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Invited editorial

Iron overload in myelodysplastic syndromes: A Canadian consensus guideline

Richard A. Wells [a,*], Brian Leber [b], Rena Buckstein [a], Jeffrey H. Lipton [c], Wanda Hasegawa [d], Kuljit Grewal [e], Karen Yee [c], Harold J. Olney [f], Loree Larratt [g], Linda Vickars [h], Alan Tinmouth [i]

[a] *Myelodysplastic Syndromes Program, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*
[b] *Hamilton Health Sciences and McMaster University, Hamilton, Ontario, Canada*
[c] *University Health Network, Princess Margaret Hospital, Toronto, Ontario, Canada*
[d] *Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada*
[e] *Health Sciences Centre, St. John's, Newfoundland, Canada*
[f] *Centre Hospitalier de l'Université de Montreal, Hôpital Notre-Dame, Montreal, Quebec, Canada*
[g] *University of Alberta, Edmonton, Alberta, Canada*
[h] *BC Cancer Agency, Vancouver, British Columbia, Canada*
[i] *Ottawa Hospital, Ottawa, Ontario, Canada*

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Abstract

In December 2005, 11 Canadian hematologists met to develop an evidence-based clinical practice guideline that would address the diagnosis, monitoring, management, and rationale for the treatment of transfusional iron overload in patients with myelodysplastic syndromes (MDS). This Expert Panel consisted of hematologists from across Canada, each with an active practice in a major population centre or a rural area. Based on an extensive literature search and years of clinical experience, their mandate was to address common clinical practice questions, particularly why treat, whom to treat, when to initiate treatment, and how to treat iron overload in patients with MDS.

Keywords: Myelodysplastic syndromes; Iron overload; Secondary hemosiderosis; Iron chelation; Deferoxamine; Deferasirox; Desferal; Exjade; Deferriprone; Ferriprox; Transfusion; Prognosis; Guideline

1. Introduction

The prevalence of MDS has not been rigorously documented, although a recent analysis suggests it may affect as many as one in 1000 Canadians over the age of 65 years [1]. The main clinical feature of MDS is anemia, which is present in about 80% of patients at diagnosis and varies in severity. Although novel therapies are being developed that enhance bone marrow function and reduce or obviate the need for blood transfusion, currently more than 80% of MDS patients require chronic red blood cell transfusion as the cornerstone of treatment [2]. As a consequence, transfusional iron overload is a very common complication of MDS. It is widely thought that this complication of MDS is physiologically important and that the use of iron chelation therapy to prevent or ameliorate iron overload is a key consideration in the management of MDS patients [3], although this is not universally accepted. In this paper we provide a critical review of the basis in evidence for iron chelation in MDS, and provide guidelines for clinical practice.

2. Methodology

In December 2005, the Expert Panel reviewed national and international data on the contribution of transfusional iron overload to the morbidity and mortality of patients with MDS, the underlying

* Corresponding author. Tel.: +1 416 480 5248; fax: +1 416 480 6002.
E-mail address: rwells@sri.utoronto.ca (R.A. Wells).

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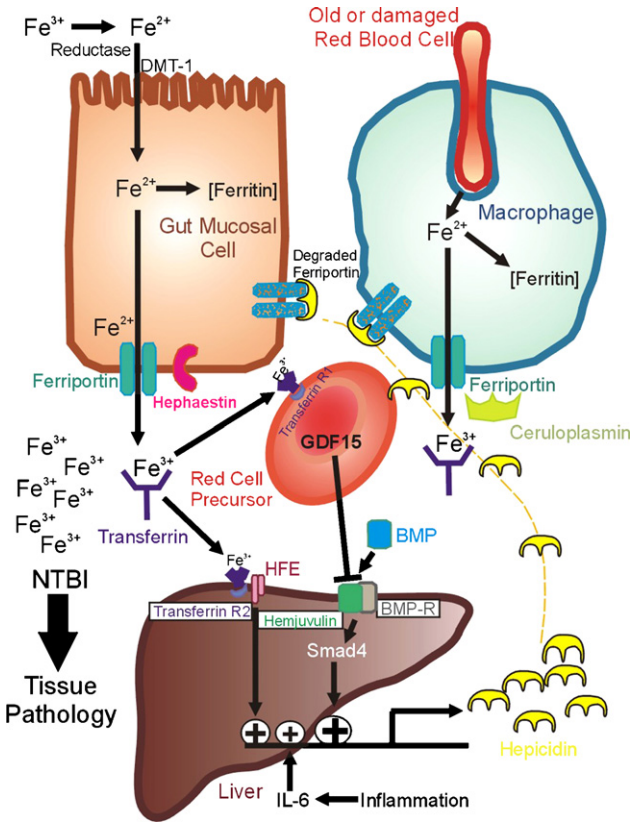

