

Canadian Oncology Nursing Journal

Revue canadienne de soins infirmiers en oncologie

Volume 26, Issue 1 • Winter 2016
ISSN: 1181-912X (print), 2368-8076 (online)



Canadian Association of Nurses in Oncology
Association canadienne des infirmières en oncologie

Management of iron overload in the Canadian hematology/oncology population: Implications for nursing practice

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ABSTRACT

Red blood cell (RBC) transfusions are vital for many patients with chronic anemias associated with oncologic/hematologic disorders. However, repeated transfusions over time can lead to iron overload, which, if left untreated, can increase the risk of further malignancy and end-organ damage.

Nurses and other health care professionals may not be aware of the significant implications of RBC transfusions and iron overload in patients with hematological/oncological disorders. This article was developed by a group of Canadian nurse practitioners and specialized oncology nurses to help improve health care professionals' understanding of iron overload in oncology patients and its associated risks, as well as provide a practical guide for the management of patients receiving treatment for this potentially serious condition.

Key words: oncology, malignant hematology, iron overload, iron chelation therapy, nursing practice

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Conflicts of interest: The authors have no conflicts of interest to declare regarding the content of this manuscript.

DOI: 10.5737/236880762611928

INTRODUCTION

As new treatments, transplant options and supportive care strategies become available for hematologic/oncologic disorders, patients with these conditions are now living longer (Fenaux et al., 2009). Given the ineffective hematopoiesis associated with many of these disorders, a significant proportion of these patients will require chronic red blood cell (RBC) transfusions, which can result in transfusion-related iron overload. If left unrecognized and untreated, iron overload can lead to an increased risk of infection, malignancy, and end-organ damage.

Through patient advocacy organizations, patients with hematologic/oncologic disorders are now well-informed about iron overload and its associated risks, and many mistakenly believe that all patients receiving transfusions should be monitored and treated for iron overload. However, monitoring for iron overload is not considered a “standard of care” for all patients and, therefore, nurses must be able to respond to patient concerns and queries and provide appropriate guidance. Often, such guidance can be as simple as advising patients that the need for monitoring iron status and treating iron overload varies from patient to patient and that this should be discussed further with their respective physicians.

In some Canadian centres, nurse practitioners are responsible for providing supportive care for patients with hematologic/oncologic disorders, including the provision of blood transfusions and monitoring of blood counts. These nurses, in particular, must be well-informed to ensure that they work collaboratively with physicians to identify and manage patients who fulfill the criteria for iron overload screening and/or treatment.

This article was developed by a group of Canadian nurse practitioners and specialized hematology/oncology nurses to provide health care professionals with a review of normal iron physiology, the consequences of transfusional iron overload, and current Canadian iron chelation guidelines, as well as a practical guide for managing treatment-related complications.

WHAT IS THE NORMAL PHYSIOLOGY OF IRON?

Under normal conditions, the human body stores approximately 3.5 g of iron. Most of this iron is distributed within the RBC (a component of hemoglobin), with the remainder being stored in muscle fibres, macrophages, the liver, and bone marrow. On average, 1–2 mg of iron is absorbed daily via the duodenum, with the same amount being excreted through sloughing of mucosal cells, desquamation of epithelial cells,

and blood loss during menstruation (Figure 1) (Andrews, 1999; Stein, Hartmann, & Dignass, 2010). Because the same amount of iron is absorbed and eliminated on a daily basis, the iron pool represents a closed system (Shah et al., 2012). Therefore, the human body has no effective means of naturally disposing of excess iron.

Although iron is physiologically critical, excess iron is toxic. Due to its ability to donate and accept electrons, iron can catalyze the conversion of hydrogen peroxide into free radicals if it is left unbound within cells. These free radicals, in turn, can cause damage to a number of cellular structures and processes, leading to cell death. To prevent this free radical formation, iron must be bound to proteins (Andrews, 1999) (see Table 1 for definitions of the most important iron-binding proteins). It is important to note that 80% of the body's daily iron needs are used for the production of new RBC, which requires only 20–25 mg of iron (Shah et al., 2012).

HOW DOES TRANSFUSION DEPENDENCE LEAD TO IRON OVERLOAD?

