



Consensus statement on iron overload in myelodysplastic syndromes

In May 2005, a meeting was held in Nagasaki, Japan, to discuss and attempt to reach a consensus on various aspects of the diagnosis, monitoring, and management of iron overload in myelodysplastic syndromes (MDS). Participants included more than 30 leading hematologists with specific expertise in MDS from three regions: Asia-Pacific, Europe, and Latin America (Table 1).

Current practice

A premeeting survey of the hematologist attendees provided an overview of current practice with iron overload in MDS.

Number of patients diagnosed with MDS

The estimated number of new cases of MDS diagnosed in the last 12 months was highest in Europe, with a mean of 59 patients (range 15–100) per center (Table 2). Hematologists from Asia-Pacific reported slightly fewer new cases (mean 35, range 10–100) and those from Latin America reported the least (range 12–20).

Classification

A number of systems for the classification of MDS patients are used internationally. The World Health Organization [1]

classification system was the most commonly used, although the French-American-British [2] system remained in common use, especially in Europe and Latin America. In addition, the International Prognostic Scoring System (IPSS) [3] was widely used to estimate prognosis, particularly in Europe and Asia-Pacific, with use declining to approximately 50% of hematologists in Latin America.

Hemoglobin levels

There was a striking variation between regions regarding what was considered to be the appropriate threshold hemoglobin level for initiation of transfusion. Similarly, there were differences in the target hemoglobin levels to be achieved by transfusion. Some centers in Asia-Pacific use a threshold of 6 g/dL hemoglobin as the trigger to commence transfusion, and the highest threshold reported in this region was 9 g/dL. In contrast, the range of threshold hemoglobin values reported in Europe was 8 to 10 g/dL, and in Latin America was 7 to 10 g/dL (Table 2). Correspondingly, median target hemoglobin levels were 7 to 10 g/dL in Asia-Pacific, 8 to 10 g/dL in Europe, and 9 to 10 g/dL in Latin America.

Table 1
Demographics of hematologist attendees

Region	Country	Number of hematologist attendees
Asia-Pacific	Australia	1
	Hong Kong	1
	Japan	6
	Korea	2
	Malaysia	1
	Taiwan	2
Europe	Belgium	2
	France	2
	Germany	3
	Italy	1
	Netherlands	1
	Spain	1
	Sweden	1
	United Kingdom	2
Latin America	Brazil	2
	Colombia	1
	Costa Rica	1
	Mexico	3
	Panama	1

Screening for iron overload

The majority of participating hematologists (67%) in Latin America and Europe initiate screening for iron overload after patients have received 10 to 20 red cell transfusions, with approximately 10% screening after 21 to 50 transfusions. In Asia-Pacific, 46% of respondents initiated screening after 10 to 20 transfusions and a similar proportion initiated screening after 21 to 50 transfusions. Screening after fewer than 10 transfusions was reported by <10% of hematologists in Asia-Pacific and Europe, and none in Latin America. At the other end of the scale, initiation of screening after 51 to 100 transfusions was reported by approximately 15% of European hematologists, but not by any from Latin America or Asia-Pacific. The most influential factor in the decision to screen was reported to be the absolute number of transfusions in Asia-Pacific and Latin America, and the transfusion frequency in Europe. Nearly all respondents had seen patients presenting with cardiac, hepatic, or endocrine symptoms considered attributable to iron overload.

Table 2
Inter-regional differences in current practice

	Asia-Pacific	Europe	Latin America
Number of new cases diagnosed per center, mean (range)	35 (10–100)	59 (15–100)	15 (12–20)
Threshold for initiating transfusion, Hb g/dL	6–9	8–10	7–10
Target for transfusion, Hb g/dL	7–10	8–10	9–10
Threshold serum ferritin level for initiating chelation therapy, ng/mL	1000–3000	500–2000	1000–2000

Abbreviations: Hb, hemoglobin.

Initiation of chelation

In Asia-Pacific, serum ferritin levels in the range 1000 to 3000 ng/mL were reported as the threshold level for considering the initiation of chelation therapy. In contrast, European hematologists reported a range of serum ferritin values of 500 to 2000 ng/mL as an indication to consider chelation. Between these two ranges, Latin American hematologists generally used serum ferritin levels of 1000 to 2000 ng/mL as a threshold to begin chelation therapy.

