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Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by ineffective hematopoiesis, cytopenia, and risk of evolution into Acute Myeloid Leukemia (AML). It was shown that anemia strongly impacts on the quality of life of patients with MDS. Red blood cell (RBC) transfusion represents the main supportive care for patients with chronic anemia including MDS, aplastic anemia (AA), and myelofibrosis (PMF). One of the most dangerous side effects of RBC transfusions is represented by iron overload (IOL). The deleterious impact of IOL has been largely demonstrated in patients affected by B-thalassemia but more recent evidences, mainly coming from retrospective studies, show that, even in MDS, IOL might have a negative impact on life expectancy and probably on transfusion requirement [1]. Adequate iron chelation therapy for at least six months improves survival in transfusion-dependent patients with lower risk myelodysplastic syndromes.

Many iron chelators have been developed over the years to reduce the iron burden mainly in patients with β-thalassemia. More recently, the development of the oral iron chelator deferasirox (DFX) focused the attention on the IOL damage even in patients with MDS. Derefasirox has been shown in prospective studies to be effective in reducing iron overload in patients with MDS with an acceptable toxic profile and good tolerability [2, 3].

Among the benefits of iron chelation, the hematological improvement and transfusion independence sporadically reported in patients treated with iron chelation is of particular interest [4, 5].

Prospective data obtained in a significant cohort of patients affected by MDS enrolled in the EPIC study and treated with deferasirox reported a percentage of 22.6% of erythroid responses [2]. However, there are limited data available outside of clinical trials in unselected patient.

Before the approval of deferasirox, deferoxamine (DFO) was the only iron chelator approved for the treatment of transfusion-dependent iron overload. At that time, very few patients with MDS received DFO, a cumbersome drug especially for elderly patients. With the introduction of deferasirox in the clinical practice, a significant number of MDS patients started iron chelation according to national and international guidelines.

The present study is a “real-life” picture of erythroid responses in a large cohort of chronic anemia with iron overload consecutively treated with iron chalation therapy (ICT), either with DFX or with DFO, in six Italian hematological centers from 1993 to 2011. Starting from a cohort of 156 patients with chronic anemia and IOL treated with iron chelation, 98 patients were finally included in the study. Forty-six patients were excluded because they received ICT for less than 3 months with a drop out rate of 29%, 10 were excluded because they received additional therapies able to modify the erythroid response and two were excluded due to the absence of the basal serum ferritin level. Among the 98 patients included, 65 were male and 33 female. The median age was 72 years. The final cohort included: 69 MDS, four chronic myelomonocytic leukemia (CMML), 15 myelofibrosis (PMF), two AML, and eight aplastic anemia (AA). Among MDS, two were 5q- syndrome, 25 refractory anemia (RA), 20 refractory anemia with sideroblasts (RARS), four unclassified MDS (MDS-U), nine refractory cytopenia with multilineage dysplasia (RCMD), five refractory anemia with excess of blasts (RAEB I), and four refractory anemia with excess of blasts (RAEB II). Fifty-six were low or intermediate I IPSS risk and 13 were intermediate II or high risk.

Thirty patients received deferoxamine and 68 deferasirox. The median dose of deferoxamine was 30 mg/kg and the median dose of deferasirox was 15 mg/kg. The median serum ferritin level at the time of ICT was 2530 ng/ml and it was not significantly different between the two cohorts (p = .8). The median transfusion requirement was 3.2 RBC units/month. Patients, at the time of ICT, had transfused a median of 30 RBC units. Hematological response (HR) was evaluated according to IWG criteria [6] as follows: achieving a RBC transfusion independency (complete HR) or hematological Improvement erythroid (HI-e) for patients showing a hemoglobin (Hb) increase of 1.5 g/dL or a reduction of 4 RBC transfusions/8 weeks.

Forty-one patients out of 98 (41.8%) evaluable patients achieved a hematologic response (Figure 1, panels A and B). In details, 18 (18.3%) became completely RBC transfusion independent, six were under DFO treatment, and 12 under DFX. The median time to response, evaluated only in patients achieving complete transfusion independence, was 15 months for DFO and 3 months for DFX. Sixteen patients (16.3%) obtained HI-e defined as a reduction of 4 U/8 weeks (five in DFO and 11 in DFX cohorts) after a median of 6 months for both DFO and DFX. HI-e defined as an increased of 1.5 g/dL was observed in seven patients (7.1%) after a median of 6 months for DFO and three for DFX. Interestingly, the hematologic improvement is not strictly related to an effective reduction of serum ferritin (p = .4).

Curiously, the four AA patients who achieved independency from RBC transfusions significantly increased the number of platelets and become platelet transfusion independent (median value of platelets: 17,000/mm3 before ICT and 35,000/mm3 and 55,000/mm3 after 6 and 12 months of ICT, respectively).