RBC transfusions are vital for many patients with chronic anemias, including those associated with α -thalassemia, myelodysplastic syndromes (MDS), and, to a lesser extent, sickle cell disease (SCD). However, multiple or repeated transfusions over time can lead to iron overload. Each unit of packed RBC contains approximately 200–250 mg of iron which, as discussed earlier, the body is unable to eliminate (Porter, 2001). After approximately 20 transfusions, an individual who is not hemorrhaging will have accumulated approximately 5 g of unexcretable iron—nearly double the amount of iron normally found in the body (List, 2010). As per normal iron physiology, this excess iron attempts to bind to transferrin to be transported to cells and stored as ferritin. However, if a person continues to have transfusions for conditions other than hemorrhaging, the capacity for transferrin to bind iron is exceeded (or saturated) resulting in “free” or non-transferrin-bound iron (NTBI). As stated earlier, this “free”, unbound iron is toxic to cells, leading to inflammation, fibrosis and organ dysfunction (Leitch, 2011). As blood levels of NTBI increase, tissue absorption of toxic NTBI results in iron deposits in various organs including the heart, liver, and endocrine glands. Elevated levels of iron in the liver leads to an increased risk of hepatic dysfunction and cirrhosis, while excess iron in the heart is associated with an increased risk of cardiac-related events including myocardial infarction, congestive heart failure, and arrhythmias. Excess iron in the endocrine system can lead to gonadal and thyroid dysfunction, as well as diabetes (Shah et al., 2012; Porter, 2001).

WHAT ARE THE CLINICAL CONSEQUENCES OF TRANSFUSION-RELATED IRON OVERLOAD IN PATIENTS WITH HEMATOLOGIC/ONCOLOGIC DISORDERS?

In patients with thalassemia, it has been well-documented that transfusion-related iron overload leads to cardiac iron deposition, heart failure, and reduced overall survival (Zurlo et al.,

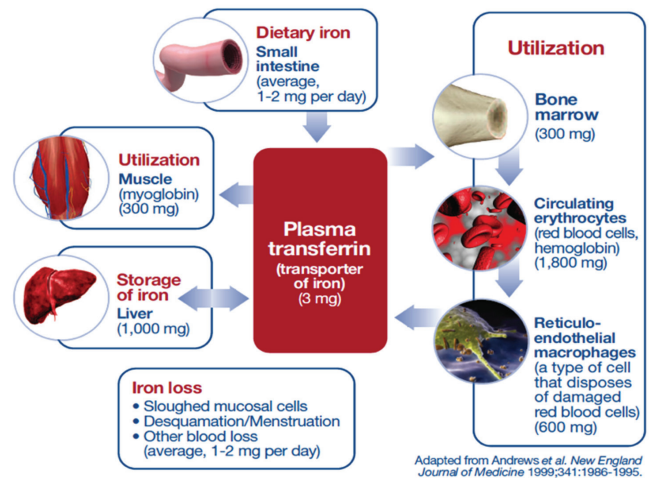


Figure 1: Iron homeostasis under normal conditions.

Protein	Function
Heme:	• Found in red blood cells (RBC)
Ferritin:	• Intracellular protein that functions as the primary form of iron storage • Provides an indirect measure of the amount of iron stored in the body
Transferrin:	• Responsible for iron transport • Provides a measure of iron circulation
Ferroportin:	• Transmembrane protein that transports iron from inside to outside the cell

1989; Schafer et al., 1981), and that long-term treatment with iron-chelating agents (drugs that trap and remove excess iron, which is then excreted in the stool or urine, depending on the iron chelator prescribed in these patients) reduces cardiac and hepatic complications and improves survival (Zurlo et al., 1989; Gabutti & Piga, 1996; Borgna-Pignatti et al., 2004).

Although chronic transfusion therapy is the primary cause of iron overload in MDS patients, the clinical importance of iron overload and its management in this patient population is somewhat controversial since data in this area has primarily been derived from retrospective studies. Further complicating this issue is the fact that age-related comorbidities are common in MDS, making it difficult to determine whether organ damage is due to transfusion therapy or these comorbid conditions. Nonetheless, findings from retrospective studies suggest that iron overload may have clinical consequences in MDS, such as organ dysfunction and reduced leukemia-free and overall survival (Schafer et al., 1981; Malcovati et al., 2005; Sanz et al., 2008; Takatoku et al., 2007). Prospective trials are required to confirm these findings.

There is also growing evidence that iron overload prior to hematopoietic stem cell transplantation (HSCT) may affect transplant outcomes. A number of primarily retrospective

Test	Advantages	Disadvantages
Ferritin test (most common method)	<ul style="list-style-type: none"> • Non-invasive • Widely available • Useful in deciding when to initiate therapy • Useful in monitoring treatment effectiveness 	<ul style="list-style-type: none"> • Measurement values are altered by inflammation, infection and ascorbic acid (vitamin C) deficiency • Does not correlate with total body iron
Liver biopsy (liver iron concentration) (Limited use due to risk)	<ul style="list-style-type: none"> • Correlates well with total body iron burden • Allows for assessment of liver histology • High levels predict risk for cardiac disease, endocrine complications and death 	<ul style="list-style-type: none"> • Invasive • Accuracy affected by sample size • Sampling errors due to fibrosis and uneven distribution of iron • Cardiac disease may be present when liver iron is low
MRI (used to evaluate abnormal liver enzymes in patients with elevated ferritin)	<ul style="list-style-type: none"> • Non-invasive • More widely available • Correlates well with liver iron concentration by biopsy 	<ul style="list-style-type: none"> • Expensive • Variety of techniques and analytic programs may limit comparability • Cardiac disease may be present when liver iron is low
Cardiac iron loading by MRI (used primarily to evaluate cardiac symptoms in patients with elevated ferritin)	<ul style="list-style-type: none"> • Non-invasive • Correlates with risk for cardiac disease 	<ul style="list-style-type: none"> • Expensive • Difficult to validate without biopsy specimen