Chelation treatment

Deferoxamine was reported to be the first-line treatment in all regions. Deferiprone in combination with deferoxamine was cited as second-line treatment in Europe but was rarely used in Latin America or Asia-Pacific because deferiprone is not reimbursed or is unavailable in these regions. Other issues affecting treatment included availability and cost of infusion pumps, and patient compliance with the deferoxamine subcutaneous infusion regimen. It was widely felt that many of the problems associated with current chelation therapy would potentially be overcome with the advent of a suitable oral chelator.

Consensus statement

Delegates discussed a number of fundamental questions relating to the use of chelation therapy in MDS patients with the aim of sharing current knowledge to develop a consensus position. It was agreed to base the consensus entirely on current knowledge, without speculating on the possible effects of future developments. The key discussion points leading to each consensus position are summarized.

What are the clinical consequences of untreated or inadequately managed iron overload in MDS?

Untreated or inadequately managed iron overload in patients with thalassemia and hemochromatosis is associated with damage to cardiac, hepatic, and endocrine systems. The most pronounced effects are seen in the heart, to the extent that heart disease is the most common cause of death in patients with thalassemia. Owing to the shortage of clinical trials and registry data on the consequences of iron overload in patients with MDS, it is necessary to extrapolate these effects from the context of thalassemia and hemochromatosis to that of MDS. Although it is reasonable to assume that these effects are

potential consequences of iron overload in any disease context, differential effects may result from intrinsic differences between the patient cohort providing the evidence base for iron overload in thalassemia and the patients at risk of iron overload in MDS. For example, MDS patients are typically older than patients with thalassemia. In an older population with increased background prevalence of heart disease and diabetes, the etiological role of iron overload in the development or deterioration of such conditions may be under-recognized.

Consensus position

The clinical consequences of untreated or inadequately managed iron overload in MDS are potential cardiac, hepatic, and endocrine complications.

What is the goal of chelation therapy in MDS patients with iron overload?

In general, the goal of chelation therapy is to remove excess iron from the body in order to prevent its accumulation in the tissues. Such accumulation can lead to serious complications with impairment of organ function and a major impact on morbidity and mortality. In addition, because many patients have already accumulated excessive iron before initiation of treatment, a further aim of chelation therapy is to reduce iron burden in order to reverse iron-mediated organ dysfunction and disease. Thus, iron chelators have the dual aim of prevention and treatment of iron-overload-related complications. In MDS, as in other indications for chelation therapy, the overall aim is to prolong the life of the patient.

Consensus position

The goal of chelation therapy in MDS patients with iron overload is to prevent and treat complications of iron overload and to improve survival.

What is the role of chelation therapy in MDS?

At present, the role of chelation therapy in MDS is largely speculative due to the absence of a sufficiently large evidence base. The impact of iron overload and the importance of iron chelation therapy in chronically transfused patients are well established in conditions such as thalassemia major, and are supported by a solid foundation of prospective clinical trials and registry data. In the case of MDS, the evidence base cur-

rently derives mainly from the physician's personal intuition and experience. However, evidence from clinical studies is emerging. In 1981, a study of 15 transfusion-dependent adult patients with acquired refractory anemias found widespread subclinical organ dysfunction associated with iron overload [4]. More recently, reports have appeared describing the effects of iron chelation therapy in patients with MDS [5–7]. Taken together, the anecdotal, intuitive, and emerging trials-based evidence indicate that chelation therapy is likely to play an important role in the management of patients with MDS who are at risk of complications due to iron overload. This comprises the subgroup of patients who are predicted to receive a sufficient number of blood transfusions to accumulate dangerous levels of iron.

Consensus position

Chelation therapy is highly likely to be clinically important in a subgroup of patients with MDS.

When should body iron stores be assessed in MDS patients?

