Secondary myeloid neoplasias: an emerging group of diseases

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Secondary myeloid neoplasias are a heterogeneous group of diseases characterized by the proliferation of myeloid cells; they were recently recognized by the World Health Organization (WHO) as an entity. The wide use of chemotherapy and better diagnosis of hematological malignancies has caused a growth in the number of secondary malignancies. Most of them are myeloid: a) myelodysplastic syndromes (MDS), a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis and dysplastic changes in bone marrow and peripheral blood with the risk of transformation to acute myeloid leukemia (AML) or b) sometimes the previous disease directly evolves to an overt AML. Usually the prognosis of patients with a secondary myeloid neoplasia is poor, especially when the previous disease is a MDS. However, patients may achieve a complete response. In this situation, progenitor stem cell transplantation is the best therapy.

Cytogenetic analysis still plays a pivotal role in the diagnosis of hematological diseases. Cytogenetics and mutational analysis are the main prognostic tools in both AML and MDS. For this reason, cytogenetic studies are critical in the correct management of these diseases. There are several cytogenetic abnormalities associated with better prognosis, such as translocations involving core binding factors in AML patients, and losses in 20q, 5q or chromosome Y in MDS. In contrast, many others abnormalities are associated with dismal prognoses, such as the presence of a complex karyotype, abnormalities of either chromosome 3 or chromosome 7 and, in case of AML, the loss of the long arm of chromosome 5.

All of these abnormalities are included in the new staging system for MDS (IPSS-2). Recently new data regarding the presence of abnormalities in chromosome 7 in primary MDS showed that the presence of a partial deletion of the long arm of this chromosome (7q-) is associated with a better prognosis than monosomy 7. This abnormality is a common event in secondary MDS and AML and the potential value of this observation in secondary MDS should be addressed. In this issue of the Revista Brasileira de Hematologia e Hemoterapia a new observation highlighted the importance of performing cytogenetic studies in secondary MDS.

Over recent years, the wide use of microarrays and, more recently, the possibility of sequencing the human genome have provided new insights into knowledge of the molecular mechanisms involved in MDS and AML. Analysis of the gene expression profile by means of microarray technology demonstrated the presence of new pathways involved in the pathogenesis of these disorders, although studies focusing on secondary myeloid diseases are lacking. Since the sequencing of the entire genome of the first hematological malignancy, a patient with AML, several papers have shown the interest of the detection of new genes involved in these diseases. Some of these papers have also described the involvement of new functions involved in myeloid diseases such as the spliceosome mechanism that could play an essential role in the genesis of both MDS and AML. Therefore, near future investigations should provide more information of the genes involved in secondary myeloid diseases. The challenges will be to understand these genes which are thought to be drivers in the genesis of secondary myeloid neoplasias and, more importantly, to identify new therapeutic targets.

References
Iron is an essential micronutrient, as it is required for an adequate erythropoietic function, oxidative metabolism and cellular immune response. In the human body, iron metabolism pathways include absorption from food, distribution to target cells, storage and recycling. Dietary iron is found as heme (10%) and non-heme (ionic, 90%) forms; absorption occurs at the apical surface of duodenal enterocytes via different, tightly regulated, mechanisms with absorption balancing losses (1-2 mg/day) as no active iron excretory mechanisms exist. Dietary non-heme iron primarily exists in an oxidized (Fe3+) form that is not bioavailable and must first be reduced to the Fe2+ form by a ferrireductase enzyme, that uses vitamin C as a coenzyme, before being transported across the intestinal epithelium by the divalent metal transporter 1 (DMT1). Heme iron is transported into the enterocyte by a putative heme carrier protein 1 and metabolized by heme oxygenase to release Fe2+, which enters a common pathway with dietary non-heme iron before it leaves the enterocyte. Iron is exported by ferroportin 1 (the only putative iron exporter) across the basolateral membrane of the enterocyte into the circulation (absorbed iron) where it binds to transferrin and is transported to sites of use and storage. Transferrin-bound iron enters target cells – mainly erythroid cells, but also immune, muscle and liver cells – through a process of receptor-mediated endocytosis.

Erythrocytes contain up to 65-70% of body iron. Senescent erythrocytes undergo phagocytosis by macrophages of the reticuloendothelial system, heme is metabolized by heme-oxygenase and the released iron stored as ferritin. Iron will later be exported from macrophages to transferrin, a process accomplished primarily by ferroportin 1, the same iron-export protein expressed in the duodenal enterocyte and in ceruloplasmin. The amount of iron required for a daily production of 300 billion red blood cells (20-30 mg) is provided mostly by macrophage iron recycling. Thus, this internal turnover of iron is essential to meet the requirements of erythropoiesis.

Hepcidin, synthesized by hepatocytes in response to low iron levels, inflammation, hypoxia and erythropoiesis, is the main iron homeostasis regulatory hormone. Hepcidin binds ferroportin on enterocytes, macrophages and hepatocytes triggering its internalization and lysosomal degradation. Therefore, increased hepcidin secretion may lead to iron deficiency (ID) and anemia. As stated above, under physiological conditions, there is a balance between iron absorption and iron losses in the human body. Thus, ID and iron deficiency anemia (IDA) may result from the interplay of three distinct risk factors: increased iron requirements, limited external supply and increased blood loss. ID can be either absolute or functional. In absolute ID, iron stores are depleted; in functional ID (FID), iron stores, although replete, cannot be mobilized as fast as necessary from the macrophages of the reticuloendothelial system to the bone marrow (treatment with erythropoiesis stimulating agents and inflammation are the most common causes of FID). In chronic inflammation, the excess of hepcidin decreases iron absorption and prevents iron recycling, resulting in hypoferremia and iron restricted erythropoiesis, in despite of normal iron stores, and finally anemia of chronic disease (ACD), which can further evolve to ACD plus true ID (ACD + ID).

Investigation of ID in the clinical practice mostly relies on laboratory tests which fall...