Reproduced from: MDS Foundation. (2011). Anemia, Blood Transfusions, Iron Overload, and Myelodysplastic Syndromes: A Handbook for Adult MDS Patients. Available at: <http://www.mds-foundation.org/pdf/AnemiaBloodTransfusionsIronOverloadAndMDS-5-16-11.pdf>

studies have found high pre-transplantation serum ferritin levels to be associated with reduced overall survival and increased complications after HSCT, particularly in the MDS and leukemia populations (Pullarkat, 2010). A prospective study of HSCT patients also found serum ferritin values $\geq 1,000$ $\mu\text{g/L}$ to be associated with a significant increase in blood stream infections (Pullarkat et al., 2008). At present, however, the role of iron chelation therapy in the pre-transplant population is unknown, and further prospective studies in this area are required.

It is important to note that iron overload has also been associated with both impaired immunity and heightened microbial virulence. Specifically, iron overload has been found to inhibit inflammatory markers and nitric oxide, and impair macrophage, neutrophil and T-cell function (Álvarez, Fernández-Ruiz, & Aguado, 2013; Pieracci & Barie, 2005; Ibrahim et al., 2011).

HOW DO WE BEST IDENTIFY IRON OVERLOAD?

Although many tests are available to assess iron overload (see Table 2), serum ferritin level (which provides an indirect estimate of iron overload) is the most commonly used since it is widely available, affordable, and easy to perform repeatedly, which can provide trends over time in patients with variable transfusion intervals. Normal values for serum ferritin are usually in the range of 12–300 $\mu\text{g/L}$ for men and 12–150 $\mu\text{g/L}$ for women. Serum ferritin levels greater than 1,000–2,500 $\mu\text{g/L}$ indicate iron overload (Malcovati et al., 2007).

Serum ferritin has been shown to correlate with the number of RBC transfusion units received, with a value of 1,000 $\mu\text{g/L}$ often reached after as few as 20 units (Malcovati et al., 2005). A major disadvantage of the ferritin test is that results are affected by inflammation, infection, liver disease and ascorbic acid (vitamin C) deficiency. Therefore, the assessment of “trends” in ferritin levels over time is most useful for monitoring iron overload (Malcovati et al., 2007). In general, it is recommended that serum ferritin be assessed at the time of diagnosis and repeated every three months in transfusion-dependent patients.

The transferrin saturation (TS) test is another sensitive and relatively inexpensive biochemical measure of iron overload that can be performed along with serum ferritin (TS levels $>50\%$ are considered elevated). In clinical practice, however, the TS test is not often used in the assessment of transfusion-related iron overload (Gattermann, 2009).

The most precise method and, therefore, the current gold standard for determining body iron is the measurement of liver iron concentration (LIC). However, its assessment requires a percutaneous liver biopsy, which may not be feasible in some patients (Malcovati, 2007). Magnetic resonance imaging (MRI) can also be used to measure tissue iron content. However, this modality is expensive and not yet widely available for the assessment of iron overload in the oncology population. Nonetheless, it has been researched and is the standard of care for the assessment of iron overload in patients with RBC disorders receiving transfusions (Carson & Martin, 2014).

In addition to the above mentioned tests, it is imperative that patients be instructed to keep track of the number

Table 3: Canadian guidelines for the identification and management of iron overload in patients with MDS (Wells et al., 2008)	
Serum ferritin level representing iron overload:	>1,000 µg/L
Patient selection criteria:	<ul style="list-style-type: none"> • Transfusion-dependent • Good prognosis • Life expectancy > 1 year • Transplant candidate
Target serum level:	<ul style="list-style-type: none"> • Decrease ICT when < 2,000 µg/L • Discontinue ICT when < 1,000 µg/L
Recommended monitoring techniques for iron status:	<ul style="list-style-type: none"> • Serum ferritin
<i>ICT: iron chelation therapy</i>	

of transfusions they have had since this will assist health care professionals in assessing the patient's overall risk of iron overload. Excellent tracking tools for patients are available through the MDS Foundation at www.mds-foundation.org (see *Building Blocks of Hope: Strategies for Patients & Caregivers Living with MDS and Anemia, Blood Transfusions, Iron Overload, and Myelodysplastic Syndromes: A Handbook for Adult MDS Patients*).

