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REVIEW

Controversies surrounding iron chelation therapy for MDS

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ABSTRACT

The myelodysplastic syndromes (MDS) are characterized by cytopenias and acute myeloid leukemia risk. Most MDS patients eventually require transfusion of red blood cells for anemia, placing them at risk of iron overload (IOL). In beta-thalassemia major, transfusional IOL leads to organ dysfunction and death, however, with iron chelation therapy survival improved to near normal and organ function was improved. In lower risk MDS, several non-randomized studies suggest an adverse effect of IOL on survival, and that lowering iron minimizes this impact and may improve organ function. While guidelines for MDS generally recommend chelation in selected lower risk patients, data are emerging suggesting IOL may impact adversely on the outcome of higher risk MDS and stem cell transplantation (SCT) and that lowering iron may be beneficial in these patients. Trials to determine whether these effects are truly from lowering iron are currently enrolling. Chelation is costly and potentially toxic, and in MDS should be initiated after weighing potential risks and benefits for each patient until more definitive data are available. In this paper, data on the impact of IOL in MDS and SCT, possible mechanisms of iron toxicity such as oxidative stress, and the impact of lowering iron on organ function and survival are reviewed.

1. Introduction

The myelodysplastic syndromes (MDS) are clonal disorders of hematopoietic progenitor cells characterized by ineffective hematopoiesis and risk of transformation to acute myeloid leukemia (AML). Survival and AML risk are predicted by the International Prognostic Scoring System (IPSS)[1]. Newer scores such as the World Health Organization Scoring System (WPSS) and others incorporate additional prognostic information, such as the impact of red blood cell (RBC) transfusion dependence[2,3]. Over 85% of MDS patients present at age 70 years or more[4], so most are ineligible for aggressive therapies such as hematopoietic stem cell transplantation (SCT), the only potentially curative treatment for MDS to date[5]. Although other treatments are now available[6–10], the usual treatment for many MDS patients is still supportive care, which aims to minimize the impact of cytopenias and maintain quality of life (QOL), and includes interventions that are not generally considered to alter MDS course.

Because of chronic anemia, many MDS patients develop dependence on RBC transfusion, a mainstay of supportive care. This places patients at risk of transfusional iron overload, which leads to cardiac, hepatic and endocrine dysfunction[11]. Recent studies suggest an adverse effect of RBC transfusion dependence and iron overload on survival in MDS[12,13] and possibly AML evolution[14]. The benefits of decreasing iron overload with iron chelation therapy are well established in thalassemia[15]. Although recent data suggest an impact of iron chelation on survival in MDS[16–18], these and other potential benefits of chelation in this group of patients remain more controversial. This paper reviews data on the clinical impact of anemia, RBC transfusion dependence and iron overload in MDS, with a focus on the potential benefits of iron chelation therapy. It summarizes data in lower risk MDS, the usual patients for whom chelation is considered, and discusses emerging data in higher risk MDS and patients undergoing hematopoietic SCT that iron overload is detrimental and lowering iron may be beneficial.

2. MDS epidemiology, impact of anemia and transfusion dependence

The incidence of MDS in the United States (US) was estimated at 3.3 per 100,000[19], and at least 10,000 new diagnoses of MDS are made per year[20]. In the cohort of patients from which the IPSS was derived, at MDS diagnosis the hemoglobin was below normal in 98% and less than 80 g/L, implying transfusion dependence, in 27%[21]. In recently diagnosed MDS, the IPSS score was low or intermediate-1 in 64%, and 22% were RBC transfusion dependent with 67% of higher risk patients requiring RBC transfusion[22]. In 467 MDS patients followed over 10 years, 182 (38.9%) developed RBC transfusion dependence[12], with 41 (82%) in 50 patients over 79.7 patient-years of follow-up requiring transfusion in other series[23]. About 40% of patients receive RBC transfusion as the only MDS intervention[24,25] and the median number of RBC units transfused per patient-year is 11.1 (range, 0–91.3)[23].

Chronic anemia may be complicated by clinical sequelae. It may impact on mortality and disability among older adults with[26] or

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without MDS[27]. In one study, 80% of patients required special processing or selection of blood products, and reactions or requirement for premedications occurred in 94%[23]. Anemia may result in cardiac sequelae. In a study examining cardiac remodeling, this was seen in eleven of twelve transfusion dependent patients (mean hemoglobin 87 ± 1.4 g/L) compared to 13 of 27 with a mean hemoglobin of 113 ± 2.4 g/L[28]. In a US Medicare population, over three years 522 of 705 (74%) experienced a cardiac event (48% congestive heart failure [CHF], 53% arrhythmia, 20% infarction) and these complications occurred in 79% of transfused compared to 54% of non-transfused patients ($P<0.0001$)[29]. In CHF, anemia may increase cardiac output, lead to left ventricular hypertrophy, exacerbate coronary syndromes, and associated renal insufficiency due to decreased left ventricular ejection fraction (LVEF) or comorbitities, complicated by decreased erythropoietin (EPO) production may in turn further exacerbate anemia (reviewed in[21]).

