Guidelines for treating Iron Overload in Myelodysplastic Syndromes in Taiwan

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Participants

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Abstract

Iron overload is common in myelodysplastic syndrome (MDS) patients, and cumulative evidences showed that iron chelation may have benefits in these patients. However, a discussion and consensus about iron chelation therapy (ICT) for MDS patients is lacking in Taiwan and other South-eastern Asian countries. An Expert Panel in Taiwan was then organized in 2011 to develop iron overload guidelines and provide unity of reference for physicians treating MDS patients with iron overload, specifically regarding when to initiate ICT, in what patients, and the clinical and scientific rationale behind its use.
Background

Myelodysplastic syndrome: epidemiology and iron overload

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal disorders marked by impaired hematopoiesis and cytopenia [1]. The age-adjusted annual incidence of MDS was 3–4 per 100,000, with around 10,300 new cases being diagnosed annually in the United States (SEER data, 2001–2003) [2], but the incidence is not clear in Taiwan and other South Asian countries. Interestingly, a single-center analysis of 410 patients from Taiwan found that the proportion of patients with lower-risk disease of MDS was less in this area than that in the West [3], and the authors concluded that patients with MDS in Taiwan have distinct clinical features and cytogenetic changes.

MDS carries significant morbidity and mortality: a high proportion of patients will have disease progression to acute myeloid leukemia (AML) in only a handful of years with fatal outcome [4]. On the other way, an estimated 39% of patients with low and intermediate-1 (Int-1) International Prognostic Scoring System (IPSS) scores will suffer from chronic anemia and require regular RBC transfusions [5], and the rate of transfusion dependency can be even higher up to 54% in patients with intermediate-2 or high IPSS scores [6]. With the impacts from large iron influx from transfusion (about 200–250 mg iron for one unit of RBC, which is equal to 2 Taiwanese units [7]) and other mechanisms such as decreased iron utilization [1], iron overload (IO) is then a reasonable long-term complication in a significant proportion of MDS patients who need chronic transfusion for their anemia [1].

Impact of iron overload on organ damage in patients with MDS

The most important biological consequence of iron overload is the increased level of free iron, which can catalyze reactions to generate free radicals, such as reactive oxygen species (ROS), and then damage cells through oxidative stress [8]. In beta-thalassemia major, the harmful impact of iron overload on organ functions has been clearly illustrated [9]; in contrast, evidence of this impact in MDS is relatively indirect and comes mostly from retrospective observational studies.

In a cohort of 1344 patients with MDS from Italy and Germany, RBC transfusion dependency was a defined risk factor for cardiac death (HR 4.12, p<0.001) [10], which was also validated by Takatoku’s analysis in Japan [11]. A retrospective, case-control study in 4546 patients showed correlations between the receipt of RBC transfusions and risk of cardiomyopathy/heart failure, conduction/rhythm disorders, liver disease, and diabetes [12]. When Goldberg
et al analyzed data from 512 MDS cases in United States Medicare database[13], they noticed that patients with RBC transfusion dependency had a clearly increased risk for cardiac related events (73.2% vs 54.5%, p<0.001), and a higher prevalence of diabetes mellitus (40% vs. 33.1%; p<0.001) or hepatic events (0.8% vs. 0.2%; p<0.0108) than those who were not transfusion dependent during 3-years’ follow up. Although these results do not provide a direct evidence for causal relationship, they still draw a high clinical attention between iron overload and organ damages.

Iron is an essential nutritional component for the growth of bacteria and fungi, and high iron burden can reasonably carry a risk for bacterial and fungal infections. A high serum ferritin level is a known risk for bloodstream [14] and pulmonary fungal infections [15] after hematopoietic stem cell transplantation (HSCT). In Goldberg’s analysis[13], a higher incidence of infectious disease (81% vs. 55.7%; p<0.001) and invasive fungal infection (14.6% vs 6.2%; p<0.001) could be found in those MDS patients with RBC transfusion dependency. In in vitro experiments, increased oxidative stress by iron has been shown to damage CD34+ hematopoietic stem cells and cause genetic instabilities in cancer cells [1]. Taken together, iron overload in MDS may promote serious complications such as infections, and have theoretical impacts on impaired hematopoiesis or leukemia progression.

