN, at baseline and after a mean of three months of deferasirox therapy.

of conclusive prospective data, the value of iron chelation therapy for improving long-term survival of patients with myelodysplastic syndromes is still unknown.[11,12] Additional clinical studies are required to fully understand the mechanisms behind the changes in the studied parameters and to evaluate their correlation with long-term morbidity, mortality and quality of life.

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