Some patients with MDS show evidence of iron overload at diagnosis. Such increased body iron burden is likely to be due to increased absorption of dietary iron in response to a physiological signal arising from ineffective erythropoiesis and anemia. In addition, some patients may have received transfusions prior to diagnosis of MDS. It is therefore recommended that body iron stores be assessed at diagnosis in patients with MDS.

Patients who are free of iron overload at diagnosis of MDS may subsequently acquire excessive amounts of iron. Therefore assessment of iron stores should be repeated at regular intervals even in patients who show no evidence of iron overload at diagnosis. The duration of the interval between assessments will depend on the likely rate of iron loading due to transfusion. For example, if a patient does not become transfusion dependent then an appropriate interval might be 1 year. However, if the patient becomes transfusion dependent during that year, assessment of iron stores should be made more frequently.

Consensus position

Body iron stores should be assessed at diagnosis of MDS and at regular intervals thereafter, depending on transfusion rate.

Which tools should be used to diagnose and monitor iron overload?

Serum ferritin concentration is a practical and readily accessible indicator of the body iron burden. While serum ferritin levels may fluctuate in the short term in response to factors such as infection and inflammation, long-term trends reflect underlying changes in body iron stores and provide a useful tool for monitoring iron overload.

However, a definitive diagnosis of iron overload requires more evidence than elevated serum ferritin levels alone. A useful additional source of evidence is transferrin saturation

index, which may complement evidence from serum ferritin concentration at time of diagnosis, although it is not as valuable as serum ferritin for monitoring trends in iron overload. Liver MR imaging and other noninvasive methods based on the magnetic properties of iron, such as magnetic susceptometry, provide excellent sources of evidence for both diagnosis and monitoring of iron overload. However, for a large proportion of patients the obvious drawbacks of these methods are poor accessibility and lack of availability. Liver biopsy is not routinely recommended for assessment of iron overload in patients with MDS because of the risk of complications such as uncontrolled bleeding.

Consensus position

The tools used for diagnosis and monitoring of iron overload should be serum ferritin, transferrin saturation, and liver MR imaging.

How frequently should iron overload be monitored?

The frequency with which each of the methods of assessing iron overload is used is generally dependent on the invasiveness of the procedure and availability of resources. For example, liver iron stores might be assessed noninvasively using MR imaging or magnetic susceptometry on an annual basis. Serum ferritin measurement is minimally invasive and is likely to be the most widely available technique for the assessment of body iron. Some centers assess serum ferritin every month in order to detect trends that may not be observed with less frequent monitoring. However, a minimal frequency of every 3 months is likely to be adequate for monitoring iron overload in regularly transfused patients.

Consensus position

Iron overload should be monitored at least every 3 months in patients receiving transfusions.

When should the initiation of chelation therapy be considered in MDS patients?

The decision to initiate chelation therapy is usually taken after considering the number of transfusions received as well as the measured iron burden. However, the number of transfusions received may not be easily established if the patient has undergone transfusion therapy prior to diagnosis with MDS. Furthermore, the rate rather than absolute number of transfusions may be more relevant to the decision. Thus, in order to provide flexibility in respect of the transfusional status of the patient, it is appropriate to consider threshold levels of serum ferritin within a wide range. Furthermore, a wide range of threshold serum ferritin levels allows flexibility to accommodate short-term fluctuations. As an example, it may be appropriate to initiate chelation therapy in a patient who has just become transfusion dependent and commenced an intensive transfusion regimen and who has a serum ferritin level of 1000 ng/mL. In contrast, chelation therapy may be delayed in a patient who is unlikely to require transfusion in the foreseeable future although they have a serum ferritin level of 2000 ng/mL.

Consensus position

The initiation of chelation therapy should be considered in MDS patients when serum ferritin levels reach 1000 to 2000 ng/mL, depending on the transfusion rate.

How long should chelation therapy continue?

Consistent with the aim of preventing and treating the complications of iron overload, it is appropriate that chelation therapy should continue as long as patients are receiving transfusion therapy. However, the individual needs of each patient may require exceptions to this general rule. For example, if MDS transforms into acute myeloid leukemia, continued chelation therapy may no longer be in the patient's overall best interests.

