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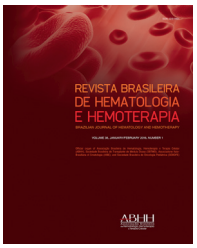

Review article

Iron deficiency in cancer patients

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ABSTRACT

Anemia is a frequent complication in cancer patients, both at diagnosis and during treatment, with a multifactorial etiology in most cases. Iron deficiency is among the most common causes of anemia in this setting and can develop in nearly half of patients with solid tumors and hematologic malignancies. Surprisingly, this fact is usually neglected by the attending physician in a way that proper and prompt investigation of the iron status is either not performed or postponed. In cancer patients, functional iron deficiency is the predominant mechanism, in which iron availability is reduced due to disease or the therapy-related inflammatory process. Hence, serum ferritin is not reliable in detecting iron deficiency in this setting, whereas transferrin saturation seems more appropriate for this purpose. Besides, lack of bioavailable iron can be further worsened by the use of erythropoiesis stimulating agents that increase iron utilization in the bone marrow. Iron deficiency can cause anemia or worsen pre-existing anemia, leading to a decline in performance status and adherence to treatment, with possible implications in clinical outcome. Due to its frequency and importance, treatment of this condition is already recommended in many specialty guidelines and should be performed preferably with intravenous iron. The evidences regarding the efficacy of this treatment are solid, with response gain when combined with erythropoiesis stimulating agents and significant increments in hemoglobin as monotherapy. Among intravenous iron formulations, slow release preparations present more favorable pharmacological characteristics and efficacy in cancer patients.

Iron deficiency is common in cancer patients

Anemia is a frequent complication in cancer patients, both at diagnosis and during treatment. In the European Cancer Anaemia Survey (ECAS), 39% of patients were anemic at the time of enrollment in the study, and 67% had anemia during chemotherapy. The cause of anemia in these patients is multifactorial, and for many of them iron deficiency is the dominant mechanism.[1,2]

Iron deficiency can be classified as absolute, when iron reserves are depleted, or functional, when iron reserves are normal or even increased. The common event in both situations is the reduction of iron availability for erythropoiesis, leading to anemia. In absolute deficiency, for obvious reasons, the lack of iron in reserves is the main triggering event of

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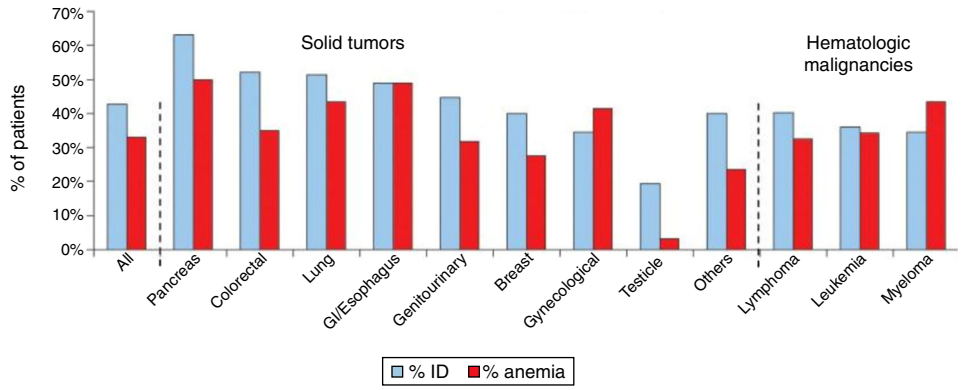

Figure 1 – Prevalence of iron deficiency anemia (ID) and anemia in different types of tumors. GI: gastrointestinal.

anemia. In the case of functional iron deficiency (FID), although the reserves are satisfactory, the presence of an inflammatory process causes the iron to become 'trapped' in macrophages and enterocytes, limiting its availability to the bone marrow, triggering anemia. As expected, FID is the predominant mechanism of iron deficiency associated with cancer. The prevalence of FID in oncology patients ranges from 29 to 46%, and of iron deficiency associated to anemia ranges from 7 to 42%. Figure 1 shows the prevalence of iron deficiency and anemia in various types of solid tumors and hematologic malignancies.[3]

Functional iron deficiency is the predominant mechanism in cancer patients

The demand for iron by the bone marrow and other tissues is supplied by the transport of this element in the circulation by transferrin. The iron taken up by transferrin can come from absorption by duodenal enterocytes or from recycling senescent erythrocytes by macrophages. Both intestinal absorption and macrophage release of iron are controlled by hepcidin, a regulatory hormone synthesized by the liver, which, under increased concentration, degrades the iron export protein, ferroportin, precluding the availability of iron for transportation from these locations.[4]

In the presence of an inflammatory process, iron availability is reduced to about 44% of the normal.[5] This is due to the release of inflammatory cytokines, particularly interleukin-6, which activates the hepatic hepcidin transcription promoting genes, increasing hepcidin concentrations, and promoting the blockage of iron input into the circulation and reducing its availability (Figure 2).[6]

Thus, even in the presence of adequate iron reserves, cancer patients may develop lack of bioavailable iron, especially when treated with erythropoiesis stimulating agents (ESAs) that rapidly increase the production of red blood cells and the use of iron. This is the basic mechanism of functional iron deficiency, the prevalence of which increases in the more advanced stages of cancer and is associated with poor performance status (The Eastern Cooperative Oncology Group – ECOG).[3]

The importance of correct diagnosis... what is there besides ferritin?

Traditionally, serum ferritin is the most widely used test for the diagnosis of iron deficiency, due to mirroring iron reserves. However, because it is a protein of the acute phase of inflammation, its diagnostic applicability is considerably impaired in the presence of acute or chronic inflammatory processes. In this context, transferrin saturation (TS) becomes more reliable for diagnostic purposes.[7]

It is remarkable that, in the clinical practice, only half of cancer patients with anemia are investigated as to iron profile and when they are, the investigation basically consists of ferritin measurements, whereas transferrin saturation is rarely used.[8] This is a valid question, as among cancer patients with reduced transferrin saturation, more than 80% have normal or elevated ferritin values.[3]

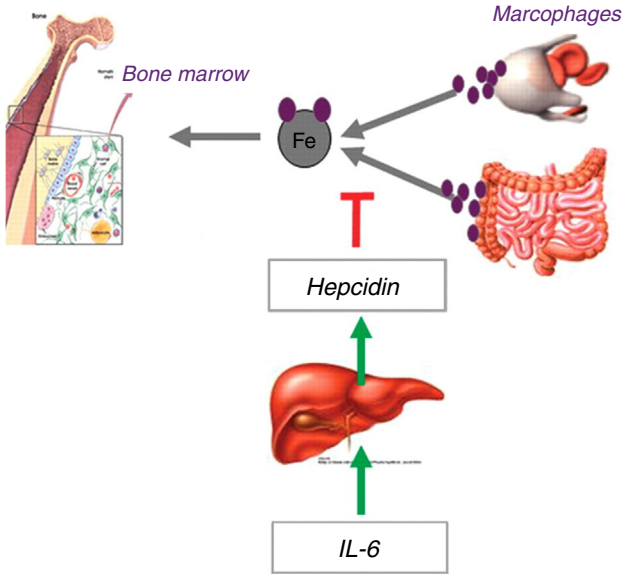

Figure 2 – Pathophysiology of anemia associated with inflammatory process, highlighting the inhibitory action of hepcidin on iron release. IL: interleukin.

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