Early observations in MDS suggested that RBC transfusion dependence might impact adversely on survival. In highly transfused patients ($n=15$), arrhythmia, CHF, hepatic fibrosis and glucose intolerance were common[30] and portended worse prognosis in refractory anemia with ring sideroblasts (RARS; $n=47$), where seven of 15 deaths were from CHF and an eighth from hepatic cirrhosis[31]. In another study ($n=46$), hepatic fibrosis and increased liver function tests were frequently seen, and CHF occurred in over 40% of patients and was frequently the cause of death[32]. The first report of an adverse impact of RBC transfusion dependence on survival in a sizeable series of MDS patients came from Italy[12]. In 467 patients, overall and leukemia-free survival (LFS) were inferior in transfusion dependent patients ($P \leq 0.001$ for both) and progressively decreased by the degree of transfusion dependence, with a hazard ratio (HR) of 1.36 and 1.40, respectively, for each additional RBC unit transfused per four weeks ($P<0.001$ for both; see Fig. 1)[13]. This effect was mainly seen in lower risk patients ($P<0.001$) in whom transfusion dependence increased the probability of non-leukemic death[12]. These important observations led to the development of the WPSS[2], which incorporates RBC transfusion dependence into calculation of patient risk. While these effects could be attributable to more advanced bone marrow failure in the transfusion dependent group, OS also decreased with increasing ferritin level, with an HR of 1.42 for every 500 ng/mL increase in ferritin over 1000 ng/mL ($P<0.001$; see Fig. 1)[13]. These observations suggest that iron overload itself may impact adversely on survival, as is well documented to occur in beta-thalassemia major[15,33–35]. Other studies suggesting an impact of transfusion dependence on clinical parameters in MDS are discussed in further detail below.

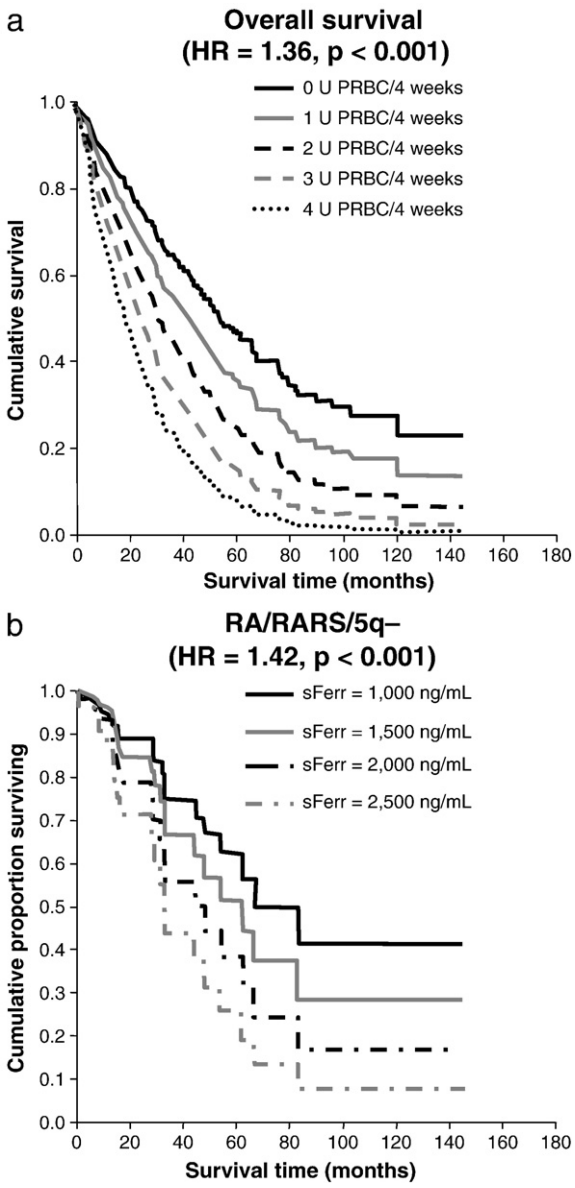

Fig. 1. Overall survival of MDS patients according to (a) severity of transfusion requirement and (b) iron overload as measured by serum ferritin level. Figure b includes patients with lower risk MDS: RA; RARS and 5q-. From Malcovati L et al., Haematologica 2006; 91: 1588–1590. With permission from the Ferrata Storti Foundation.

3. Iron balance

3.1. Overview of iron metabolism and distribution

Under normal conditions, 1–2 mg of iron is absorbed daily by the gastrointestinal (GI) tract and the same amount lost by desquamation of GI epithelial cells. The release of non-heme iron into the circulation is regulated by ferroportin, expressed on the basolateral cell surface (and on cells of the reticuloendothelial system [RES] and hepatocytes ([reviewed in[36]]). Ferroportin is downregulated by hepcidin, and under conditions of iron deficiency hepcidin is low, allowing GI iron absorption to increase and stores to be mobilized from RES cells (reviewed in[37,38]). When iron is plentiful, hepcidin levels increase and result in decreased iron absorption and RES export. Absorbed iron is transported by transferrin and taken up into erythroid cells via the transferrin receptor. The distribution of iron is influenced by multiple factors and under normal conditions, cells maintain a pool of labile iron by controlling uptake via expression of receptors and storage via ferritin. Most cells have no mechanism for iron efflux.

Iron is vital for survival but an excess may be harmful. Essential functions include oxygen transport and exchange, cellular respiration and electron transfer, metabolic reactions including heme synthesis, production of oxygen radicals and conversely, anti-oxidation, DNA synthesis and repair, ribosome function and translation to polypeptides, cellular proliferation, and inflammation. The harmful effects of excess iron may result from direct deposition into tissues and organs but in addition from its redox chemistry. If adaptive defenses against excess iron are overwhelmed, reactive oxygen species (ROS) are produced, which may damage lipids, proteins and nucleic acids, possibly leading to cell death or transformation[39,40], both recognized features of MDS[41,42]. As each unit of RBC contains 200–250 mg of iron and the body has no mechanism to excrete this, iron overload can readily occur in patients who are regularly transfused for disorders not associated with blood loss. The RES has a capacity of about 10–15 g, which corresponds to about 50 units of RBC; when this is overwhelmed, parenchymal deposition and tissue damage occur[35,37].

Other possible contributions to iron overload in MDS include ineffective erythropoiesis resulting in increased GI absorption,