Critical Reviews in Oncology/Hematology 117 (2017) 57–66

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Review

Overcoming barriers to treating iron overload in patients with lower-risk myelodysplastic syndrome

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Contents

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 12 June 2017
Accepted 3 July 2017

Keywords:
Acute myeloid leukemia
Iron chelation
Iron overload
Myelodysplastic syndrome

ABSTRACT

Myelodysplastic syndromes (MDS) constitute a group of heterogeneous hematopoietic neoplasms characterized by ineffective erythropoiesis, anemia, and/or cytopenias. Supportive care for patients with MDS involves frequent red blood cell transfusions, which places patients with ongoing transfusional dependence (TD) at risk for iron overload (IO). Development of IO and tissue iron deposition can increase the risk of cardiac, hepatic, and endocrine toxicities, infection, and progression to acute myeloid leukemia. Iron chelation therapy (ICT) is an option for lower-risk MDS patients to reduce their degree of IO and possibly improve survival; use of these agents in thalassemia patients with TD and IO has been associated with reduced IO-associated complications and better survival. At present, there are several barriers to the regular use of ICT, such as a lack of randomized trial evidence and consistent guidance on diagnosis of IO and when to implement ICT, as well as barriers in adherence to/tolerability of ICT.

1. Introduction

Myelodysplastic syndromes (MDS) constitute a heterogeneous group of hematopoietic neoplasms, which are characterized by ineffective hematopoiesis, cytopenias, and heightened risk of progression to acute myeloid leukemia (AML) (Garcia-Manero, 2015; Merkel and Nagler, 2014; Mitchell et al., 2013; Petrou et al., 2015).

Since most patients with MDS develop anemia, supportive therapy for MDS frequently involves regular transfusions, which can lead to iron overload (IO) (Mitchell et al., 2013; Petrou et al., 2015; Shenoy et al., 2014). Transfusion-dependent patients with MDS have an increased risk for IO as a result of receiving regular red blood cell (RBC) transfusions (Mainous et al., 2014; Shenoy et al., 2014). Goals of therapy for patients differ in lower-risk and higher-risk MDS; in lower-risk MDS, the goal of treatment is to reduce dependence on RBC transfusion, as well as to alleviate cytopenias and related complications, whereas in higher-risk MDS, treatment is geared to alter the natural history of disease, delay transformation to AML, and improve overall survival (OS) (Garcia-Manero, 2015; Komrokji

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http://dx.doi.org/10.1016/j.critrevonc.2017.07.002
1040-8428/

et al., 2013). RBC transfusion dependency has been associated with poor outcome in MDS, as has the degree of IO, as manifested by an elevated serum ferritin (SF) level, typically of 1000 ng/mL or higher (Pullarkat, 2009; Delea et al., 2009). IO may result in an increased risk of mortality in patients with MDS, and retrospective and/or observational studies suggest iron chelation therapy (ICT) may improve survival (Leitch et al., 2008; Mainous et al., 2014; Remacha et al., 2015; Lyons et al., 2014a). In particular, patients with lower-risk MDS who are likely to survive for longer periods are also at greater risk for developing complications from IO and would benefit from ICT (Mast and Field, 2012; Temraz et al., 2014).

The benefit of ICT has been clearly established in younger patient populations such as those with sickle cell disease and thalassemia, but its role in the treatment of IO in the older MDS population remains controversial (Mast and Field, 2012; Oliveiri et al., 1994; Merkel and Nagler, 2014; Neukirchen, 2014). There are several unresolved issues that currently exist regarding the regular use of ICT in patients with MDS (Neukirchen, 2014). These include barriers regarding the diagnosis of IO in patients with MDS, as the methods for evaluation of IO in this population have not yet been standardized. The lack of evidence-based clinical guidelines and the absence of randomized controlled trials of ICT in patients with MDS are also barriers to the implementation of ICT after diagnosis of IO in patients with MDS. Lastly, there are barriers to adherence to ICT; available ICTs differ in terms of their route of administration and overall tolerability profile, and there is also a general lack of guidance on how long therapy should be continued. In this review, we consider the issue of IO in patients with MDS and the potential benefit of ICT as a means to improve outcomes and extend survival. The potential barriers to the use of ICT and the means to overcome these barriers in patients with MDS are also discussed in relation to the available clinical evidence.

