Critical Reviews in Oncology/Hematology 113 (2017) 156–170

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

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

Toxicity of iron overload and iron overload reduction in the setting of hematopoietic stem cell transplantation for hematologic malignancies

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Contents

ARTICLE INFO

Article history:
Received 17 December 2016
Received in revised form 13 February 2017
Accepted 4 March 2017

Keywords:
Iron overload
Iron chelation therapy
Phlebotomy
Stem cell transplantation

ABSTRACT

Iron is an essential element for key cellular metabolic processes. However, transfusional iron overload (IOL) may result in significant cellular toxicity. IOL occurs in transfusion dependent hematologic malignancies (HM), may lead to pathological clinical outcomes, and IOL reduction may improve outcomes. In hematopoietic stem cell transplantation (SCT) for HM, IOL may have clinical importance; endpoints examined regarding an impact of IOL and IOL reduction include transplant-related mortality, organ function, infection, relapse risk, and survival. Here we review the clinical consequences of IOL and effects of

Abbreviations: AL, acute leukemia; ALL, acute lymphoblastic leukemia; ALT, alanine aminotranferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; CHF, congestive heart failure; CRP, C-reactive protein; DFO, deferoxamine; DFS, disease-free survival; DFX, deferasirox; DW, dry weight; EFS, event free survival; EPO, erythropoietin; g, grams; GVH, graft versus host; IOL, iron overload; ICT, iron chelation therapy; LFS, leukemia-free survival; LIC, liver iron concentration; LPI, labile plasma iron; MDS, myelodysplastic syndrome; mL, milliliter; MVA, multivariate analysis; ng, nanograms; NTBI, non-transferrin bound iron; OS, overall survival; RBC, red blood cells; SCT, (hematopoietic) stem cell transplantation; SF, serum ferritin; SOS, sinusoidal obstructive syndrome (veno-occlusive disease); SQUID, superconducting quantum interference device; TD, transfusion dependent; TRM, transplant related mortality; TS, transferrin saturation; U, unit(s); ULN, upper limit of normal.

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http://dx.doi.org/10.1016/j.critrevonc.2017.03.002

IOL reduction before, during and following SCT for HM. IOL pathophysiology is discussed as well as available tests for IOL quantification including transfusion history, serum ferritin level, transferrin saturation, hepcidin, labile plasma iron and other parameters of iron-catalyzed oxygen free radicals, and organ IOL by imaging. Data-based recommendations for IOL measurement, monitoring and reduction before, during and following SCT for HM are made.

1. Introduction

1.1. Iron physiology

Iron is essential for all living organisms, as it is required for the function of proteins and enzymes involved in key metabolic roles. For example, hemoproteins include hemoglobin, proteins of the mitochondrial electron transport chain and hepatic cytochromes. Iron-sulphur cluster proteins are involved in oxidation-reduction reactions, hydroxylases in the degradation of organic compounds, and superoxide dismutases in limiting the cellular toxicity of oxygen radicals. Ribonucleotide reductase is an iron protein and therefore iron is essential for nucleic acid metabolism. Iron is required for the survival and growth of microorganisms and tumor cells (Morgenthau et al., 2013; Tortorella and Karagiannis, 2014).

Under normal circumstances, total body iron in a human adult is approximately 4 g, distributed in the red blood cells (RBC), 1800 mg; liver, 1000 mg; reticuloendothelial system (RES), 600 mg; bone marrow, 300 mg; and other cells and tissues, 400 mg. Approximately 3 mg of iron circulates bound to transferrin, with the transport of 20–25 mg iron per day between tissues and organs. Gastrointestinal (GI) absorption of dietary iron is approximately 1–2 mg per day, with an equivalent amount lost by the turnover of GI epithelial cells. The body has no other mechanism for disposing of excess iron (Hentze et al., 2004).

Iron overload (IOL) in patients with hematologic malignancies occurs primarily via RBC transfusion, but in some patients there may also be a contribution via the hepcidin pathway. As a result of anemia, hepcidin is suppressed, allowing continued cellular functioning of ferroportin and GI import of iron, as well as iron export from hepatocytes and the RES (Ganz and Nemeth, 2012). The recent identification of erythroferrone as a key regulator of iron physiology will likely result in increased insight into iron physiology in the future (Kautz et al., 2014). Iron overload may also occur from ineffective erythropoiesis, or from decreased erythropoiesis following cytotoxic chemotherapy. Iron overload is toxic to cells, tissues and organs, as discussed below.