WHAT ARE THE CURRENT CANADIAN GUIDELINE RECOMMENDATIONS FOR THE IDENTIFICATION AND MANAGEMENT OF IRON OVERLOAD?

Definitive evidence has shown that iron overload negatively impacts overall survival and morbidity, and that iron chelation therapy improves both survival and complication rates in the thalassemia population. As a result, iron chelation therapy has been incorporated into the Canadian guidelines for thalassemia management (Anemia Institute for Research & Education, Thalassemia Foundation of Canada, 2009) and is a standard of care in current clinical practice for this patient population. Although similar iron overload guidelines have been in existence since 2008 for patients with MDS (Wells et al., 2008), their integration into the clinical management of these patients has not yet been fully adopted. Therefore, we have focused this section on these latter recommendations to help increase awareness and utilization of these Canadian consensus guidelines, which are summarized in Table 3 (Wells et al., 2008). As can be seen in the table, these guidelines recommend that iron chelation therapy be considered in transfusion-dependent MDS patients with a good prognosis (as indicated by an IPSS score of low or int-1), a serum ferritin level >1,000 µg/L, a life expectancy > 1 year, or in those who are candidates for allogeneic hematopoietic stem cell transplantation (Wells et al., 2008). In general, the Canadian consensus recommendations for iron overload in MDS are consistent with other published guidelines as identified through a MEDLINE search (Gattermann, 2008;

NCCN 2015) in terms of: the subgroups of MDS patients who should be considered for iron chelation therapy; the serum ferritin level that defines iron overload; the use of chelating agents; and the monitoring of chelation therapy (Wells et al., 2008).

As mentioned earlier, another patient population that may be negatively affected by iron overload are those who have had, or who are scheduled to undergo HSCT. Although several publications on the impact of iron overload in these patients have been noted in the literature (Meyer et al., 2013; Trottier et al., 2013; Pullarkat 2010; Lee et al., 2009), we were unable to locate any guidelines through a MEDLINE search that specifically addressed this patient population.

ARE THE CURRENT CANADIAN GUIDELINES FOR IRON OVERLOAD BEING USED CONSISTENTLY IN CLINICAL PRACTICE?

As a group of nurses working with MDS patients in two major Canadian cancer centres, we continue to witness inconsistent use of guideline recommendations for identifying and managing iron overload and hypothesize that this is due, at least in part, to the low level of evidence supporting these recommendations. We refer the readers to an interesting article by Steensma (2011), which highlights the controversy surrounding the importance of iron chelation and the lack of strong evidence supporting guideline recommendations.

Even the authors of the Canadian guidelines have acknowledged that their recommendations are based, for the most part, upon a low level of evidence (i.e., evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities) and extrapolation from data in other diseases, particularly thalassemia major. Specifically, the patient selection criteria for iron chelation therapy and monitoring recommendations are based on the least desirable level of evidence (IV) and the lowest grade (C) according to the British Committee for Standards in Hematology. The recommendations for chelation therapy, however, are based on stronger evidence (level IIb, grade B). The guideline authors further highlight that although prospective randomized studies of the effects of iron chelation therapy are needed, these are unlikely to be conducted in the near future given the expense of such trials and the ethical considerations associated with a “no chelation” arm. Nonetheless, attempts are currently being made to validate and strengthen the Canadian guideline recommendations. A study comparing the effects of iron chelation (with deferasirox) to placebo on cardiac and liver function and mortality in patients with low-risk MDS and transfusion-related iron overload (ClinicalTrials.gov Identifier: NCT00940602 – Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy Study) was initiated in 2010, with completion expected in 2018. There is also a Canadian MDS Patient Registry that has been collecting health information, such as serum ferritin levels and number of RBC transfusions, since 2010. This registry, which continues to collect data, will provide valuable information about iron overload in the Canadian MDS population in the near future.

Table 4: Overview of iron chelating agents available for the treatment of iron overload (Shah et al., 2012; Bring et al., 2008).

	Iron-Chelating Agent		
	Deferoxamine (Desferal)	Deferasirox (Exjade)	Deferiprone (Ferriprox)*
Route of administration	Subcutaneous, intramuscular or intravenous	Oral	Oral
Dosage	25–50 mg/kg/day over 8–24 hours	20–30 mg/kg/day	75 mg/kg/day
Frequency of administration	3–7 days/week	Once daily	Three times daily
Efficiency of chelation (drug: iron ratio)	1:1	2:1	3:1
Oral bioavailability	Poor (due to large size)	High	High
Half-life	10-20 min	8-16 hrs	2-3 hrs
Time to peak	4 hrs (SC infusion)	1.5 – 4 hrs	1 hr
Target site for iron removal	Plasma and liver	Liver and kidneys	Liver and heart
Routes of iron excretion	Urine, bile	Feces	Urine
Adverse effects	<ul style="list-style-type: none"> • Injection-site reactions • Hearing and vision abnormalities • Skeletal abnormalities • Yersinia infections 	<ul style="list-style-type: none"> • Skin rash • Mild GI symptoms • Non-progressive serum creatinine elevations • Mild aminotransferase elevations • Hearing and vision abnormalities 	<ul style="list-style-type: none"> • Agranulocytosis • Transient neutropenia • Arthralgias/arthropathy • Mild GI symptoms • Mild aminotransferase elevations

*In Canada, deferiprone is only approved for the treatment of iron overload in patients with some thalassemia syndromes who have had an inadequate response to previous iron chelation therapy.