2. Iron metabolism: a brief overview

Iron is an essential nutrient for survival due to its requirement for oxygen transport and cellular respiratory processes, but it becomes toxic when present in excess. With no physiologic mechanism for its excretion, iron will accumulate in the body; levels of iron in the body must therefore be tightly regulated to maintain homeostasis. Iron is absorbed as a nutrient through the gut and also recycled from macrophage digestion of senescent RBCs via the reticuloendothelial system (RES) (Mitchell et al., 2013; Wood et al., 2015). Hepcidin, the principal negative regulator of iron export, acts by causing the degradation of the cellular iron export protein ferroportin, thereby reducing the absorption of iron through the gut, and preventing the release of stored iron from macrophages and hepatocytes (Fig. 1A) (Mitchell et al., 2013; Wood et al., 2015). When iron levels are low, hepcidin levels are low and intestinal iron absorption and release from stores is enhanced; conversely, when plasma iron levels are high, hepcidin levels are high, and the net uptake and release of iron into the blood is inhibited (Fig. 1B) (Mitchell et al., 2013; Wood et al., 2015). Transferrin serves as the principal binder of iron in the blood and facilitates its uptake and storage via the transferrin receptor (Mitchell et al., 2013; Shenoy et al., 2014). IO occurs when the capacity of transferrin to bind and store excess iron is saturated (Fig. 1B), resulting in the accumulation of reactive nontransferrin bound iron (NTBI) and labile plasma iron (LPI) (Mitchell et al., 2013). While IO is thought to be primarily due to chronic transfusions in MDS, IO may also occur as a result of ineffective erythropoiesis, which leads to anemia and increased erythropoetin levels, because iron is needed in the bone marrow for red cell production; the net result is hepcidin levels being inappropriately low (Fig. 1A), resulting in unrestrained iron absorption from the gut and release from the RES, and continued iron release into the plasma; (Temraz et al., 2014; Mitchell et al., 2013; Merkel et al., 2014; Shenoy et al., 2014).

The clinical impact of IO is substantial. Iron deposition in heart, liver, and endocrine tissues results in organ complications. Clear associations between SF level and cardiac disease-free survival, for example, have been demonstrated in patients with β-thalassemia (Oliveiri et al., 1994). Excess iron in the blood may also create a more favorable environment for infection by promoting the growth of certain types of bacteria and fungi (Mitchell et al., 2013). Elevated levels of toxic iron species such as LPI and NTBI result in increased reactive oxygen species (ROS), cellular damage to nucleic acids, proteins, and lipids, and may increase risk for transformation to AML (Mitchell et al., 2013). Recent animal models further support a deleterious impact of IO on hematopoiesis; in one study, hematopoietic potential was strongly inhibited with IO and this was related to oxidative stress (Chai et al., 2015). Accordingly, there are multiple mechanisms whereby IO can both exacerbate the disease process and contribute to adverse outcomes in patients with MDS.

3. Barriers to iron overload diagnosis in MDS: lack of standardized monitoring

One of the principal barriers to the regular use of ICT in patients with MDS is the lack of a standardized measure of clinically significant IO and defined criteria for implementation of ICT. Degree of IO may not be consistently monitored in patients with MDS due to a lack of prospective evidence from clinical trials. Diagnosis of IO can also be limited by the diagnostic resources available at the treating center. Some of the principal parameters for evaluating IO are summarized in Table 1. Simple and low-cost methods for assessment include counting the number of transfused units and measurement of SF levels (Merkel and Nagler, 2014; Mitchell et al., 2013; Shenoy et al., 2014; Temraz et al., 2014). SF is used to estimate the overall degree of IO and is a ubiquitously available, low-cost, and relatively well-standardized measure (Shenoy et al., 2014). Because it is an acute phase protein, however, SF can also be impacted by other factors, such as infection (Shenoy et al., 2014; Merkel and Nagler, 2014; Porter et al., 2016). Despite these limitations, a reasonably good correlation between SF and liver iron concentration (LIC), as evaluated by magnetic resonance imaging (MRI), has previously been observed across various populations (Roy et al., 2011; Porter et al., 2016).

LIC has been the reference standard to estimate body iron stores and is also used to estimate IO through biopsy. Due to its invasive nature, determinations of LIC via biopsy may not be feasible and/or indicated in patients with MDS, especially in the case of cytopenias such as thrombocytopenia (Shenoy et al., 2014; Merkel and Nagler, 2014; Temraz et al., 2014). Newer assessments such as MRI R2 may be used as a noninvasive alternative to measure LIC, although at present such measures may not be widely available for use in patients with MDS and may not necessarily be indicated for patients without evidence of liver dysfunction (Temraz et al., 2014). Cardiovascular MRI using T2* is a validated, noninvasive method used to identify patients with myocardial IO and appears to be superior to surrogates such as SF, LIC, ventricular ejection fraction, and tissue Doppler parameters (Petrou et al., 2015). Cardiac T2* MRI is correlated with left ventricular function but not with SF and LIC; at present, there is insufficient evidence that cardiac death in MDS results from IO (Neukirchen, 2014; Shenoy et al., 2014). LIC and MRI-based methods may also be less widely applicable and associated with higher costs compared with SF.

Further studies will be needed to establish the best assessments and exact indications for ICT in patients with MDS as well as its clinical impact on survival (Petrou et al., 2015). The TELESTO trial (NCT00940602), which is currently underway, aims to overcome