Iron overload in Myelodysplastic Syndromes

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Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders. They are characterized by abnormal differentiation and maturation of myeloid cells, bone marrow failure and genetic instability with an enhanced risk of progression to secondary leukaemia. The International Prognostic Scoring System (IPSS) for MDS is based on the percentage of marrow blasts, the number of cytopenias and cytogenetic characteristics and has shown to be effective in predicting outcome mainly for MDS patients treated with supportive care[1]. A new scoring system is under discussion: the WHO classification-based Prognostic Scoring System (WPSS). This classification system is based on the WHO classification, transfusion dependency and cytogenetic abnormalities.

The diagnosis and treatment of iron overload and iron toxicity is of great importance in the clinical management of MDS patients, because iron overload is likely an important predictor of morbidity and mortality. In a retrospective study[2], heart failure was the most important non-leukemic cause of death (50%), followed by infection (31%) and liver cirrhosis (8%). These causes can be the result of iron overload.

Iron overload in MDS is mainly caused by red blood cell transfusions[3]. Transfused iron probably accumulates initially in the liver before it is loaded into the heart as is described in β-thalassemia patients[4]. In a study with transfusion-dependent MDS patients, iron accumulation of the heart occurred after 75-100 blood transfusions when patients did not receive iron chelation therapy[6].

Additionally to iron overload caused by red blood cell transfusions, the ineffective erythropoiesis may also play an important role in iron accumulation in MDS patients. Similar to β-thalassemia patients, the ineffective erythropoiesis may lead to an increased growth differentiation factor (GDF)15 level, which subsequently lowers the hepcidin levels and results in an increased iron absorption from the intestinal tract[7]. Until now, only small studies have been performed in MDS patients to evaluate the hepcidin level[8-10], but GDF15 has shown to be increased in RARS patients[11]. It is not clear if the ineffective erythropoiesis itself leads to significant symptomatic iron

overload. However, the serum ferritin levels can be elevated before blood transfusions are given, especially in patients with RARS[12], suggesting that iron overload is already present.

Besides iron accumulation, iron toxicity probably plays an important role in MDS. Free iron in the plasma becomes available when the capacity of transferrin to carry iron is exceeded. This non-transferrin-bound iron (NTBI) is even elevated in MDS patients who did not yet receive any blood cell transfusions and is associated with a higher level of apoptosis[13]. In a recent study with thalassemia patients, NTBI was correlated with transferrin saturation but not with serum ferritin level. Patients with heart diseases had significantly higher NTBI levels than those without heart disease, suggesting that NTBI will be responsible for functional organ damage[14]. The presence of NTBI will be reflected in a rise of labile plasma iron (LPI) and reactive oxygen species (ROS) that causes cell and tissue damage[15, 16]. LPI is the fraction of NTBI that is redox active and eliminated by iron chelators[17]. The determination of NTBI remains difficult and new methods are under investigation to improve the reliability of this important iron toxicity parameter. In the near future a more reliable assessment of NTBI in combination with LPI will be most valuable to determine iron toxicity in MDS patients.

Recently new oral iron chelation therapy has become available (deferasirox), which makes iron chelation therapy more feasible and effective despite possible side effects. Several prospective studies have demonstrated that oral iron chelation therapy is effective in the reduction of the iron accumulation, but it is not yet clear which patients benefit most of this treatment[18-21]. Iron chelation therapy will probably reduce iron accumulation in end target organs as well as decrease iron toxicity by reducing potentially toxic iron[19, 22]. Some studies have shown benefit of iron chelation therapy for survival in MDS patients[23, 24].

Several guidelines for iron chelation therapy in MDS patients have been published the last years, without clear evidence for the optimum treatment of iron overload[25]. By gaining more insight into the pathophysiology and toxicity of iron overload in MDS patients, the guidelines for iron chelation therapy can be optimized to reduce iron related morbidity and mortality.

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