1.2. Iron overload in congenital anemias

Patients with homozygous forms of thalassemia are markedly anemic due to decreased production of globin chains, and rely on RBC transfusions to sustain life. In RBC transfusion-dependent (TD) anemias, iron may accumulate quickly. Every unit of transfused blood contains 200–250 mg of iron, and a RBC transfusion requirement of 2 units (U) per month will result in over 20 g body iron in 4 years (Hellstrom-Lindberg, 2005). Unless iron intake is addressed, IOL inevitably occurs in the liver, heart, and endocrine organs, resulting in hepatic fibrosis, cirrhosis, hepatocellular carcinoma, cardiac arrhythmias, congestive heart failure (CHF), glucose intolerance, growth retardation, and limited life expectancy. In the era of iron chelation therapy (ICT) with deferoxamine (DFO), which because of its short half-life is ideally given by continuous subcutaneous infusion over many hours, life expectancy and organ function (cardiac, hepatic, endocrine) were associated with patient compliance with DFO infusions (Gabutti and Piga, 1996; Davis et al., 2004; Jensen et al., 2003; Davis and Porter, 2000; Olivieri and Brittenham, 1997; Taher et al., 2011).

Iron overload is an established risk factor for inferior outcome in thalassemia patients undergoing stem cell transplantation (SCT). Three classes of risk were described, including hepatomegaly over 2 cm; the presence of portal fibrosis; and irregular chelation history where DFO was not initiated within 18 months of the first RBC transfusion, and not administered over 8–12 h daily, 5–7 days per week (Lucarelli et al., 1990). Follow-up of patients with IOL and not undergoing IOL reduction showed that normalization of SF and liver iron concentration (LIC) were achieved by 5 years post-SCT only in patients with the lowest risk class (Lucarelli et al., 1993). Phlebotomy post-SCT reduced iron stores and improved organ function (Angelucci et al., 1997; Gaziev et al., 2005).

1.3. Iron overload in acquired anemias

The bulk of data regarding IOL in TD acquired anemias address the myelodysplastic syndromes (MDS), clonal bone marrow failure syndromes characterized by ineffective hematopoiesis and a variable risk of progression to acute myeloid leukemia (AML). Overall survival (OS) and AML progression are predicted by the International Prognostic Scoring System (IPSS) and newer scores (Greenberg et al., 1997; Greenberg et al., 2012; Malcovati et al., 2007; Kantarjian et al., 2008; Schanz et al., 2012; Statistics Canada, 2012). The incidence and prevalence of MDS are increasing with the ageing of the population in Western countries and availability of treatments that improve survival (Fenaux et al., 2009; Williamson et al., 1994). Approximately 40% of lower risk and 80% of higher risk MDS patients are RBC TD and at risk of IOL (Balducci, 2006). Guidelines for addressing IOL in MDS are extrapolated from recommendations for congenital anemias, and it is uncertain whether these recommendations over- or under-estimate a clinical impact of IOL (Gattermann, 2008; Bennett, 2008; Greenberg et al., 2011; Wells et al., 2008). ICT in MDS is generally recommended in lower-risk patients, since they have a sufficiently long life expectancy to achieve organ and total body IOL reduction. However, ICT may provide relief from iron-catalyzed production of toxic oxygen free radicals, which may impact on outcomes of higher risk MDS (Gattermann and Rachmilewitz, 2011; Chan et al., 2010), and more recent guidelines endorse the use of ICT in higher risk MDS receiving potentially disease-modifying therapies (Santini et al., 2010). In the DFO era, an SF of 1000 ng/mL was generally the threshold for initiating ICT, and the therapeutic target, since opthalmologic- and oto-toxicity increase in incidence at a lower SF. An IOL threshold that should trigger intervention with newer agents and in older patients has yet to be defined. Studies show variability in hepcidin levels between MDS subtypes, indicating that ferroportin levels and therefore GI iron absorption probably differ (Santini et al., 2011; Winder et al., 2008).

For lower risk MDS in the non-SCT clinical setting, RBC TD is associated with inferior OS and leukemia-free survival (LFS) (Malcovati et al., 2007, 2006, 2005; Sanz et al., 2008; De Swart et al., 2011; de Swart et al., 2010). Malcovati et al. showed a hazard ratio (HR) for death and LFS of 1.36 and 1.40, respectively, for every increase in transfusion requirement of 1 RBC unit per week