GI: gastrointestinal

WHAT IRON-CHELATING AGENTS ARE CURRENTLY AVAILABLE FOR THE MANAGEMENT OF IRON OVERLOAD?

There are currently three iron-chelating agents available for the treatment of iron overload: deferoxamine (Desferal), deferasirox (Exjade) and deferiprone (Ferriprox) (see Table 4). Introduced more than 40 years ago, most clinical experience is associated with deferoxamine. However, because it must be administered via parenteral infusions over eight to 24 hours, three to seven days per week, maintaining treatment with deferoxamine is often suboptimal.

Deferasirox is an oral iron chelator that was approved in Canada in 2006 for the treatment of chronic iron overload in patients with transfusion-dependent anemias and non-transfusion-dependent thalassemia syndromes. The drug is administered once daily and should be dissolved (dispersed) in non-carbonated water or juice (except grapefruit juice) prior to ingestion. Deferasirox has been associated with greater patient satisfaction and continuation with therapy than deferoxamine (Taher et al., 2010) given its ease of administration.

Deferiprone is another oral iron chelator that has been available for more than 25 years in several countries. Because its iron-binding efficiency (drug-to-iron ratio of 3:1) is less than that of deferoxamine and deferasirox, it is generally

used as second-line therapy in patients who have had suboptimal responses to prior iron chelation therapies. In Canada, deferiprone has recently been approved for the treatment of iron overload in patients with some thalassemia syndromes who have had an inadequate response to previous iron chelation therapy.

It is important to note that access to these iron-chelating agents can be difficult for many patients without private drug insurance coverage, since government-assisted coverage varies from province to province. In fact, this may represent yet another barrier to implementation of current Canadian guideline recommendations for the management of iron overload. Drugcoverage.ca is an excellent online resource that provides information on drug reimbursement across Canada.

WHAT ARE THE SIDE EFFECTS ASSOCIATED WITH IRON CHELATION THERAPY AND HOW CAN NURSES HELP MANAGE THESE ADVERSE EVENTS?

Careful selection and identification of patients who will clearly benefit from iron chelation therapy must be performed on a case-by-case basis and be continuously re-evaluated against the potential for chelation-associated adverse events (Shah et al., 2012).

Table 5: Strategies for the management of adverse events associated with iron chelation therapy (Vichinsky, 2008; UHN, 2012)