Finally, for 68 patients, a long-term follow up was available (32 responder patients and 36 non-responder patients). The follow-up of the remaining 30 patients is not available because six patients underwent hematopoietic stem cell transplantation, 12 patients died, 12 were lost at follow-up because they were followed in home day care. The median follow up for responder patients was 18 months from the achievement of the hematological response and 21 months from iron chelation for non-responder patients. After 12 months, 40.6% of the patients (13 out of 32) maintained the hematological improvement (Figure 1, panels C and D). The duration of response is longer for patients treated with DFO compared with DFX. The molecular basis of erythroid response is still too obscure to allow an explanation of this observation. What is becoming more and more evident is that the two drugs acts with different mechanisms. One example is represented by our previous study which demonstrated that DFX but not DFO acts as a potent NF-kB inhibitor [7]. The present study suggests that the hematological improvement observed during DFX treatment is probably not strictly related to an efficient iron removal since it occurs early during ICT when the serum ferritin is often still high. By contrast, the effect of DFO seems to parallel the iron chelation. This can be only speculated by the data provided and not definitively proved. To address this point, further studies are required.

Our data show a high rate of complete responses, mainly in AA and RARS but also in high-risk MDS/AML representing 11% of those achieving complete transfusion independency. Notably 50% of AA achieved RBC and platelet transfusion independency. Despite the limitation due to the retrospective collection of data, we suggest the ICT could result in hematologic improvement in a wide population including patients who are, at present, outside the published ICT guidelines. This study warrants further investigation on the mechanism of action of ICT in inducing hematological improvement.

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Potential conflict of interest
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Figures

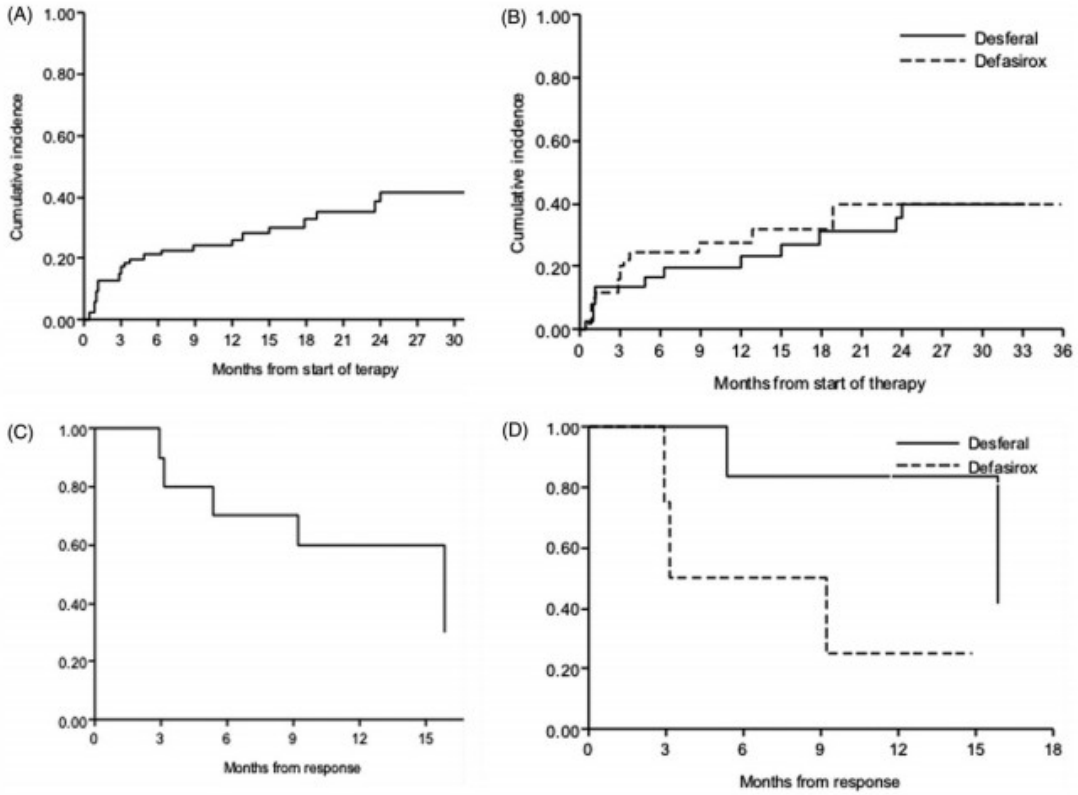

Figure 1.
Panel A: cumulative incidence of erythroid response in the entire cohort of patients and (panel B) in the same cohort divided accordingly to the treatment the patients received. DFX: deferasirox; DFO: deferoxamine. Panel C: duration of erythroid response during ICT in the entire cohort of patients and (panel D) in the same cohorts of patients according to the treatment the patients received. DFX: deferasirox; DFO: deferoxamine.