Consensus position

Chelation therapy should continue as long as transfusion therapy continues and as long as iron overload remains clinically relevant.

Which MDS patients are likely to benefit most from treatment of iron overload?

An important consideration in deciding which patients are likely to benefit from chelation therapy is the degree of transfusion dependency. Patients with significant transfusion dependency are most likely to need chelation therapy (and vice versa). In terms of iron burden, elevated serum ferritin levels or other evidence of significant tissue iron overload are probable indicators of the anticipated benefit of chelation therapy.

Other key considerations include the patient's prognosis and life expectancy. In patients with a short life expectancy, iron chelation therapy may not be justified because iron overload-related complications may not have time to emerge. However, it should be noted that chelation therapy can in many cases reverse existing complications arising from iron overload. Its use, therefore, may be justified in the presence of existing problems such as iron-mediated heart disease. In general, patients with an IPSS score of low or intermediate-I, and with WHO classification of refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), or cytogenetic 5q-, are those most likely to benefit from chelation therapy to prevent emergence of complications due to iron overload. Nevertheless, patients with higher IPSS scores may manifest stable disease at 12 or 18 months and may thus go on to develop complications of iron overload if they are heavily transfused. Moreover, because successful transplantation changes prognosis radically and optimal organ function is critical to minimize transplant-related morbidity, candidates for allograft should be considered for chelation treatment irrespective of their prognosis based on IPSS criteria. Iron chelation therapy may help to avoid iron-related organ dysfunction, which might otherwise lead to an increased risk of transplant-associated morbidity and mortality.

Consensus position

MDS patients likely to benefit most from treatment of iron overload include:

- Transfusion-dependent patients
- Patients with serum ferritin levels >1000 to 2000 ng/mL or other evidence of significant tissue iron overload
- Patients with low-risk MDS
 - IPSS low or intermediate-I
 - WHO RA, RARS, and 5q-
- Patients with documented stable MDS
- Patients free of comorbidities that severely limit prognosis
- Candidates for allograft

Unanswered questions

It was recognized that the current knowledge base for iron overload in MDS is inadequate. Research using clinical trials and/or patient registries is essential in order to advance the field onto a durable evidence base. Several specific questions need to be addressed objectively using such research. In addition, although the consensus position was deliberately restricted to existing evidence, delegates were conscious that this is a rapidly moving field and that emerging technologies are likely to influence the management of iron overload of MDS in the future. Several unanswered questions relate to the possible impact of such emerging technologies.

Diagnosis of iron overload in MDS

Methods for assessing iron burden in particular organs other than the liver are currently in their infancy. As these methods develop in the fields of thalassemia and hemochromatosis, they are likely to shape the future of diagnosis and treatment of iron overload in MDS. What will be the impact of emerging techniques such as cardiac MR imaging T2* on the diagnosis and treatment of iron overload in MDS?

Effects of iron overload in MDS

Pivotal unanswered questions relate to the morbidity and mortality due to iron overload in MDS. In thalassemia major and hemochromatosis there is objective evidence that a large proportion of deaths, and significant morbidity, are due to iron overload [8,9]. There is a need for comparable research in MDS to determine objectively the consequences of iron overload. In addition, the pattern and pace of iron deposition in patients with MDS remain to be determined. For example, the characteristics of excess iron deposition in transfusional iron overload with thalassemia differ from those seen in absorptional iron overload with hemochromatosis. What effect will differences in age and underlying disease have on the features and tempo of iron deposition in MDS?

Treatment of iron overload in MDS

The efficacy, safety, and tolerability of iron chelators in the management of iron overload are well established in the context of thalassemia. Deferoxamine, the reference-standard chelator, has been shown to reduce body iron burden and protect against diabetes mellitus, cardiac disease, and early death in patients with thalassemia major [10]. Although research on the effects of

IRON OVERLOAD IN MYELOYDYSPLASTIC SYNDROMES

Consensus statement

- The clinical consequences of untreated or inadequately managed iron overload in MDS patients are potential cardiac, hepatic, and endocrine complications.
- The goal of chelation therapy in MDS patients with iron overload is to prevent and treat complications of iron overload and to improve survival.
- Chelation therapy is highly likely to be clinically important in a subgroup of patients with MDS.