Adverse Event	Management Approach
Deferoxamine	
Localized injection-site reactions	<ul style="list-style-type: none"> • Ensure: <ul style="list-style-type: none"> • Patient is rotating administration sites (lateral arms, legs and abdomen) • Correct dilution and rate of infusion • Patient is not experiencing a reaction/allergy to dressing or adhesives used to secure needle • If reactions persist despite the above, consider diluting the drug or adding 1 mg of hydrocortisone to the infusion. • Advise patient on the use of Thalaset needles which have a small gauge and needle size.
Auditory adverse events	<ul style="list-style-type: none"> • Baseline auditory assessment to rule out sensorineural hearing loss. • If tinnitus occurs, hold drug and refer for repeat audiology assessment (monthly) until hearing stabilized. • Reinitiate treatment at a lower dose once complaints have resolved, and monitor hearing closely.
Ocular adverse events	<ul style="list-style-type: none"> • Baseline ophthalmological assessment to rule out macular or retinal pigment epithelial disease. • If ocular events occur, hold drug and refer patient for repeat ophthalmological assessment. • Re-initiate drug at lower dose once visual complaints have resolved, and monitor vision closely.
Elevated serum creatinine or liver enzymes	<ul style="list-style-type: none"> • Obtain baseline measurements of serum creatinine and aminotransferases. • If serum transaminase elevations occur, consider other possible causes (e.g., viral hepatitis, increasing hepatic hemosiderosis, inadequate chelation, or concomitant medications). • If renal toxicity suspected due to increasing creatinine levels, interrupt therapy or reduce dose. • Inform patients that their urine may show a reddish discoloration.
<i>Yersinia enterocolitica</i> / <i>Yersinia pseudotuberculosis</i> infections	<ul style="list-style-type: none"> • If patient complains of diarrhea, discontinue treatment until infection resolves and send stool specimen for testing.
Deferasirox	
GI events	<ul style="list-style-type: none"> • Change timing of administration (evening administration, with or without food, may significantly improve GI tolerability). • Diarrhea: Advise patient to take antidiarrheals for up to 2 days, and keep hydrated. If patient is lactose intolerant, advise on lactase supplementation (e.g., Lactaid) and/or avoidance of dairy. • Abdominal pain: Advise patient to sip water or other clear fluids and avoid solid food for the first few hours. Avoid narcotic pain medication and NSAIDs. • Nausea/vomiting: Drink small, steady amounts of clear liquids, such as electrolyte solutions, and keep hydrated.
Skin rash	<ul style="list-style-type: none"> • Mild-to-moderate: Continue therapy without dose adjustment as rash likely to resolve spontaneously. • Severe: Interrupt treatment; reintroduce at a lower dose and gradually escalate dose. Consider long-acting antihistamines and/or short-course of low-dose oral corticosteroids if required.
Changes in serum creatinine	<ul style="list-style-type: none"> • Assess serum creatinine levels in duplicate before therapy (baseline), then monthly (more frequent monitoring if patient has additional renal risk factors). • >33% increase above pretreatment values at two consecutive visits (not attributable to other causes): Reduce dose by 5-10 mg/kg. • Persistent or progressive increases beyond ULN: Discontinue. <ul style="list-style-type: none"> • If clinical benefit of deferasirox outweighs the potential risks, reinitiate at a lower dose once levels have normalized, followed by gradual dose escalation if appropriate.
Liver function changes	<ul style="list-style-type: none"> • Monitor liver function at baseline then monthly. • Severe and/or persistent elevations in transaminase levels: Modify dose and re-introduce with a slow escalation schedule once levels return to normal.
Deferiprone (Ferriprox)	
Agranulocytosis	<ul style="list-style-type: none"> • Stop the drug immediately and consider use of G-CSF. • Do not rechallenge in the future.
Neutropenia	<ul style="list-style-type: none"> • Temporarily discontinue drug until resolved.
Arthropathy	<ul style="list-style-type: none"> • Monitor for signs/symptoms and consider referring patient for X-ray of ultrasound or joint. • Consider dose reductions and/or analgesics (NSAIDs). • If symptoms become debilitating, refer to rheumatology and/or orthopedic surgery.
GI: gastrointestinal; ULN: upper limit of normal; G-CSF: granulocyte-colony stimulating factor; NSAIDs: non-steroidal anti-inflammatory drugs	

The adverse events associated with the currently available iron chelation therapies are reviewed in this section, and practical strategies for their management are summarized in Table 5. It is important to bear in mind that the side-effect profile and management of adverse events with chelators has been well researched in hemoglobinopathy patients (thalassemia and sickle cell anemia). The following nursing management considerations are based on research and experience with this population, since there is a lack of research on the side-effect profile in oncology patients.

Deferoxamine (Desferal)

Localized injection-site reactions are common with deferoxamine use. It is important for nurses to ensure patients are rotating the site of administration (lateral arms, legs and abdomen) and that the correct dilution and rate of infusion are being utilized (Eckes, 2011). Patients should also be advised on the use of Thalaset needles, which may be less likely to cause localized reactions given their small gauge and needle size.

Ocular and auditory adverse events have also been observed with deferoxamine, as well as deferasirox use (Wells et al., 2008; Eckes, 2011), and tend to occur at lower serum ferritin levels (<1,000 µg/L). Therefore, prior to treatment, patients require baseline ocular and audiology testing (note that the consult form/letter should specifically state that these tests are being ordered as baseline assessments prior to the initiation of deferoxamine or deferasirox therapy). If the patient complains of tinnitus and/or visual loss while on treatment, it is important to hold deferoxamine and refer the patient for repeat ophthalmologic or auditory assessment. Once these complaints have resolved, deferoxamine can be re-initiated at a lower dose.

Elevations in serum creatinine levels and liver enzymes have also been noted in patients taking deferoxamine and, therefore, baseline measurements should be obtained prior to treatment. If transaminase increases occur following treatment initiation, other possible causes of altered liver function should be considered. If renal toxicity is suspected due to increasing creatinine levels, deferoxamine should be interrupted or the dose reduced. Patients using deferoxamine should also be informed that their urine may reveal a reddish discoloration.

Iron overload increases susceptibility to the Gram-negative bacterial infections *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*, which result in gastrointestinal (GI) and tuberculosis-like symptoms. In rare instances, treatment with deferoxamine has enhanced this susceptibility, resulting in generalized infections. In patients complaining of diarrhea, a stool specimen should be sent for testing and deferoxamine should be discontinued until the infection resolves.

