# Using Iron Chelators - deferasirox in the Treatment of Hypersiderosis

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*Hemosiderosis is a condition characterized by a pathological increase of iron levels in the body. One of the main etiologies of hemosiderosis is represented by massive transfusions of packed red blood cells, as it happens in major beta-thalassemia or in myelodysplastic syndromes, haematological disorders evolving with low values of haemoglobin which require transfusion frequently. Hypersideremia therapy consists of the administration of iron chelators. Deferasirox is a next generation iron chelator, which is administered to multiple transfused patients. It is used to prevent iron storage in deposits by increasing its excretion rate.The purpose of this paper is to highlight the role of the treatment with iron chelators, respectively Deferasirox in preventing the onset of hemosiderosis and its complications. We also intend to analyze aspects of the chemical and pharmacological profile of Deferasirox. We present the case of a 27 year-old man diagnosed with myelodysplastic syndrome of the refractory anemia type, in which increased transfusion treatment imposed by the severely low hemoglobin values, led to the risk of secondary hemosiderosis installation. We intend to emphasize the beneficial effect of iron chelators therapy, which prevents the installation of hypersideremia complications, reduces the transfusion requirements and improves patient's quality of life.*

*Keywords: iron, toxicity, deferasirox, hypersideremia*

Myelodysplastic syndromes are clonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis (variable cytopenias in peripheral blood, bone marrow in contrast with normo-/hypocellular hematopoietic marrow) that is associated to an increased risk of transformation into acute leukemia [1-3]. This type of pathology occurs, usually in elderly subjects (mean age 60-75 years); only 8-10% of adults with SMD are aged <50 years. In the past 20 years there has been an increased incidence of the disease, currently estimated at 3-15 cases/ 100,000 inhabitants/year in people aged between 50-70 years and 15-50 cases/100,000 inhabitants/year in people over 70 years [4]. In most cases, the etiology remains unknown (SMD *de novo*), but in 20% of patients the disease occurs as a result of exposure to medicinal or industrial toxics [5]. Exposure to benzene and derivatives was clearly correlated with the occurrence of myelodysplastic syndromes and acute leukemias preceded by myelodysplastic syndromes. Less conclusive data are available for exposure to insecticides, pesticides or smoking [5, 6].

Myelodysplasia, in essence, is the result of a pathological transformation of a normal myeloid stem cell. The transition from this to the dysplastic cell occurs as a result of successive events that confer the resulting cell an increased proliferative capacity. The end result of the transformation is an inefficient clonal hematopoiesis, the process being regulated by gene mutations [7-9]. Studies of bone marrow in patients with myelodysplastic syndrome have noted an increased turnover of bone marrow cell. The dramatic increase in the rate of marrow cell division contrasts starkly with peripheral cytopenias, which suggested the existence of an increased apoptosis; this has been documented in the CD34 + bone marrow cells [10, 11]. The impairment of the cellular function is another element of myelodysplasia. Erythrocyte precursors have a decreased response to erythropoietin, which contributes to anemia. In addition, the differentiated terminal cells of myelodysplastic syndrome have functional alterations. Mature granulocytes have a decreased myeloperoxidase activity, and platelet have the aggregation function affected [1, 12]. Cytogenetic studies revealed structural and numerical chromosomal abnormalities the study of which could clarify the pathogenic mechanism.

## Experimental part

### *Material and method*

We present the case of a patient S.V. aged 27 years, male, from the countryside coming to the Department of Hematology of University Hospital Sf. Spiridon Iasi, Romania in September 2012 accusing bleeding phenomena, bruising and petechiae disseminated in the upper and lower limbs, gums bleeding, anterior epistaxis, marked asthenia, fatigue, dyspnea at small efforts, tachycardia, pronounced symptomatology three days prior to the presentation. The objective clinical examination revealed an overall influenced condition of the patient with cold sweats, sclera-tegumentary paleness, ecchymotic syndrome at the level of bilateral upper and lower limbs, hepatomegaly, splenomegaly grade II. Anamnesis showed no significant collateral family history and medical history noted the presence of chronic hepatitis with C positive virus. In order to establish the certainty diagnosis biological, cytogenetic and imaging investigations were performed.