MONITORING IRON OVERLOAD

When should body iron stores be assessed in MDS patients?

- At diagnosis of MDS and at regular intervals thereafter, depending on the transfusion rate

Which tools should be used to diagnose and monitor iron overload?

- Serum ferritin
- Transferrin saturation
- Liver MR imaging

How frequently should iron overload be monitored?

- At least every 3 months in patients receiving transfusions

TREATING IRON OVERLOAD

When should the initiation of chelation therapy be considered in MDS patients?

- When serum ferritin levels reach 1000 to 2000 ng/mL, depending on the transfusion rate

How long should chelation therapy continue?

- As long as transfusion therapy continues and as long as iron overload remains clinically relevant

PATIENT PROFILE

Which MDS patients are likely to benefit most from treatment of iron overload?

- Transfusion-dependent patients
- Patients with serum ferritin levels >1000 to 2000 ng/mL or other evidence of significant tissue iron overload
- Patients with low-risk MDS
 - IPSS low or intermediate-I
 - WHO RA, RARS, and 5q-
- Patients with documented stable MDS
- Patients free of comorbidities that severely limit prognosis
- Candidates for allograft

iron chelation therapy in MDS is beginning to emerge [5–7], further studies are required to clarify the efficacy and safety of iron chelators in this disease context. Another key question relating to treatment is whether iron chelation therapy is compatible with other therapies for MDS. In the case of concomitant treatment with erythropoietin, what is the risk of inducing a functional iron deficiency? Uncertainty also remains about the effects of iron chelation on the efficiency of hematopoiesis per se.

Regional considerations

Approaches to the diagnosis and management of MDS and iron overload differ in a number of key respects between the regions of Europe, Latin America, and Asia-Pacific. There is also some intraregional variation, particularly in Asia-Pacific.

Asia-Pacific

Hemoglobin levels and transfusion thresholds

The threshold hemoglobin level for initiating blood transfusion therapy in MDS appears to be lower in Asia-Pacific compared with both Europe and Latin America, and may reflect better tolerance of lower hemoglobin levels by patients in this region. It is hypothesized that this tolerance may be related to the low average body weight of these patients. The hemoglobin trigger levels are lowest in Japan (6–8 g/dL). Many Japanese patients are reported to be asymptomatic at lower concentrations, while some may be apprehensive of the potential risk of acquired viral infections following transfusion therapy. In Taiwan, hemoglobin levels are generally maintained at 7 to 8 g/dL. However, the relative scarcity and high cost of blood products in this country may discourage the initiation of transfusion therapy in asymptomatic patients with low hemoglobin levels. Patient choice is also a key factor in the Asia-Pacific region; patients are thought to be well-placed to evaluate the balance between symptom alleviation and the inconvenience of transfusion therapy.

Candidates for chelation therapy

Asia-Pacific MDS patients with stable disease and a good prognosis (3–5 years) are likely to receive iron chelation therapy; prognostic assessment is generally based on IPSS and an observation period. There are, however, intraregional variations in the age of MDS patients who are eligible for chelation. In Australia, patients aged 75 to 80 years and above would not generally be considered due to the burdensome nature of available chelation regimens and the high level of health care resource needed to support chelation therapy. Similarly, many clinicians in Malaysia and Korea are unlikely to recommend chelation therapy in patients aged 70 years and above. In Japan, however, age is not a major factor when making treatment decisions. Japanese clinicians consider 70 years as ‘young’ in terms of MDS patient demographics, and if this age was set as an upper limit for chelation therapy, then 30 to 50% of patients would be ineligible. Clinicians will prescribe chelation therapy regardless of age if Japanese patients experience symptoms of iron overload, although preventative administration would not be favored in older patients.

