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Review Article

Clinical Safety And Efficacy of Iron Supplementation in Cancer Patients

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Abstract

It has been widely demonstrated that in patients with chronic diseases or cancer, iron homeostasis may be dysregulated. Iron deficiency with or without anemia is a frequent complication in cancer patients and may be associated, even in the absence of anemia, with weakness, fatigue, and worsening of quality of life, which may ameliorated by iron therapy. The present review will analyze the scientific evidence about iron deficiency diagnosis and management with particular regards with the different formulations of iron available on the market. Iron deficiency is usually treated with oral iron salts, however this approach is very usually accompanied by gastrointestinal side effects, which consequently reduce the compliance with treatment. Interestingly, an innovative oral iron formulation with ferric pyrophosphate covered by a phospholipids plus sucrose esters of fatty acids matrix that, represent a valid option since it is more efficacious and tolerable than oral iron salts and has emerged as a first choice of treatment.

Keywords: Iron Supplementation; Cancer; Sucrosomial iron

Iron Deficiency in Cancer Patients

Iron (Fe), an important trace element, plays a fundamental function in oxygen metabolism, oxygen uptake, electron transport in mitochondria, energy metabolism, muscle function, and hematopoiesis. It has been widely demonstrated that in patients with chronic diseases or cancer, iron regulation and homeostasis may be dysregulated [1], leading, consequently, to an insufficient iron supply to erythroblasts that causes anemia, that may be the cause of weakness and fatigue or may worsen these symptoms, if already present [2].

Anemia is a quite common condition in cancer patients which may negatively impact on quality of life and overall prognosis, compromising patient expectancy of life. Cancer-related anemia pathogenesis is complex and typically multifactorial, and Iron Deficiency (ID) represents the most usual contributor. Early recognition and management of anemia in oncologic patient has been associated with improvement of clinical outcomes, leading also to a better tolerance and response to antitumoral therapy.

ID with or without anemia is a frequent complication in cancer patients and may be associated, even in the absence of anemia, with weakness, fatigue, and worsening of quality of life, which may be ameliorated by iron therapy [3]. Cancer patients may have either functional or absolute iron deficiency (FID or AID, respectively). FID is the most frequent condition [4] and is characterized by a normal amount in iron stores, but an insufficient iron supply for erythropoiesis. FID is mainly due to the release of cancer-associated pro-inflammatory cytokines (e.g., IL-6, IL-1, TNF-_, and interferon-), that upregulate hepcidin synthesis in

the liver [5]. Hepcidin is a small peptide hormone that represents the main regulator of systemic iron homeostasis. It blocks the iron exporter, ferroportin, thus consequently inhibiting iron flows into plasma from macrophages responsible for recycling of senescent erythrocytes, duodenal enterocytes responsible for iron absorption from the diet, and hepatocytes that store iron [6]. FID is one of the major contributors to the so-called anemia of chronic disease, including cancer [7]

It may also develop as a consequence of increased erythropoiesis induced by erythropoiesis-stimulating agents (ESA) s therapy and, not infrequently, it is the cause of unresponsiveness to ESA [40]. On the other hand, AID is a condition in which iron stores are actually depleted. It is usually caused by nutritional deficiencies, which may be also associated to cancer, as it occurs in anorexia or malabsorption in gastrointestinal or pancreatic cancers and, mainly, to blood losses as it occurs in colon cancer or after major surgery.

Prevalence, Pathophysiology and Prognostic Impact

In a prospective, large, multinational epidemiological survey conducted in 34 European countries (European Cancer Anemia Survey (ECAS)) the prevalence of anemia was investigated among 15,000 subjects affected by solid or hematological tumors. The results of this analysis showed that 39% of patients was anemic (Hb <12 g/dL) at the enrolment. More interestingly, after 6 months of follow-up, the prevalence increased to 67% [8]. Among these patients, only 10 % showed Hb values lower than 10g/dl. In these patients, FID is much more prevalent than absolute iron deficiency. Interestingly, evidence showed also a relationship between anemia and tumor recurrence, as the prevalence increases with the progression of the disease and in patients subjected to antitumoral treatment, furthermore the risk of mortality was significantly increased in cancer patients with anemia compared with those without anemia [39]. Although solid evidence supporting the idea that correction of anemia would improve prognosis is not available, a close correlation between the relevant range of hemoglobin levels (8–14 g/dl) and quality of life cancer patients was reported [46]

Diagnosis of iron deficiency

Diagnosis of ID in cancer patients may be complicated and confused by the concomitant presence of a diffuse inflammatory state, or by liver disease. Indeed, laboratory parameters such as ferritin which may normally reflect the status of iron stores are altered in patients with cancer as well as values of transferrin saturation (TSAT), percentage of hypochromic erythrocytes (%HYPO), Hb-content of reticulocytes (CHr), and Soluble Transferrin Receptor (sTfR), which are index of the amount of biologically available iron in healthy subjects.