Deferasirox (Exjade)

Transient GI symptoms, such as abdominal pain, diarrhea, nausea and vomiting, are the most common adverse events associated with deferasirox therapy. Many of these GI disturbances can be avoided or minimized if patients are initiated on a low dose, with gradual dose increases every 3-5 days until the full dose is achieved. Although the prescribing information for deferasirox states that the drug should be taken in the

morning on an empty stomach, it is important that patients experiencing GI events try administering deferasirox at different times of the day, with or without food intake (e.g., two hours after the evening meal), since this has been associated with improved GI tolerability (Vichinsky et al., 2008; Goldberg et al., 2013). Also, altering the timing of administration does not impact drug efficacy.

In patients experiencing diarrhea with deferasirox, adequate hydration should be maintained and the administration of antidiarrheals for up to two days when initiating treatment is advised (Vichinsky, 2008). Patients experiencing abdominal pain should be advised to avoid solid food for the first few hours after ingestion, and to avoid narcotic pain medication and non-steroidal anti-inflammatory drugs (NSAIDs). Although skin rash can occur in some patients treated with deferasirox, it tends to resolve spontaneously without the need for treatment interruptions or dose adjustments (Vichinsky et al., 2008).

Elevations in serum creatinine levels and proteinuria have also been observed in patients receiving deferasirox, and these tend to be dose-related and non-progressive in nature. Management should be individualized based on the magnitude of the patient's elevations (see Table 5) (Vichinsky, 2008). Liver enzyme elevations have also been reported in a small proportion of patients treated with deferasirox. If severe or persistent elevations occur, treatment interruption or dose modifications should be considered and a hepatologist should be consulted (Vichinsky et al., 2008).

Deferiprone (Ferriprox)

Transient GI side effects have also been noted in patients treated with deferiprone. Although less common, more serious side effects, such as agranulocytosis, neutropenia, arthropathy and arthralgias, have also been observed in patients treated with this agent (Eckes, 2011; Hoffbrand, Taher, & Cappellini, 2012). In cases of agranulocytosis and neutropenia, deferiprone should be held until neutropenia resolves. Treatment with granulocyte-colony stimulating factor (G-CSF) can be considered if neutropenia is not resolving. Dose reductions and the use of analgesics/NSAIDs should be considered for those with arthropathy/arthralgias.

WHAT NON-PHARMACOLOGICAL INTERVENTIONS ARE AVAILABLE FOR IRON OVERLOAD?

In some circumstances, hemoglobin normalizes as a response to treatment, such as those with a successful stem cell transplant or those who respond to chemotherapy such as azacitidine. Depending on how many transfusions were required, a certain population of these patients may have iron overload. In these situations, the most effective way to rid the body of excess iron is through phlebotomy (blood removal): 200–400 mL every four to eight weeks, depending on patient tolerance. Careful monitoring of hemoglobin and ferritin levels is important during this time to ensure the patient does not become anemic. The duration of phlebotomies will be directly related to the degree of iron overload.

Table 6: Baseline assessment and monitoring recommendations for patients on iron chelation therapy (Wells et al., 2008; UHN, 2012)

	Baseline	Monitoring
Deferoxamine (Desferal)	<ul style="list-style-type: none"> • Ferritin • ALT, Cr • Cardiac MRI T2*, R2 Liver MRI (Ferriscan®) • Ophthalmology and audiology assessments 	<ul style="list-style-type: none"> • Ferritin every 3 months • ALT, Cr every 3 months • Cardiac MRI T2*, R2 Liver MRI (Ferriscan®) annually • Screen for ocular/auditory events at every visit • Ophthalmology and audiology assessment annually
Deferasirox (Exjade)	<ul style="list-style-type: none"> • Ferritin • ALT, Cr, urinalysis • Cardiac MRI T2*, R2 Liver MRI (Ferriscan®) 	<ul style="list-style-type: none"> • Ferritin every 3 months • ALT, Cr, urinalysis monthly (weekly initially if underlying issues with renal function) • Cardiac MRI T2*, R2 Liver MRI (Ferriscan®) annually
Deferiprone (Ferriprox)*	<ul style="list-style-type: none"> • Ferritin • CBC, ALT, Cr • Cardiac MRI T2*, R2 Liver MRI (Ferriscan®) 	<ul style="list-style-type: none"> • Ferritin every 3 months • CBC weekly • ALT, Cr every 3 months • Cardiac MRI T2*, R2 Liver MRI (Ferriscan®) annually

*In Canada, deferiprone is only approved for the treatment of iron overload in patients with some thalassemia syndromes who have had an inadequate response to previous iron chelation therapy.

ALT: alanine transaminase; Cr: creatinine; MRI: magnetic resonance imaging; CBC: complete blood count

HOW SHOULD RESPONSE TO IRON CHELATION THERAPY BE MONITORED AND WHEN CAN TREATMENT BE DISCONTINUED?