Chelation regimens

Deferoxamine is the first-line chelator for iron overload in MDS in the Asia-Pacific region, as is the case in both Europe and Latin America. Although deferiprone is available in some Asia-Pacific countries, such as Malaysia, Hong Kong, and Taiwan, it is rarely used in MDS. The deferoxamine infusion pump is not approved in Japan and costs are therefore not covered. Many patients in Asia-Pacific are unwilling to accept parenteral chelation therapy with deferoxamine, particularly as a preventative measure. This is partly because the serious consequences of untreated iron overload and the benefits of chelation therapy have not yet been firmly established within the medical community or effectively communicated to patients with MDS.

The regimen used in some Australian practices, where patients are transfused on a Monday and receive continuous 5-day deferoxamine infusion via the same vascular access device, would not be considered acceptable in other Asia-Pacific countries or be practicable within local health care systems. In other countries, such as Taiwan, Korea, and Japan, deferoxamine is instead administered as an intermittent bolus injection or together with transfusion therapy as a preventative measure. However, it is acknowledged by these clinicians that continuous exposure to deferoxamine provides optimal efficacy. Where intermittent deferoxamine is used, the dose interval will be reduced or patients hospitalized for a period of continuous infusion if iron levels continue to increase.

It is thought that the availability of a more convenient chelator would reduce the threshold for initiation of chelation therapy in MDS and improve patient acceptance and compliance.

Latin America

Evaluation of body iron levels

Assessment of serum ferritin levels is the most widely used method for measuring body iron levels in Latin America, as in both Europe and Asia-Pacific, and it is often used together with the transferrin saturation index. For example, a common threshold for initiating chelation therapy is a serum ferritin level of 2000 ng/mL and transferrin saturation of 60%. However, the availability and quality of laboratory facilities in Latin America vary, which can impede definitive diagnosis of iron overload.

Prognostic assessment of MDS

In Latin America, important decisions regarding the treatment of MDS patients are based on a predictive prognosis. The use of karyotype analysis is limited due to the relative scarcity of cytogenetic facilities. As a result, the prognostic assessment of MDS patients using the IPSS scale, which relies on karyotyping, is not possible in many centers in the region.

Health care issues

There are currently no specific guidelines available for the management of MDS or iron overload in Latin American countries. Although guidelines developed in other regions may be useful, they are often not entirely applicable due to differ-

ences in available health care resources. In addition, there is a lack of official programs to help with the education of MDS patients, particularly regarding the consequences of iron overload and potential benefits of chelation therapy.

The development of a regional registry for patients with MDS is considered a valuable resource as this would provide clinical and government decision-makers with a solid evidence base relating to the disease and its management. The Brazilian Pediatric MDS group, which was formed 10 years ago, has created a patient registry and the group is now beginning to receive recognition and support from the national government.

Access to chelation therapy

The proportion of patients with MDS who receive iron chelation, with deferoxamine being the first-line therapy, differs widely between Latin American countries (ranging from <5% in Panama to 40–50% in Brazil). Together with poor patient compliance to its demanding therapeutic regimen, the cost of infusion pumps is a key barrier to the use of deferoxamine in Latin America. In Brazil, for example, although deferoxamine is reimbursed by the government, the cost of the infusion pump must be borne by the patient. Deferiprone is available in some Latin American countries; however it is not reimbursed and therefore is not commonly used.

Europe

Hemoglobin levels and transfusion thresholds

In Europe, the general threshold hemoglobin value for initiating transfusions is 8 to 10 g/dL. However, individual threshold levels are recommended since needs may vary according to factors including gender, smoking habits, or heart problems. The post-transfusion target is not generally considered to be an important parameter in MDS patients and is not commonly monitored in Europe.

Evaluation of body iron levels

The assessment of serum ferritin is widely used for evaluating body iron levels, although the use of quantitative MR imaging is increasing in Europe. This contrasts with the situation in both Latin America and Asia-Pacific, where MR imaging is rarely used.

The St-Pierre MR imaging method for measuring liver iron is accurate and sensitive over a wide concentration range, is relatively easy to set up in a hospital with a modern MR imaging facility, and can potentially be standardized internationally. However, as a single assessment may take up to 20 minutes, it can be time-consuming to conduct. The T2* MR imaging method is faster to perform but not as easy to set up and is more suited to estimation of cardiac rather than liver iron levels. Once MR imaging is more widely available in Europe, it is likely to become the reference standard method for assessing body iron levels.