Thus, in cancer patients, a higher ferritin cut-off (e.g., <100 ng/mL) appears more reliable [3], as in other chronic inflammatory conditions such as kidney disease or heart failure [9]. At the same time, is possible that TSAT may be falsely elevated in cancer patients, thanks to the reduced transferrin levels due to inflammation and/or malnutrition. However, the lack of specific guidelines indicating the ferritin cut-off for defining a FID and establishing the utility of an iron supplementation therapy, strongly complicated the treatment of anemia in oncologic patients. It is widely accepted that the evaluation of both ferritin and TSAT is fundamental, in order to make a diagnosis of FID, TSAT is <20% with variable ferritin levels ranging from 100 up to 800 ng/mL is usually accepted to diagnose FID in cancer patients. Since the most common used tests have limitations, an increased sTfR and a reduced sTfR/log ferritin index have been reported as possible indicators of FID [10].

A promising tool for a more reliable diagnosis of ID in cancer patients is the assessment of circulating hepcidin [11], since its values decreased in ID patients, also in presence of inflammatory diseases like rheumatoid arthritis and inflammatory bowel diseases [12]. Of note, low hepcidin levels may be useful not only for diagnosis of ID, but also to predict the response to iron treatment [13] although if this correlation in cancer patients remains to be demonstrated. Moreover, to improve the clinical application of this parameter, a standardized cut-offs values should be defined [11]. On the other hand, manipulation of the hepcidin-ferroportin axis is the most logical experimental approach also for the treatment and not only for diagnosis of iron disorders. The rationale is to use hepcidin agonists for iron overload disorders caused by inappropriate/low hepcidin and hepcidin antagonists to release sequestered iron in IRIDA and in anemia of inflammation [14]

Clinical Consequences of Iron Deficiency in Cancer Patients

The most important consequence of IDis the risk for developing anemia or the worsening of already existing anemia. Moreover, an impairment of clinical outcomes, associated to a worsening of quality of life [15] by deterioration of the performance status, and often a loss of adherence to chemotherapy may occur. For these reasons, iron deficiency should not be underevaluated since it may be associated with several complications. Typical symptoms are pallor, cold skin, weakness and fatigue, reduced physical fitness [16], brittle nails (onychoschizia),, angular cheilosis, impairment of cognitive functions [17-19], headaches, insomnia, restless legs syndrome, depression, loss of libido, dyspnea, tachycardia, thrombocytosis, increased thromboembolic complications, alopecia, and in rare severe cases Plummer–Vinson syndrome (a condition characterized by iron-deficiency anemia, glossitis, cheilosis, esophageal webs, and dysphagia)..

Treatment Options

The management of anemia in cancer patients often requires a multidisciplinary approach, aimed at recognizing and treating the underlying cause (whenever possible) and at restoring hemoglobin levels. The pharmacological treatment of ID aims at avoiding anemia and improving the symptoms, thus ameliorating the patients' quality of life. In cancer patients, three principal therapeutic options are available, namely red blood cell (RBC) transfusions, ESAs, and iron. The latter two treatments can be combined to enhance the effectiveness of either one.

Recent findings from animal models and epidemiological studies have raised concerns about the risk of tumor growth promotion and enhanced oxidative stress induced by iron therapy [41]. However, it has to be underlined that the doses used in preclinical studies are very high and also iron formulations are different, since larger clinical trials should be performed to assess whether this risk is present also in a clinical setting.

Up to now, just short-term studies have been performed, and they did not show any increase in tumor progression in IV Iron-treated patients compared to untreated patients [39]. However, long term prospective trials evaluating outcomes of IV iron therapy (alone or in combination with ESAs) in anemic cancer patients are necessary to clarify this issue. Regarding the risk of infections, no alarming signal has emerged in cancer patients treated with IV iron. Nevertheless, given the role of iron in immune response and microbial proliferation, current guidelines prudentially advise to avoid IV iron administration in patients with suspected active infections [3]