**Impact of iron overload and survival in patients with MDS**

A number of studies have reported that RBC transfusion dependency and high serum ferritin levels are associated with adverse survival in patients with MDS. A retrospective study of 467 patients with MDS patients found that those who were transfusion dependent had inferior overall survival (OS) with an HR of 1.36 for every 500 ng/mL increase in ferritin (p<0.001) [16]. The number of transfusions per month also affected OS (HR=1.35, p<0.001) and leukemia-free survival (HR=1.75, p<0.001). Malcovati et al also demonstrated that serum ferritin concentration significantly affected OS and risk of non-leukemic death in MDS (HR=1.34 and HR=1.51, respectively, for a 500 ng/mL increase in serum ferritin; p<0.001) [10]. In a Spanish study of 2994 MDS patients, iron overload and transfusion dependence were reported to influence OS in a multivariate analysis [17]; both parameters also had an impact on AML transformation.

**Materials and Methods**

Given the background reviewed, ameliorating iron overload in patients with MDS may offer improvements in organ function and OS. Several global or region-specific guidelines have been promulgated in the past years [18-24],
but a discussion or consensus about evaluating and treating MDS patients with IO is still lacking in Taiwan and other South-eastern Asian countries. With the fact that the clinical landscape of MDS may differ depending upon region, therefore, we are engaged to develop the Taiwanese guidelines designed to address the impact of iron overload in patients with MDS, to clarify the benefits of iron chelation therapy (ICT), and to provide evidence-based recommendations as a reference for physicians to treat these patients in Taiwan.

The preparation of these guidelines made use of the Conference On Guideline Standardization criteria [25]. Since late 2011, an Expert Panel organized by the Taiwan Society of Hematology started to review Taiwanese and worldwide evidences regarding iron chelation in MDS. The guidelines were developed by consensus of the experts based on their own clinical experiences and a review of all articles found in the PubMed database over the past 10 years using the search terms “MDS and iron overload” or “MDS and iron chelation therapy” as well as key abstracts presented in annual meetings of the American Society of Hematology (ASH). The Expert Panel then held two meetings, respectively. A consensus was then made based on the evidence, or expert agreement in areas that lack enough evidence. The recommended evidence levels originate from the British Committee for Standards in Haematology [26], as illustrated in Table 1.

**Discussion Points and Recommendations**

1. **Can iron overload and related organ dysfunction be reversed with iron chelation therapy?**

   A prospective, open-label, nonrandomized phase II trial of deferiprone in treating 38 nonthalassemic anemic patients with IO (18 with MDS) found that only 20 patients completed the 12-month treatment; 56% (20/36) achieved negative iron balance, while 15/20 had a >20% reduction in serum ferritin levels [27]. Two patients no longer depended on transfusions. The EPIC study looked at 341 patients with MDS, 175 of whom completed 1-year treatment with deferasirox. [1] Overall median serum ferritin levels significantly decreased by 253 ng/mL from a baseline of 2730 ng/mL (p=0.002), as did the Labile plasma iron (LPI) levels. Alanine aminotransferase (ALT) levels also significantly decreased (-27.7±37.4 U/L; p<0.0001), with an observed dose-dependent effect. The decline in the levels of ALT and serum ferritin were highly correlated (p<0.0001).

   Of 292 adult patients with MDS, aplastic anemia, pure red cell aplasia, myelofibrosis, or other conditions in Japan, 43% had previously received deferoxamine treatment[11]. In the small percentage (8.6%) of patients who had received daily and continuous deferoxamine treatment, a significant decline in serum ferritin levels (-1135 ng/mL),
AST (-9.2 mU/mL), ALT (-28.8 mU/mL), and fasting blood sugar (-4.8 mg/dL) was observed. On the contrary, increases in these parameters were observed in patients with intermittent (once every almost 2 weeks) deferoxamine use. A prospective study in 24 patients with MDS who were heavily transfused and continued to require RBC transfusion found that deferasirox therapy reduced LPI and liver iron concentrations (LIC) at 24 and 52 weeks of therapy [28]. Notably, in an uncontrolled study of 15 patients with chronic transfusion and iron overload, the 12-month deferoxamine treatment with vitamin C supplementation resulted in an improvement in left ventricular ejection fraction (LVEF), whereas a reduced LVEF was seen when deferoxamine was used alone [29], suggesting the necessity of combination treatment with deferoxamine and vitamin C.

Hematopoiesis

Hematopoietic improvement after ICT have been reported in a number of MDS patients with iron overload. An early prospective study in 11 patients with MDS found that deferoxamine treatment for up to 60 months could reduce RBC transfusion requirements and increase neutrophil and platelet counts [30]. The investigators also found a ≥50% reduction in the transfusion requirement in 64% of the patients. Improved hemoglobin levels or even transfusion dependence after deferasirox treatment has also been shown in a few case reports [31-33]. However, the biological mechanisms behind these hematopoietic recoveries after ICT have yet to be elucidated.

