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Acquired and hereditary red cell anomalies - Section 2

Iron overload before, during and after hematopoietic stem cells transplantation

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Take-home messages

- Iron toxicity depends on the presence of free iron species [non transferrin bound iron (NTBI), labile plasma iron (LPI) and labile cellular iron (LCI)].
- Iron toxicity during hemopoietic stem cell transplantation (HSCT), can impair the bone marrow microenvironment, the quantity and quality of bone marrow mesenchymal stem cells, the ratio of immature hematopoietic cells and the clonogenic capacity of hemopoietic stem and progenitor cells.
- After successful hemopoietic stem cell transplantation, one should aim to achieve normal iron levels (i.e. normal transferrin saturation).

Introduction

Iron overload (IO) and consequent cellular iron toxicity are conditions often accompanying hemopoietic stem cell transplantation (HSCT) and have been associated with transplant outcome since the pioneering Pesaro experience in thalassemia[1,2]. Here will be discussed the implications of IO with HSCT and the mechanisms of iron toxicity, where our understanding has significantly evolved in the last few years[2].
In physiological situations, most iron in the plasma is bound to transferrin, a carrier protein that mediates cellular iron uptake. In the presence of IO, i.e., when transferrin saturation is >70%, plasma iron appears as non-transferrin bound iron (NTBI). A component of NTBI, called labile plasma iron (LPI), is potently redox-active and capable of permeating into cells, inducing cellular iron overload[3] and impacts the delicate equilibrium of labile cellular iron (LCI). The breakage of this balance catalyzes the formation of reactive oxygen species (ROS), which, with concomitant decrease in antioxidant enzymes, leads to cytotoxic cell injury (DNA damage, lipid peroxidation, protein modification and mitochondrial damage).
The mechanism underlying tissue iron toxicity has been recently summarized by the following equation[4]:

Tissue iron toxicity:
Σ tissue reactive iron x genetics x environmental factors x time.

Tissue iron toxicity depends on many factors in addition to the iron level per se[4]: the quantity of toxic iron related species, duration of exposure, individual's anti-oxidant genetics and environmental factors.

Current state of art

Iron overload before HSCT (before the start of conditioning)

In transfused patients, an effort should be made to continuously and regularly reduce the level of LCI and ROS in the years before transplant to prevent tissue damage because it is now clear that the critical point is duration of exposure to tissue reactive – toxic- iron forms[2,4]. This can be achieved with regular iron chelation. In any patient receiving significant transfusion therapy that may have an HSCT in the future, a decision on starting regular chelation is critical and should be undertaken as soon as possible.
There are limited data on the rationale for intensive pre-transplant chelation therapy unless sufficient time is available to correct IO and permit tissue repair.

Iron overload during HSCT (from the start of conditioning up to sustained engraftment)

Recent animal studies demonstrated that iron toxicity could impair the hematopoietic niche by damaging hematopoietic stem cells' (HSCs) self-renewal potential, proliferation, differentiation and the marrow microenvironment. This suggests that IO can impact the HSCT engraftment and outcome.

Xiao Chai and coworkers[5] described, in a IO mouse model, how iron overload can increase ROS levels of HSCs progenitors, leading to defective ratio of immature hemopoietic cells and clonogenic capacity compared to a control group. In the same paper, in a mouse-transplant-model, flow cytometry analyses demonstrated that recipient mice of iron-overloaded donors had lower levels of myeloid, B and T- lymphocytic lineage engraftment compared to control transplants. Both effects were reversed after treating iron overloaded mice and transplant recipient mice with an iron chelator or a powerful anti-oxidant. The same group demonstrated that iron overload could impair the bone marrow microenvironment and the quantity and quality of mesenchymal progenitor's cells[6].
From a clinical point of view, apart from single case reports, little evidence is available. Visani and colleagues demonstrated that in cases of poor and delayed engraftment, iron chelation can help in stabilizing hemopoietic engraftment[7]. Studies are ongoing in patients undergoing allogeneic HSCT which addressing the issue of the positive effects of iron chelation on NTBI and LPI during conditioning and their prognostic value.[8,9]

Iron overload after transplantation (after sustained engraftment has been achieved)

After successful transplantation, patients are usually free from transfusion support. It should be examined whether in the absence of further blood–iron input, LCI levels can be maintained within the physiological range by existing iron homeostatic mechanisms that coordinately regulate uptake vs storage, so as to support iron utilization and minimize iron oxidation.
However even in this condition it is reasonable to think that the already acquired iron intracellular storage could continue to disrupt the delicate equilibrium of LCI and promote the generation of ROS by reacting with respiratory oxygen intermediates and thereby overriding the cellular antioxidant defenses leading to chemical damage to cell components and functions. From the clinical point of view, it has been demonstrated in transplanted thalassemia patients (transfusion free but still with acquired IO) that elevated transferrin saturation persists and liver disease progresses even in the absence of other comorbidities[10].
In this context, an iron toxic effect can be present even with a lower level of accumulation, and can result in cumulative tissue damage as demonstrated in the case of IO and hepatitis C infection in the development of liver fibrosis and cirrhosis[10].
Therefore, even because of the results of epidemiologic studies in thalassemia[11,12] and in the normal population[13] in the post-transplant setting (i.e., a patient cured from his/her disease) the target should be a normal iron levels, normal transferrin saturation and no evidence for toxic iron reactive species (NTBI, LPI and LCI).
Taken together, these findings implicate that iron chelation or phlebotomy[14] have a key role in the post-transplant setting. Table 1 reports the pros and cons for selecting iron chelation versus phlebotomy.

Future prospective

A growing body of evidence demonstrates how iron toxicity could impair the hematopoietic microenvironment niche by damaging hematopoietic stem cells' self-renewal potential, proliferation, and differentiation.
Standardization of the quantification methods for NTBI, LPI and ROS levels are emerging[15]. In the near future, availability and validation of these tools could contribute to a "precision medicine" clinical decision regarding IO before, during and after HSCT.

Table 1. Factors in favor or against the use of phlebotomy or deferasirox in long follow-up after successful hematopoietic stem cell transplantation.

	Phlebotomy	Chelation
Pros	Efficient	Efficient
	Safe	Safe
	Inexpensive	Immediate effect on NTBI/LPI
	Permits complete iron removal and normalizes iron body content	Hospital access not required
Cons	Requires sustained engraftment (not usable in the early post-HSCT period)	Expensive
	Immediate effect on NTBI/LPI still remains to be verified	Warning of renal toxicity in the case of concomitant use of cyclosporine
	Hospital access required	Possible increase in toxicity for low level of iron burden

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Iron toxicity depends on many factors in addition to the level of iron per se.

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A normal iron level is the main goal to obtain in order to avoid tissue damages after a successful hematopoietic cell transplant.
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Availability and validation of methods to detect NTBI, LPI and ROS levels are mandatory for a "precision medicine" and adequate clinical decision.