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Critical Reviews in Oncology/Hematology 91 (2014) 64–73

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Iron overload and chelation therapy in myelodysplastic syndromes

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Accepted 14 January 2014

Contents

Abstract

Iron overload remains a concern in MDS patients especially those requiring recurrent blood transfusions. The consequence of iron overload may be more relevant in patients with low and intermediate-1 risk MDS who may survive long enough to experience such manifestations. It is a matter of debate whether this overload has time to yield organ damage, but it is quite evident that cellular damage and DNA genotoxic effect are induced. Iron overload may play a critical role in exacerbating pre-existing morbidity or even unmask silent ones. Under these circumstances, iron chelation therapy could play an integral role in the management of these patients. This review entails an in depth analysis of iron overload in MDS patients; its pathophysiology, effect on survival, associated risks and diagnostic options. It also discusses management options in relation to chelation therapy used in MDS patients and the impact it has on survival, hematologic response and organ function.

Keywords: MDS; Myelodysplastic syndrome; Iron chelation; Iron overload; Transfusion-dependent; Deferasirox; Deferoxamine; Deferiprone

1. Introduction

Myelodysplastic syndromes (MDS) represent a group of hematologic disorders characterized by dysplastic and ineffective hematopoiesis. Approximately 80% of patients present with anemia and a substantial percentage of them

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http://dx.doi.org/10.1016/j.critrevonc.2014.01.006

will become transfusion-dependent during the course of their disease [1].

Chronic transfusions lead to secondary iron overload (IO). The relatively longer survival of low and intermediate-1 risk MDS groups classified by the International Prognostic Scoring System (IPSS) [2,3] places them at an increased risk of damage by IO from prolonged red cell transfusions compared to high risk patients who have a markedly reduced survival [1]. MDS population consists mainly of elderly with co-morbid conditions and a propensity to have cardiac failure, infection, hemorrhage and hepatic cirrhosis IO may rapidly exacerbate these pre-existing conditions [4].

In this review, we provide an overview of IO in MDS patients, its pathophysiology, associated risks and management options as recent and more systematic data on chelation therapy in MDS patients has become available in the past few years.

2. Iron overload

2.1. Pathophysiology

The pathophysiology of IO in MDS patients is related to that observed in thalassemia syndromes and consists of ineffective erythropoiesis and hepcidin dysregulation in some subtypes of MDS (primary IO) as well as transfusional siderosis (secondary IO). There are however some differences. Hepcidin is a key hormone mediating iron homeostasis. Hepcidin has a role in the down-regulation of ferroportin, the membrane transporter delivering duodenal iron from enterocytes to transferrin, thus resulting in decreased duodenal iron absorption [5,6]. In disease states of ineffective erythropoeisis, serum hepcidin levels are low that result in unrestrained duodenal iron absorption and subsequent IO [7]. Recently, we measured serum hepcidin by mass-spectrometry in 113 MDS patients, and found the lowest levels in refractory anemia with ring sideroblasts (RARS, 1.43 nM) and the highest in refractory anemia with excess blasts (RAEB 11.3 nM) [8]. RARS patients are particularly refractory to therapy with erythropoietic stimulating factors, and thus are frequently transfusion dependent, have a particularly expanded erythropoiesis, with an extremely frequent presence of acquired mutations in SF3B1, a gene encoding a core component of the RNA splicing machinery in MDS patients with ring sideroblasts [8,9]. A genetic study has confirmed our findings, correlating SF3B1 with ring sideroblasts and low hepcidin levels [10]. The growth differentiation factor 15 (GDF15), which has been shown to suppress the activity of hepcidin in thalassemia [11], did not seem to regulate hepcidin in our work and that of our authors. Therefore, low levels of hepcidin further predispose patients with RARS subtype of MDS to the risk of IO.

Anemia affects 80% of MDS patients and in their disease course many of them will receive transfusions. Red blood cell transfusions, while alleviating anemia may improve quality of life and prolong survival, but expose to several risks [12]. Patients with MDS may have an extremely high frequency of transfusions and may accumulate excess iron in a short time lapse. The rapidity and intensity of transfusions accounts for IO more than the total number [13]. In this state of iron repletion, ferritin production is increased to permit adequate storage of iron and transferrin receptor production is decreased to prevent further entry of iron into the cell [14,15]. When the binding capacity of transferrin in the blood is exceeded, iron is found in the plasma as non-transferrin bound iron (NTBI) [16]. Since iron cannot be actively excreted out of the body, it initially accumulates in the reticuloendothelial macrophages and is later deposited in the parenchymal cells of liver, heart and endocrine organs [17]. Intracellular iron can be found in endocytotic vesicles following entry of iron into the cell through the transferrin receptor-1, in ferritin where each ferritin molecule can hold up to 4500 atoms of iron or in association with proteins that form prosthetic groups involved in biological reactions [18]. In this IO state, NTBI changes to its redox active form termed labile plasma iron (LPI). Patients with low risk MDS have the higher NTBI levels compared to high risk MDS; highest levels are seen in RARS followed by 5 q-syndromes and CMML, respectively [8]. Entry of LPI into cells is mediated via several transporters; DMT1 in enterocytes [19], Zrt-Irt-like protein in hepatocytes [20] and L-type voltage dependent calcium channels in cardiac myocytes [21]. LPI is a toxic compound that enters the cell forming the labile cell iron (LCI) [22]. LPI in MDS is high and correlates with ferritin levels quite well. LCI results in the formation of reactive oxygen species (ROS) that can suppress renewal and number of hematopoietic stem cells [23] and can induce DNA damage and genomic instability [24]. This results in tissue damage and subsequent fibrosis which could result in complications as cardiomyopathy, cirrhosis and diabetes [25,26].

2.2. Impact of IO on survival

Several retrospective studies suggest a negative association between transfusion dependency in MDS and overall survival (OS) [27–29]. Whether this is due to the transfusions themselves or to the fact that more severe diseases require more frequent transfusions is a matter of debate. Furthermore, the impact of IO on OS in MDS patients has also been demonstrated. In a retrospective nationwide survey of Japanese patients, Takatoku et al. found that in 37 of 38 patients who died of hepatic or cardiac failure had ferritin levels >1000 μg/L suggesting that IO resulted in increased mortality [30]. On the other hand, in a retrospective analysis of a US database, complications potentially attributable to IO in MDS such as cardiac events, diabetes and liver disease occurred at a higher frequency in MDS patients receiving blood transfusions [31]. Also, Sanz et al. confirmed these results in a large series of 2994 patients where they showed that IO is an independent prognostic variable of OS and also AML transformation [32]. However, the results have never