Chelation regimens

Deferoxamine is the first-line chelator used for treating iron overload in MDS and is reimbursed in many European coun-

tries. Although commonly used, clinicians acknowledge that deferoxamine subcutaneous infusion is inconvenient for patients. A number of Italian and German clinicians give deferoxamine in two daily bolus injections, although this method is difficult to administer and is uncomfortable for the patient. The discomfort can be eased by diluting the drug, however, it has been reported that a hypotonic injection can cause an increase in tissue fibrosis in patients with thalassemia. It is interesting that certain Swedish centers use the same deferoxamine administration technique used in Australia, as this is regarded as more convenient for the patient. In Germany, insurance companies keep a pool of infusion pumps that are given to patients when required. This ensures that the insurance company does not have to purchase a new pump for each individual patient. Patients in some European countries use disposable pumps, either 24-hour infusers or 5-day infusers. Although these infusers improve patient compliance, they are very expensive and require individual permission from the health authority.

Deferiprone is used for treating transfusional iron overload in Europe but it has not received European Medicines Agency approval in MDS. It is thought that the availability of an oral iron chelator may be beneficial for European patients and improve compliance, although specific data in MDS would be required.

Health care issues

A growing number of European health authorities are using guidelines and evidence-based data to determine the reimbursement of drug costs. With the current lack of data assessing chelation therapy in iron overloaded MDS patients, guidelines are becoming increasingly important. These are currently available in certain European countries such as France, Germany, and some Nordic countries. Specific guidelines for the treatment of MDS, including the treatment of iron overload in MDS, are being developed in Italy; these guidelines may be applicable to the whole of Europe.

Summary

The most significant regional considerations and intra-regional differences for the management of MDS and iron overload are apparent in Asia-Pacific. The major issue within this region, and the most striking point of difference with Europe and Latin America, relates to the use of deferoxamine, ie, intermittent as opposed to continuous administration. For Latin America, the most important issue is the relative lack of available diagnostic and therapeutic resource for managing MDS and iron overload, particularly compared with Europe; this is underlined by the relative availability of MR imaging in Europe. The development of a Latin American MDS Cooperative Group may help to persuade national governments as to the value of providing greater resource for the management of this disease.

References

- [1] Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, et al. World Health Organization classification of neoplastic dis-

- eases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. *J Clin Oncol* 1999;17:3835-49.
- [2] Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol* 1982;51:189-99.
- [3] Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89:2079-88.
- [4] Schafer AI, Cheron RG, Dluhy R, Cooper B, Gleason RE, Soeldner JS, et al. Clinical consequences of acquired transfusional iron overload in adults. *N Engl J Med* 1981;304:319-24.
- [5] Gattermann N, Cazzola M, Greenberg P, Maertens J, Soulieres D, Rose C, et al. The efficacy and tolerability of ICL670, a once-daily oral iron chelator, in patients with myelodysplastic syndrome (MDS) and iron overload. *Leuk Res* 2005;29(Suppl 1):S67.
- [6] Gonzalez FA, Arrizabalaga B, Villegas A, Alonso D, Castro M, Remacha A, et al. [Study of deferoxamine in subcutaneous profusion treatment of iron overload in myelodysplastic syndromes.] *Med Clin (Barc)* 2005;124:645-7.
- [7] Jensen PD, Heickendorff L, Pedersen B, Bendix-Hansen K, Jensen FT, Christensen T, et al. The effect of iron chelation on haemopoiesis in MDS patients with transfusional iron overload. *Br J Haematol* 1996;94:288-99.
- [8] Borgna-Pignatti C, Rugolotto S, De Stefano P, Piga A, Di Gregorio F, Gamberini MR, et al. Survival and disease complications in thalassemia major. *Ann NY Acad Sci* 1998;850:227-31.
- [9] Yang Q, McDonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of Multiple-Cause Mortality Data. *Ann Intern Med* 1998;129:946-53.
- [10] Brittenham GM, Griffith PM, Nienhuis AW, McLaren CE, Young NS, Tucker EE, et al. Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med* 1994;331:567-73.