Initially, blood samples were collected. Hematological examination revealed severe pancytopenia (Hb = 5g% of Macrocytic type, Leukocytes = 970/mmc, Platelets = 11.000/mmc). Peripheral blood smear revealed erythrocyte anisocytosis and macrocytosis, very rare leukocytes, neutrophils with hipo-granulations, platelets on smear absence. Biochemistry revealed hypersideremia (Fe = 214 micrograms/dL, ferritin = 1181 ng/mL), elevated values of LDH (LDH = 300 U/L), and liver and kidney samples within normal limits. Bone marrow puncture was

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conducted, which highlighted dysplastic elements on all cell series, advocating for the diagnosis of myelodysplastic syndrome (erythroid series with erytroblastoid changes, granulocytic series with dysgranulopoietic changes, with granulocytes with hypo-segmented core, megakaryocytic series with dysmegakaryopoetic changes, with large megakaryocytes with separated nuclei, and Pearls staining revealed the presence of macrophages with granular iron); later the appearance of osteo-medullary biopsy raised the same suspicion of diagnosis, highlighting the presence of an increased number of megakaryocytes with dysplastic morphology and the marked increase of reticulin fibers, with the change of normal bone marrow architecture (fibrosis grade III). Also, a series of investigations for the exclusion of pathologies with similar development were conducted, such as those evolving with ineffective hematopoiesis, with myelofibrosis or secondary changes in the bone marrow. Imaging tests (abdominal ultrasound, upper gastrointestinal endoscopy) denied the presence of portal hypertension and secondary hypersplenism syndrome that could occur in the evolution of chronic hepatitis C positive virus and would lead to a similar appearance of blood picture.

Thus, after clinical, laboratory and imaging investigations performed which excluded a secondary etiology, the correct diagnosis was: myelodysplastic syndrome refractory anemia type, severe secondary pancytopenia, cutaneous-mucous bleeding syndrome, chronic hepatitis with C positive virus-inactive. Subsequently, a series of investigations were conducted in order to assess therapeutic response: chromosome analysis, the dosage of erythropoietin, HLA-DR tipization, cardiac echocardiography. Chromosome analysis did not identify numerical or structural chromosomal abnormalities; the level of serum erythropoietin was normal, echocardiography revealed cardiac parameters in correct limits, and in the HLA-DR tipization, allele HLA-DR 15 was not found, which indicated a poor response to administration of anti-thymocyte globulin or cyclosporine A. Based on the outcome of these investigations the adequate therapeutic attitude was established.

## Results and discussions

The main therapeutic objectives of this case targeted anemic syndrome rebalancing, cutaneous-mucosal bleeding syndrome reduction and eradication of malignant clone. The hematopoietic progenitor cell transplantation is the only potentially curative treatment, representing the indication of choice in young patients, but the lack of a suitable donor has prevented the achievement of this aim.

Chemotherapy and that with differentiators could not be administered due to severe cytopenias. In addition, immunosuppressive therapy was not an option because the patient was HLA-DR 15, and the therapeutic response was weak at the administration of anti-thymocite globulin or cyclosporine A. In these conditions, supportive therapy remained the mainstay of treatment. For severely anemic syndrome, the patient received transfusions with erythrocyte mass- initially 4-5 units at 4 weeks and after 4 months, 1-2 units at 6 weeks; between transfusion treatments he received treatment with growth factors on erythrocyte series. For severe thrombocytopenia, he received treatment with platelet concentrate transfusion and for neutropenia he was administered broad-spectrum antibiotics in case of thermal ascents, and subsequently with granulocyte growth factors. Considering the severe anemia syndrome, the patient presented increased transfusion requirements, resulting in the installation of hypersideremia and elevated serum ferritin values: Fe = 214 micrograms/dL, Ferritin = 1782 ng/mL (at diagnosis), with progressive increase in the values thereof. To combat secondary effects, the patient received treatment with iron chelators – Deferasirox - 1500mg/day with serum ferritin values tracking. Surveillance of iron therapy load was performed monthly, so that after four months of treatment ferritin values were reduced to 1000 ng/mL and transfusion requirements were reduced by 2 units of erythrocyte mass per month. In addition, the other cell lines evolution was favourable, with the reduction of the cutaneous-mucous bleeding syndrome treated with platelet concentrate and of severe neutropenia at the administration of growth factor on the granulocyte line. Patient prognosis remains reserved due to severe peripheral cytopenias and severe dysplasia at the level of myelography and reticulin fibrosis (grade III).

This case shows the importance of using Deferasirox in combating hypersideremia in a patient with increased transfusion requirements.

Chemically, Deferasirox belongs to the class of iron chelating agents [13]. It is known under the name of 4-[bis (2-hydroxyphenyl) -1H-1,2,4-triazol-1-yl] benzoic acid (fig. 1).