To monitor response to iron chelation therapy, it is generally recommended that serum ferritin be monitored every three months following treatment initiation (Table 6). However, since ocular and auditory adverse events have been associated with lower ferritin levels in patients using deferoxamine, consideration should be given to monitoring ferritin monthly, or even more frequently in patients using this agent, particularly if they are experiencing any hearing or ocular issues. If available, annual cardiac MRI T2* and R2 liver MRI (Ferriscan) are also recommended for monitoring patient response to iron chelation therapy (Wells et al., 2008).

In patients using deferasirox, alanine transaminase (ALT), creatinine and urinalysis should be assessed monthly given the potential for renal- and liver-related adverse events (Table 6). In patients with underlying renal function issues, creatinine and urinalysis should be performed weekly during treatment initiation. In patients using deferoxamine, monthly assessment of ALT and creatinine is recommended, as well as annual ophthalmological and audiology assessments. Patients on this agent should also be instructed to immediately report any vision or hearing issues. For patients prescribed deferiprone, a weekly complete blood count (CBC) is essential during the first six to 12 months of therapy (Table 6), since this is the time when most episodes of neutropenia and agranulocytosis occur (Wells et al., 2008; UHN, 2012).

According to current Canadian guidelines, iron chelation dose reductions can be considered when ferritin falls below 2,000 µg/L, and treatment can be discontinued when a ferritin level of < 1,000 µg/L is reached (Wells et al., 2008). However, given that ferritin values are affected by inflammatory markers, it is more important to focus on trends in ferritin measurements over time rather than a single ferritin value.

Table 7: Factors contributing to difficulties in following administration recommendations

Practical	<ul style="list-style-type: none"> • Subcutaneous infusion over many hours • Frequent treatment • Time-consuming • Variety of equipment required • Restriction of activities • Training required • Infusion site pain and adverse effects
Psychological	<ul style="list-style-type: none"> • Complacency and lack of motivation • Reluctance to accept need for therapy • Negative body image • Effect on family and personal relationships • Effect on social activity • Constant reminder of underlying illness
Other	<ul style="list-style-type: none"> • Lack of knowledge about disease • Lack of understanding about the consequences of iron overload

Adapted from: Cappellini, M.D. (2005). Overcoming the challenge of patient compliance with iron chelation therapy. *Semin Hematol*, 42(2 Suppl 1), S19–21.

WHAT IS THE ROLE OF THE NURSE TO ASSIST PATIENTS IN SELF-MANAGING THEIR IRON CHELATION THERAPY?

Following the recommended oral administration instructions for iron chelation therapy is essential for the effective management of iron overload. Altering the chelation regimen can lead to the development or worsening of iron overload in target organs, which will not only necessitate the intensification of chelation therapy and further commitment from the patient (such as the need to insert a portacath or PICC line for continuous IV deferoxamine infusion), but will also require treatment for the complications associated with iron overload.

Table 8: Dialoguing with patients about their iron chelation therapy

Open-Ended Questions:

- What medications are you taking?
- Why are you taking them?
- How are you taking your iron chelating therapy?
- If you are not taking it, what is preventing you from taking it?

In general, the more disruptive the treatment is to activities of daily living, the less likely the patient is to follow administration guidelines. This tends to be a greater issue in those taking deferoxamine given the requirement for parenteral administration and long infusion times. However, even patients treated with deferasirox can find it difficult to continue therapy given the associated GI side effects, particularly early in the course of therapy. Factors contributing to difficulties in following administration recommendation for iron chelation therapy are summarized in Table 7 (Cappellini, 2005).

The nurse plays a pivotal role in helping patients self-manage their therapy through patient education and using a collaborative patient-focused approach in the prevention, early recognition, and management of the side effects associated with iron chelation therapy. Minimizing the impact of chelation therapy on quality of life is key and necessitates not only a thorough understanding of the pharmacology of the available chelators, but also frequent communication and feedback between the nurse and the patient/caregiver(s) (Eckes et al.,

2011). Examples of questions that can be utilized when collaborating with patients are shown in Table 8. It is also important to note that utilizing newer modes of communication for patient contact, including web-based instant messaging and mobile phone SMS text messaging, may be more effective in engaging certain patient groups, particularly teenagers and adolescents, in their management regimen. A patient support program for deferasirox is also available in Canada, which can complement the information, support and motivation provided by nurses to patients prescribed this agent (please go to drugcoverage.ca for more information on this program).

CONCLUSIONS

Although essential for many patients with chronic anemias, repeated RBC transfusions can lead to iron overload and subsequent end-organ damage. Therefore, the management of iron overload is vital for many transfusion-dependent patients, and it is essential that nurses responsible for the care of these patients have a thorough understanding of iron homeostasis, the pathophysiology of iron overload and its consequences, and the available iron chelation therapeutic options. Furthermore, nurses play a central role in educating patients and caregivers about iron overload and iron chelation therapy, empowering patients to manage the adverse events associated with chelation therapy and, ultimately, ensuring long-term patient continuation of therapy and improved patient outcomes.

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