Recommendations

1. ICT in patients with MDS can effectively lower serum ferritin level (Evidence level IIa) along with liver and cardiac iron content (Evidence level IIa). ICT can improve abnormal liver functions (Evidence level IIa). These effects depend on drug dosing, length of therapy, patient compliance, and transfusion amount.

2. The precise effects of ICT on cardiac functions are currently unknown. Furthermore, if deferoxamine is used for iron chelation in MDS patients, concurrent vitamin C administration may be required to prevent the potential deleterious effects on LV functions (Evidence level IIb).

3. Further research is required to confirm the impact of ICT on hematopoiesis in patients with MDS.

2. Can iron chelation therapy improve survival in MDS patients with iron overload?

The idea that ICT can improve survival is extrapolated from research results in patients with beta-thalassemia.
There are only nonrandomized studies examining this idea in patients with MDS. These retrospective studies suffered from a number of inherent limitations, especially selection bias, because those patients who were treated with ICT might have significant difference in various aspects, including prognosis and transfusion burden, from those patients who did not receive ICT. Precautions then should be paid in interpreting the results of these studies.

A retrospective review of 178 patients with low-risk MDS and clinically suspected iron overload in Canada showed that, in the 18 patients receiving iron chelation with deferoxamine, the serum ferritin levels fell significantly and the survival improved significantly (160 mo vs. 40 mo)[34]. In multivariate analysis, IPSS score (p<0.008) and receiving ICT (p<0.02) were the only 2 factors impacting survival.

In another study of 97 low-risk MDS patients (Low or Int-1 IPSS score) with transfusion dependency in France, 53 of them nonrandomly received ICT with deferoxamine, deferiprone, or deferasirox [35]. Those with ICT had better OS than those without (124 mo vs. 53 mo; p<0.0003), and adequate chelation was the strongest independent factor for better OS in a multivariate Cox analysis. Similar findings were reported by Raptis, et al.[4]. A matched-pair analysis of 188 patients with MDS on long-term ICT compared with those not on such therapy also demonstrated that patients who received ICT had a better median OS (74 mo vs. 49 mo; p=0.002) [36].

Recommendations

1. ICT might improve the survival of MDS patients with IO (Evidence level IIa).

2. Prospective studies are required to eliminate confounding factors and to determine the proper drug dosing and schedule. In addition to measuring OS and morbidity, they should include clinically meaningful measurements of iron burden, oxidative stress, liver and heart function, and quality of life. Results of the TELESTO trial, a randomized, double-blind and multicenter study to compare the event-free survival between MDS patients receiving deferasirox and placebo, are expected to be available in 2016, which may address some of these points [37].

3. How can we quantify iron load in patients with MDS?

In the absence of an ideal measurement of the body’s total iron burden, the decision about when to start ICT in patients with MDS is therefore based on a determination of actual or predicted physiological iron overload and characteristics of individual patient. Table 2 summarizes several methods currently available to determine
physiological iron overload [38].

**Recommendations**

In Taiwan, the serum ferritin level is the most widely available tool to determine body iron status, although significant confounding factors may exist. MRI for evaluating hepatic or cardiac iron status is an effective alternative in some institutes. Liver biopsy for the measurement of LIC, although the gold standard, is not recommended for patients with MDS. Superconducting quantum interference device (SQUID), Non-transferrin-bound iron (NTBI), and LPI tests are not currently available in Taiwan.

4. **What are the Indications for the initiation of iron chelation therapy?**

Unlike thalassemia in which the threshold levels of LIC to trigger iron chelation has been established, there is currently no evidence-based validation for this aspect in MDS. It is also noteworthy that the harmful effects of IO could be a continuous rather than a categorical variable. Nonetheless, a variety of recommendations have been promulgated by guidelines as to when to initiate ICT (Table 3)[18-24, 39].

