



Iron Chelation Therapy in Patients with Myelodysplastic Syndromes: Consensus Conference Guidelines

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The myelodysplastic syndromes are a group of clonal stem cell disorders, characterized by ineffective hematopoiesis, abnormal differentiation and maturation, qualitative hematopoietic cellular defects, peripheral cytopenias, and high incidence of leukemic transformation [1]. More than 90% of MDS patients have anemia, and many of them are symptomatic enough to require treatment [1,2]. Although, the introduction of recombinant human erythropoietin [3], and more recently thalidomide [4] and lenalidomide [5], have improved our therapeutic armamentarium for symptomatic anemia in MDS, red blood cell transfusion remains the gold standard therapy for most of these patients. From lessons we have learned while treating patients with thalassemia [6], and more recently with MDS patients [7,8], it is becoming clear that multiple blood transfusions – although correcting the hemoglobin and hematocrit, reducing blood transfusion requirements and improving quality of life – lead to iron accumulation and iron overload, eventually causing organ damage, especially in the heart, liver and endocrine glands [9,10]. However, most of the data were obtained from patients with thalassemia, who are younger than the MDS patients. Therefore, the consequences of iron overload might be somewhat different.

A unit of packed RBC contains 250–300 mg iron. The iron assimilated by a single transfusion of two units of packed RBC is thus equal to a 1 to 2 year intake of iron. Iron accumulates in chronically transfused patients because the human body lacks an effective mechanism for increased iron excretion [11].

As iron loading progresses, the capacity of serum transferrin, the main transport protein of iron, to bind and detoxify iron may

be exceeded. Consequently, the non-transferrin-bound fraction of iron and labile plasma iron within the plasma, which can be measured, may lead to the generation of free hydroxyl radicals, propagators of oxygen-related damage [12-14]. The effectiveness of an iron-chelating agent depends in part on its ability to bind NTBI over sustained periods, thereby ameliorating iron-catalyzed toxicity of free radicals [9].

In a retrospective analysis of 46 MDS patients who had received 50 units or more (range 50–150, mean 79) of RBC, 20 patients (43%) had cardiac hemosiderosis, 9 (20%) had arrhythmias, and 14 (30%) died of heart failure. In addition, 12 patients (26%) suffered from hepatic dysfunction, and 5 (11%) developed diabetes mellitus [15].

Taking into consideration that evidence-based medicine on this topic is limited, The MDS Foundation has initiated an international project and several parallel roundtable discussions were organized in different countries. The summarized consensus guidelines will be written and published by the MDS Foundation. Here, the summary of the Israeli panel is presented.

In Israel, the consensus committee included experts in thalassemia (H.T., E.R.) having a broad experience with iron chelation therapy, iron experts (C.H.) and others interested in MDS (G.L., D.M., N.S., M.M., and E.R.). The conference was recorded and audio-taped (supported by an unrestricted grant from Novartis, Israel). The issues and relevant questions raised by The MDS Foundation and addressed by the expert panel are presented below.

What types of patients are potential candidates for iron chelation therapy?

Most committee members believe that the following criteria should be met by MDS patients in order to be eligible for iron chelation therapy:

MDS = myelodysplastic syndromes

RBC = red blood cells

NBTI = non-transferrin-bound fraction of iron

Criterion 1: Patients with a relatively more favorable prognosis, i.e., patients with expected survival longer than one year. These are usually patients classified as low or Int1, according to the International Prognostic Scoring System [16]. The group felt that since the beneficial effect of iron chelation occurs after several years in thalassemic patients, it may not make sense to treat MDS patients who have a short expected survival, since they will probably not benefit from such treatment.

Criterion 2: a) patients with serum ferritin level exceeding the 1000 µg/L threshold level; b) patients who have received a total of 20–25 RBC units; c) patients whose blood transfusion requirement has increased significantly, i.e., has required more than two units of RBC per month over a 6 month period; and d) patients who have developed organ damage, especially in the liver, heart or endocrine glands, related to iron overload.

Criterion 3: Patients who are currently transfused, and still do not meet the above criteria but are candidates for a curative therapeutic approach, such as stem cell transplantation.

In order to be eligible for iron chelation therapy, a patient needs to meet criterion 1 and either one of the criteria 2 (2a, 2b, 2c, or 2d) or criterion 3, i.e., 1+2 or 1+3.

How many of your transfused MDS patients are currently on iron chelation therapy, and what are the reasons for not treating them with iron chelating agents?