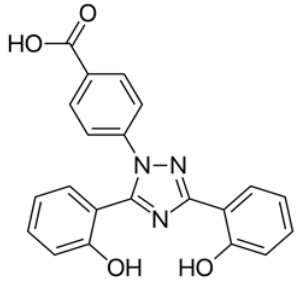


Fig. 1. The chemical structure of 4- [bis (2-hydroxy-phenyl) -1H-1,2,4-triazol-1-yl] benzoic acid (Deferasirox)

Deferasirox is synthesized from salicylic acid and thionyl chloride. The resulting product condensates with salicylamide under dehydrating conditions a reaction which results in 2- (2-hydroxyphenyl) -1,3 (4H) benzoxazin-4-one. This intermediate is isolated and reacts with 4-hydrazinobenzoic acid in the presence of a base forming -[bis (2-hydroxyphenyl)-1H-1,2,4-triazol-1-yl] benzoic acid (Deferasirox) [14]. The synthesis reaction of Deferasirox is shown in figure 2.

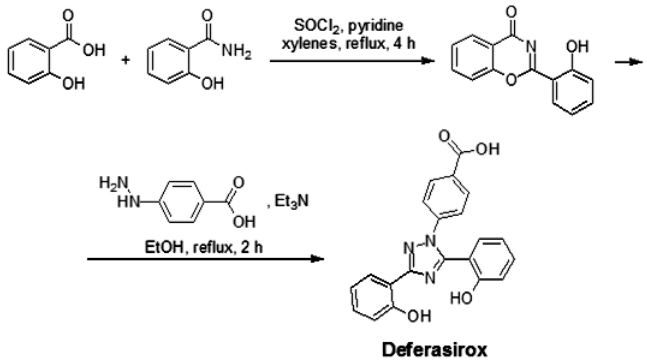


Fig. 2. The synthesis reaction of Deferasirox

It appears in the form of crystals in ethanol or yellowish-white powder. It is insoluble in water, slightly soluble in alcohol, oil-soluble and soluble in polar solvents such as DMF. Although it is insoluble in water, it has a high pH-dependent solubility. At a *p*H =6.8 it remains insoluble, until the buffer resistance is modified in order to obtain the optimum dissolution profile. It is relatively stable in the presence of acids and bases. It melts at 116-117ºC. It has a molecular weight M = 373.362 g/mol and molecular formula $C_{21}H_{15}N_3O_4$.

Deferasirox belongs to the class of trident iron chelators. It is recommended in the therapy of hypersideremia secondary to repeated blood transfusions in patients with major beta-thalassemia or myelodysplasia [15-17]. It works by incorporating iron in deposits in soluble, stable complexes, which will be eliminated by faecal excretion. It is administered orally in the form of dispersible tablets containing 125 mg, 250 mg or 500 mg of active substance (Deferasirox) [18]. Due to insolubility in aqueous medium, it has a poor solubility and low bioavailability. Many strategies have been implemented with the aim of creating new pharmaceuticals to improve the solubility and bioavailability limit of Deferasirox. Dedimeric conjugation method was used, the ionizable salt formation, the use of co-solvents or co-cyclodextrin complexation. Methods for solubilization to improve absorption of the drug are still expected [19-21].

The half-life is 8-16 h in case of the administration of a single dose per day. Two molecules of Deferasirox are able to engage 1 atom of iron, complex which will then be removed through faecal excretion. Due to oral bioavailability and long half-life, it is superior to desferrioxamine, oral inactive substance with short half-time [22-24].

Concomitant use with cholestyramine decreases absorption of Deferasirox. Also, the combination with enzyme inducers such as rifampicin, phenytoin, phenobarbital or aluminum-containing antacid preparations should be avoided.

## Conclusions

This paper emphasizes the importance of using Deferasirox in the therapy of hypersideremia secondary to repeated transfusions in patients with myelodysplastic syndrome. Based on the study of the chemical and pharmacological profile of this pharmaceutical substance significant data on pharmacodynamics, dosage and therapeutic efficacy of Deferasirox were obtained. By means of the correlation of this information with the clinical and laboratory data of the patient presented we highlight the importance of administering iron chelating agents of the tridentate triazole class in the therapy of hypersideremia.

The myelodysplastic syndrome records an increase of the incidence of the disease - requiring an awareness of this diagnosis in young people as well. It has increased morbidity and mortality due to complications secondary to severe peripheral cytopenias, and iron overload due to increased transfusion requirements. Thus, the treatment protocol includes supervising the loading of the iron and using the chelator treatment with Deferasirox in case of value of serum ferritin of over 1000 ng / ml. Chelation therapy – prevents hypersideremia complications, reduces transfusion requirements and improves patient's quality of life.

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