A serum ferritin level threshold is usually recommended by experts to guide the initiation of ICT. Most studies addressing the impact of iron overload on survival focused on low-risk MDS patients, probably because the short survival (< 2 years) of high-risk patients usually make it impossible to demonstrate enough benefits from a therapy requiring prolonged drug exposure, such as ICT. Accordingly, most guidelines recommend that ICT be used only for low-risk patients or patients with significantly long survival. A transfusion requirement can also be used to determine the future risk of iron overload. Another issue pertains to patients eligible for allogeneic HSCT. Evidence suggests that high pretransplant serum ferritin levels predict poor survival [40] and that iron chelation can improve OS after allogeneic HSCT [41] in patients with MDS. Another study in patients with myelodysplasia and other diseases found an adverse impact of iron overload on the outcome of allogeneic HSCT [42], although a prospective observational study in 45 patients with MDS or acute leukemia undergoing myeloablative HSCT found that the adverse prognostic impact of pre-HSCT hyperferritinemia might be related to factors independent of overloaded iron [43]. Many guidelines recommended that ICT should be initiated in patients with MDS who are eligible for allogeneic HSCT [18, 19, 21, 22, 24, 39].
Recommendations

1. In MDS patients with a Low or Int-1 IPSS score, ICT is suggested when the serum ferritin level is more than 1000 ng/mL, and also with one of the following:
   (a). Further RBC transfusion is required (Evidence level IIa)
   (b). Eligible for allogeneic HSCT (Evidence level IIa)

2. In patients with an Int-2 or High IPSS score, ICT is suggested when the serum ferritin level is more 1000 ng/mL and also with one of the following:
   (a). Eligible for allogeneic HSCT (Evidence level IIa)
   (b). Life expectancy more than 1 year with a need for future transfusion (Evidence level IV)

5. **How can we treat iron overload in patients with MDS**

   Table 4 summarizes the administration, pharmacokinetics, potential adverse effects, and indications for the three drugs available for ICT. Currently, there are three drugs available for ICT in Taiwan, i.e. deferiprone, deferasirox and deferoxamine. Deferiprone has not been licensed by the Taiwan Food And Drug Administration for use in patients with MDS, therefore only deferasirox and deferoxamine are recommended. The choice between deferasirox and deferoxamine should be done case by case, according to patient adherence and potential toxicities.

   The follow-up schemes of most published guidelines are variable, because of the lack of evidence and the variability of treatment initiation.

Recommendations

1. Serum ferritin may be the most convenient parameter for following body iron status after ICT in patients with MDS. It should be determined at least every 3 months (Evidence level IV).

2. The target serum ferritin level for ICT in patients with MDS may be 500–1000 ng/mL (Evidence level IV).

   Whether ICT should be continued after this point is reached should be determined individually, especially with regard to future transfusion requirements and patient adherence.

Conclusion

In addition to the clinical rationale behind these guidelines, other factors such as patient preferences and cost-
benefit of the drugs should be taken into account. Barriers to the implementation of these guidelines may stem from the provisional nature of many of the recommendations, being based mostly on retrospective studies. It is expected that as further evidence becomes available these guidelines will be updated accordingly.
Table 1. The evidence levels for recommendation in Taiwanese guidelines.

<table>
<thead>
<tr>
<th>Classification of evidence levels</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidences obtained from meta-analysis of randomized controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidences obtained from at least one randomized controlled trials</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidences obtained from at least one well-designed controlled study without randomization</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidences obtained from at least one other type of well-designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidences obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidences obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.</td>
</tr>
</tbody>
</table>
Table 2. Summary of methods to determine iron content.

<table>
<thead>
<tr>
<th>Tools</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin</td>
<td>Convenient and cheap</td>
<td>Low specificity; can be affected by prior ICT, tissue damage, inflammation, and abnormal hepatic function</td>
</tr>
<tr>
<td>Non–transferrin-bound iron (NTBI)</td>
<td>Biologically meaningful</td>
<td>Not standard lab technique and not available in Taiwan</td>
</tr>
<tr>
<td>Labile plasma iron (LPI)</td>
<td>Biologically meaningful</td>
<td>Investigational technique, not available in Taiwan</td>
</tr>
<tr>
<td>Liver biopsy (For LIC measurement)</td>
<td>Gold standard</td>
<td>Large sample needed</td>
</tr>
<tr>
<td></td>
<td>Pathological review for liver damage</td>
<td>Invasive and thus with risk of bleeding and infection</td>
</tr>
<tr>
<td>SQUID</td>
<td>Noninvasive</td>
<td>Expensive equipment required</td>
</tr>
<tr>
<td></td>
<td>Precise measure of LIC [44]</td>
<td>Not available in Taiwan</td>
</tr>
<tr>
<td>MRI (R2 or T2*)</td>
<td>Noninvasive</td>
<td>Various technical protocols, especially T2*</td>
</tr>
<tr>
<td></td>
<td>Correlated with LIC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Organ-specific iron load</td>
<td></td>
</tr>
</tbody>
</table>

ICT = iron chelation therapy; LIC = liver iron concentration; SQUID = superconducting quantum interference device.
Table 3. Summary of a variety of international guidelines on the use of iron chelation therapy for patients with MDS