Although no hard data on Israeli MDS patients are available to answer that question, the committee members assess that the percentage of heavily transfused MDS patients who are routinely iron chelated is currently no more than between 10 and 20% of the transfused patients.

The reasons that were mentioned as responsible for not chelating the patients are:

- Lack of awareness among the treating physicians (hematologists as well as non-hematologists).
- Poor compliance with the only iron-chelating agent currently approved in Israel, desferrioxamine. It is known that the other two agents are not available (yet) for routine use in this group of patients.
- Patients do not meet the proposed criteria (see the first question, and guidelines published elsewhere) [17,18].

What are the targets of iron chelation therapy?

There was a consensus among the panel members regarding the following targets:

- Reduce the serum ferritin level; the number proposed as a target is < 1000 µg/L, or even below 500 µg/L.
- Minimize or reduce and, if possible, prevent organ damage and dysfunction.
- If possible prolong survival, although it is clear that it may take years until we have enough data to support and justify this goal.

What are the parameters to evaluate the effectiveness of iron chelation therapy?

The panel agreed on several possible follow-up parameters:

- *Serum ferritin level.* This is a simple and cheap method, available for most physicians and patients, including patients treated in the community. Although other pathological processes such as inflammation and infectious diseases may result in a non-specific increased serum ferritin level, its general trend along the disease course and treatment can be used as a good predictive practical marker for a successful iron removal.
- *Non-transferrin-bound iron, free iron or labile plasma iron.* This is considered today as an accurate marker, since it represents the real fraction (FI) that might be responsible for the oxidative toxicity caused by iron to the organs. However, all panel members appreciate that the assay for NTBI or labile plasma iron is not available for routine use in the majority of patients. Therefore, at the present time it should be used only in certain cases or as a part of an investigational protocol.
- *Liver and, more rarely, myocardial biopsy.* This is used to assess iron content and damage related to iron. In contrast is the case with thalassemic children where biopsies are occasionally performed, the panel members feel that this will be absolutely impractical and probably unethical to perform in the MDS patient population, unless there is another indication for a biopsy. Clinical research protocol might also be an exception.
- *Magnetic resonance imaging R2* (T2*).* The panel holds that this "hot topic" might eventually prove itself as the most precise and reliable way of assessing cardiac and hepatic iron overload and damage, as several recent reports suggest [19-21]. However, at the present time, not only is this a novel technique, still in the learning curve period, it is available in only a few centers. It is noteworthy that two recent studies on T2* MRI in MDS, including one by a joint Israeli team, demonstrated excess of iron in the liver but not in the heart [22,23].

Thus, at the present time, repeated measurements of serum ferritin levels appear to be quite reliable and available for the vast majority of patients. Although we have no data to use as a basis, the panel recommends repeating measurements of serum ferritin levels every 3–6 months in order to follow the trend.

How long would you continue the iron chelation therapy?

Again, although no data are available regarding the elderly MDS patient population, the panel refers to the experience gained with thalassemic children. Thus, the panel recommends continuing iron chelation therapy as long as the patient requires repeated RBC transfusions. In many patients this is a commitment for life.

Transient discontinuation of iron chelation therapy can be

FI = free iron

considered, especially if serum ferritin levels show a decrease tendency, and preferred if they fall below the 1000 µg/L or even below the 500 µg/L threshold level.

What iron chelating agents can be used?

- *Deferoxamine (desferrioxamine, Desferal®)* is currently the only available agent in Israel for MDS patients. We have more than 40 years experience with this agent, mainly in thalassemic patients. It is effective, but has to be administered intravenously, usually with a pump, causing low compliance and minimizing its use in clinical practice [10,24].
- *Deferipron (LI®)* is an oral agent and there is less experience with this drug. Unfortunately, neutropenia and agranulocytosis, although rare, has limited the wide use of this agent in the MDS patient population [10,25].
- *Deferasirox (ICL670, Exjade®)* is the most recent oral product. Most of the experience so far has been gained with thalassemic patients [10,25]. A recent case report suggests also a possible reduced blood transfusion requirement with this agent [26].

In conclusion, iron overload is becoming a serious problem as MDS patients receive more RBC units and live longer. Physicians treating such patients are urged to be aware of the problem and prevent it (if possible) or treat it (when it occurs). Serious organ damage related to iron accumulation can be prevented or treated by using an iron chelating therapy. These guidelines, based on the little information collected so far and the experience of the authors, are intended to help physicians in managing the problem.

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