Fig. 1. Overview of Mechanisms Iron Transport. Iron enters the central transport and utilization compartment through two portals: as elemental iron that must be reduced from ferric (3+) to ferrous (2+) before transport though the DMT-1 transporter into Gut Mucosal Cells (or alternatively as heme iron through a selective heme receptor – not shown), and within the hemoglobin when old or damaged red cells are engulfed and digested by Macrophages. The latter entry point carries ~100–1000 times more iron flux than through the gut, especially in heavily transfused patients like those with MDS. In these cells, intracellular iron concentrations control the production of Ferritin, which sequesters iron in stores for later use, whereas unsequestered iron may be transported out of the cell. Iron exits the cell via Ferriportin, an activity which requires an associated oxidase – this function is performed for gut cells by the membrane bound Hephaestin, while for macrophages it is the plasma protein Ceruloplasmin. The oxidase activity allows the binding of ferric (3+) iron to Transferrin which tranports iron in blood and tissue fluid to its sites of use, predominantly Red Cell Precursors where it is taken up by Transferrin Receptor-1 and ultimately used to make hemoglobin. Iron egress from the portal cells is controlled by the liver protein Hepcidin, which acts as a plug to prevent iron release from these cells by binding to Ferriportin and targeting it for proteosomal destruction. Hepcidin production is controlled by many factors including inflammation through the IL-6 receptor, hypoxia through HIF1α (not shown) and at least two pathways that sense body iron load. One of these pathways involves Transferrin binding to hepatic Transferrin Receptor-2 which forms a complex with the HFE gene product to turn on hepcidin transcription; the other, stronger pathway is mediated by members of the Bone Morphogenetic Protein (BMP) family binding to one of the TGF receptors (BMP-R) in concert with Hemjuvulin; receptor binding activates the SMAD-4 transcription factor to make more Hepcidin. Recently it has been shown [82] that red cell precursors contain GDF15, that when released from these cells during the intramedullary hemolysis associated with ineffective erythropoieisis in thalassemia and some cases of MDS, prevents the Hemjuvulin/BMP upregulation of Hepcidin; this then causes increased iron uptake and overload. Inherited loss of function mutations in HFE, Hemjuvulin, Hepcidin, Transferrin Receptor-2, Ferriportin and Ferritin are associated with hereditary hemochromatosis types I, IIA, IIB, III, IV and V, respectively. In all cases of iron overload, whether hereditary or due to transfusion, the egress of iron from the portal cells overwhelms the ability of Transferrin to bind to iron (Fe3+) leading to free, Non-Transferrin Bound Iron (NTBI), that mediates the Tissue Pathology.

pathology of iron-related tissue and organ damage, and the current evidence for iron chelation therapy in patients with MDS. The panel examined existing clinical guidelines, discussed standard practices in Canada, and devised a comprehensive outline to guide their investigation. This work focused on the critical questions mentioned above: why, whom, when, and how to treat iron overload in patients with MDS.

The Expert Panel was divided into four subgroups, each responsible for the investigation of one key question. Each subgroup was assigned the task of conducting an extensive search and thorough review of the medical literature pertaining to their question. The Expert Panel agreed on a protocol for the literature search and review, which included an extensive search terminology and the ranking of clinical evidence according to currently accepted standards as outlined by the British Committee for Standards in hematology [4]. The literature search considered all articles on MDS published prior to January 2006 (EMBASE, Ovid MEDLINE®) and key abstracts from annual meetings of the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH), dating from 2000, and the 8th International MDS symposium in 2005. The search was designed to unearth clinical studies of any size dating from 1980, physiological studies dating from 1960, and review articles. Each subgroup presented their findings to the Expert Panel for discussion. A second scan for recent clinical studies was performed in December 2007, encompassing publications in 2006 and 2007.

In February 2006, the Expert Panel reviewed the results of the literature search and proposed recommendations for clinical practice. Based on the clinical evidence in the literature, and on expert opinion in areas where this evidence was lacking or rated as poor, the Expert Panel reached a consensus on recommendations for iron chelation in patients with MDS. These recommendations are presented in this article.

To aid this project, Novartis Canada provided an educational grant to support the cost of meetings and literature searches.

3. Why treat iron overload in patients with MDS?

Since each unit of red blood cells (RBCs) contains 200–250 mg of iron, approximately 100 times the normal daily iron flux, patients who require chronic blood transfusions are prone to develop iron overload. In addition to transfusional iron loading, MDS patients have increased intestinal absorption of iron, similar to patients with hemoglobinopathies and genetic hemaochromatosis (HH) [5]. Hence, MDS patients may show evidence of iron loading even prior to initiation of transfusion therapy.

Iron overload may cause or contribute to organ failure and is associated with a variety of disorders, including infections, renal disease, liver disease, and malignancy. Most evidence pertaining to transfusion-associated hemosiderosis is derived from the hemoglobinopathy literature. Zurlo et al. evaluated