

## **Update on Iron Toxicity in Myelodysplastic Syndromes**

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Myelodysplastic syndromes (MDS) are a heterogeneous group of diseases representing a broad range of median survivals. The International Prognostic Scoring System (IPSS) can be used to prognosticate patients with MDS, with scores pointing to corresponding expected median overall survivals. A patient score of 0 to 2.5 points or higher is derived based on the variables of bone marrow blast count, karyotype, and cytopaenias. In low-risk patients, the median overall survival is relatively long at nearly 6 years, whereas in high-risk patients, median overall survival is less than 1 year. Furthermore, the likelihood of acute myeloid leukaemia evolution is much less in low-risk patients.

In recent years the diagnostic classification system used for MDS has changed from the French-American-British, or FAB, system to the World Health Organization (WHO) system, resulting in the development of a prognostication system. The WHO Classification-Based Prognostic Scoring System (WPSS) has been calculated from two databases, including the Italian database from Pavia, Italy, and the German cohort from Düsseldorf, Germany. Patient scores are based on three parameters: WHO diagnostic classification, karyotype, and transfusion dependency.

One critique of this system is the inclusion of transfusion dependency, due to the fact that some patients require transfusion earlier than others for reasons unrelated to MDS. For example, patients with a cardiac comorbidity may require transfusion at a haemoglobin level of 9.5 g/dL to 10.0 g/dL, while other patients who are relatively fit and lack a cardiac comorbidity do well with haemoglobin levels 8.0 g/dL or lower. However, an alternate view of this disparity suggests a strength of WPSS, because it acknowledges the impact of comorbidity in transfusion-dependent patients. A patient who tolerates a low haemoglobin is less comorbid than a patient who needs transfusion at a higher haemoglobin. Comorbidity is an important factor in MDS. In 2008, Della Porta et al reported a MDS-specific comorbidity index that is scored based on the presence of cardiac disease, hepatic disease, severe pulmonary disease, renal disease, or solid tumour. A total score of 0 indicates a low comorbidity index with a 2-year risk of nonleukaemic death of 24% compared with 61% for a patient with a total score of >2.

Red blood cell transfusions are among the therapeutic options for patients with low-risk MDS. Transfusions, however, quickly add an excessive amount of iron to the total body iron stores, at a rate of at least 5 g/year for a patient receiving a moderate 2 units/month. At this rate of transfusion, serum ferritin levels will exceed 1000 µg/L by 1 year. Data from Sanz et al have shown that serum ferritin levels and transfusion dependence are independent factors for both survival and leukaemic evolution.

Iron overload is a significant feature of MDS and is associated with toxicity of multiple organs, including the heart, and contributing to an increased rate of cardiac death. Non-transferrin-bound iron enters myocytes through calcium channels. When iron levels are chronically elevated, excessive free radical generation leads to depletion of antioxidants and increased cellular damage due to oxidation of lipids, proteins, and nucleic acids. Additional factors that may modulate the degree of oxidative stress include infection, endocrinopathies, and hypoxia related to chronic anaemia. Oxidative stress causes direct myocardial impairment, endothelial dysfunction, and hypercoagulation. Importantly, among low-risk patients, cardiac failure is the most important cause of nonleukaemic death, particularly among transfusion-dependent patients.

Several nonrandomized trials have investigated whether effective iron chelation can prolong survival in patients with MDS. Data presented by Leitch et al showed that patients who were on desferrioxamine had much longer overall median survival compared with patients not on chelation therapy. Although the trial was not randomized, the median survival in the chelated group (not reached at 160 months) so far surpassed the median survival in the nonchelated group (40 months) that a beneficial effect of chelation therapy on survival is likely. EPIC and US03 trials have analyzed deferasirox in patients with MDS. Data from these trials have demonstrated consistent reductions in serum ferritin levels over 12 months. In addition, data reported by Armand et al suggest a potential role for chelation therapy pre- and post-haemopoietic stem cell transplant.

## Suggested Readings

Armand P, Kim HT, Cutler CS, et al. Prognostic impact of elevated pretransplantation serum ferritin in patients undergoing myeloablative stem cell transplantation. *Blood*. 2007;109:4586-4588.

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