<table>
<thead>
<tr>
<th>Guideline (year)</th>
<th>Serum ferritin levels to guide start of ICT</th>
<th>MDS risk</th>
<th>Transfusion requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel (2008) [21]</td>
<td>&gt;1000 ng/mL</td>
<td>Low and Int-1 IPSS (i.e., life expectancy &gt;1 yr)</td>
<td>≥20–25 U RBC OR &gt;2 U RBC over 6 mo OR Patients with increase in transfusion requirement OR Evidences of organ damage</td>
</tr>
<tr>
<td>Japan (2008)[23]</td>
<td>&gt;1000 ng/mL for &gt;2 mo in at least 2 successive tests</td>
<td>Life expectancy &gt;1 yr</td>
<td>≥20 U RBC</td>
</tr>
<tr>
<td>Canada (2008)[39]</td>
<td>&gt;1000 ng/mL</td>
<td>Low-risk MDS (WHO RA, RARS, 5q- or Low/Int-1 IPSS score) AND Life expectancy &gt;1 yr</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>&gt;1000 ng/mL</td>
<td>High-risk MDS (Int-2 or High IPSS score) AND Life expectancy &gt;1 yr</td>
<td>NR</td>
</tr>
<tr>
<td>Austria (2008)[24]</td>
<td>&gt;2000 ng/mL</td>
<td>Life expectancy &gt;2 yr</td>
<td>Transfusion dependent (any frequency)</td>
</tr>
<tr>
<td>MDS Foundation (2008) [18]</td>
<td>&gt;1000 ng/mL</td>
<td>Life expectancy &gt;1 yr</td>
<td>≥2 U/mo for more than 1 yr OR Low-risk MDS (WHO RA, RARS, 5q- or Low/Int-1 IPSS score)</td>
</tr>
<tr>
<td>Italian (2010) [22]</td>
<td>Not recommended</td>
<td>Low and Int-1 IPSS with regular RBC therapy Int-2 and High IPSS</td>
<td>&gt;20 U pRBC (i.e., 4 g iron) Life expectancy modified after treatment or HSCT</td>
</tr>
<tr>
<td>NCCN (2011) [19]</td>
<td>&gt;2500 ng/mL</td>
<td>Low or Int-1 IPSS score</td>
<td>≥20 times of RBC transfusions</td>
</tr>
<tr>
<td>Australia (2011)[20]</td>
<td>1000-2500 ng/ml</td>
<td>NR</td>
<td>10-20 times of transfusions</td>
</tr>
</tbody>
</table>
HSCT = hematopoietic stem cell transplantation; ICT = iron chelation therapy; IPSS = International Prognostic Scoring System; NCCN: National Comprehensive Cancer Network; NR = not remarkable; pRBC = packed red blood cells; RA = refractory anemia; RARS = RA with ringed sideroblasts; U = units; WHO = World Health Organization.
<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Deferoxamine</strong> [46]</th>
<th><strong>Def eriprone</strong> [47]</th>
<th><strong>Deferasirox</strong> [48]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual dose</td>
<td>40–50 mg/kg/day</td>
<td>75–99 mg/kg/day</td>
<td>20–40 mg/kg/day</td>
</tr>
<tr>
<td>Route and frequency</td>
<td>SC infusion (with pump) over 8–12 hr for 5 d/wk</td>
<td>PO 3 times daily</td>
<td>PO 1 time daily</td>
</tr>
<tr>
<td>Half-life</td>
<td>20 min [49]</td>
<td>1.9 hr</td>
<td>8–16 hr</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urinary, fecal</td>
<td>Urinary</td>
<td>Fecal</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Injection site reactions</td>
<td>Agranulocytosis</td>
<td>GI intolerance</td>
</tr>
<tr>
<td></td>
<td>Ocular and otic toxicity</td>
<td>Liver toxicity [38]</td>
<td>Skin rash</td>
</tr>
<tr>
<td></td>
<td>Risk of increased fungal and bacterial infection</td>
<td></td>
<td>Renal toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potentially risk of liver function impairment or failure</td>
</tr>
<tr>
<td>Indications and notes</td>
<td>Acute iron intoxication</td>
<td>Limited information in MDS</td>
<td>Chronic IO</td>
</tr>
<tr>
<td></td>
<td>Chronic IO</td>
<td>Not licensed for MDS by Taiwan FDA</td>
<td></td>
</tr>
</tbody>
</table>

FDA = Food And Drug Administration; GI = gastrointestinal; IO = iron overload; MDS = myelodysplastic syndrome; PO = per oral.
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