According to the NCCN guidelines on cancer- and chemotherapy- induced anemia, iron supplementation by oral or intravenous route should be considered in absolute iron deficiency, defined as ferritin < 30 ng/mL and TSAT < 20 %. In case of ferritin levels between 30 and 100 ng/ mL and TSAT between 20 and 50 %, iron stores can be considered sufficient if these patients do not receive ESA, whereas in patients receiving ESAs, since they may develop FID and thus not respond to the treatment, intravenous iron should be discussed, even if the benefit from its use is controversial. In anemic patients with a TSAT < 20 % a combination of intravenous iron and ESA should be used. The shared "American Society of Hematology/American Society of Clinical Oncology clinical practice guideline on the use of epoetin and darbepoetin in adult patients with cancer" [42], recommends to monitor iron homeostasis at the beginning and during ESA therapy, in order to establish if iron supplementation is needed. Furthermore the guidelines of the "European Society for Medical Oncology" (ESMO) [3], recommend periodic monitoring of iron homeostasis (iron, CRP, transferrin, and ferritin) as well. Furthermore, intravenous iron in patients with ID is more effective in increasing Hb than oral or no iron supplementation, and that iron supplementation reduces the number of patients receiving blood transfusions.

Red Blood Cell Transfusion

For many years the most used approach for the treatment of cancer-associated anemia was blood transfusions. However, besides the possibility to obtain a rapid increase in Hb levels, the benefits of this approach are transient, since they may be associated with relevant adverse effects, such as anaphylactic reactions, transfusion-related acute lung injury (TRALI), circulatory overload, iron accumulation, infectious pathogens transmission, as well as an increased susceptibility to infections because of transfusion-related immunosuppression [20]. Even if the safety of RBC has been established and several experiences have been publishing stating their feasibility even in outpatient settings [21,22], they should be considered only in case of need of a rapid Hb increase. In other situations it is then important to consider alternative therapeutic approaches Numerous studies and meta-analysis have demonstrated that cancer patients receiving transfusions during the perioperative period have an increased risk for mortality, morbidity and tumor recurrence [23].

Intravenous iron

Few studies have analyzed the efficacy of intravenous iron as treatment for cancer-associated anemia or chemotherapy induced anemia. A significant reduction of transfusion requirements was observed in patients with gynecological tumors treated with intravenous iron sucrose and receiving chemoradiotherapy or platinum-based chemotherapy [24]. Since iron is an important growth factor for rapidly proliferating cells including bacteria or tumor cells, some concerns have been raised about the safety of intravenous high dose iron supplementation. Currently, at the moment, there is no definitive evidence that intravenous iron may increase the risk for infections or tumor growth in cancer patients, but this issue has not been completely clarified.

There are currently several fully published trials comparing the association of intravenous iron and ESAs with ESAs alone. Most of them [25-27] show that the combined therapy allowed significantly higher hematological response rates, shorter time to response, higher quality of life, reduction in transfusion need, and lower doses of ESAs. The increase in the hematological response rates correlated with the total dose of intravenous iron and was independent of baseline iron status. Mortality and tolerability did not differ between patients with and without intravenous iron [28].

Oral Iron Supplementation

Oral iron formulations are available as ferrous or ferric salts, and are indicated as first-line of treatment for uncomplicated ID [29]

High doses (100-200 mg elemental iron) are usually

prescribed. Doses are usually 1–3 times a day. However, the bioavailability is about 10% to 15% for ferrous iron preparations (sulfate, gluconate, fumarate, etc.), and it is even lower for ferric iron salts or ferric iron complexes (amino acids, polysaccharide, ovo-albumin, etc.). The absorption of these formulations is negatively affected by proton pump inhibitors or antacids, or meals, or presence of an inflammatory status. In addition, up to 50% of patients on oral iron (depending on the iron formulation) report gastrointestinal side effects due to the direct toxicity of ionic iron, which may lead to reduced tolerance and adherence to iron supplementation [30]. For this reason, single low doses of iron supplements (40–60 mg/day) are preferred as they are associated with less gastrointestinal side effects and lower hepcidin secretion [31,32].

Oral sucrosomial iron

The risk of potentially fatal hyper-sensitization reactions caused by IV iron, which leaded to the recommendation warning by the Italian Medicines Agency (AIFA) in agreement with the European Medicines Agency (EMA) in 2013, strongly reinforced the idea of defining more effective and safer ways of iron supplementation [33].

Recently, a new oral formulation of ferric pyrophosphate (Sideral® Forte), has become available in most European countries. This formulation presents a high bioavailability, of approximately compared to the gold standard, ferrous sulfate and a better safety profile [34-37].

Sucrosomial® Iron (SI) is an innovative oral iron formulation in which ferric pyrophosphate is protected by a phospholipid and sucrose ester of fatty acids (scurester) matrix, which is absorbed through para-cellular, trans-cellular and M cells routes [36]. This renders this formulation peculiar for structural, physicochemical and pharmacokinetic characteristics, together with a high iron bioavailability and excellent gastrointestinal tolerance. In particular, differently from other formulations, the presence of a low non-toxic dose of sucresters protects iron from the gastric acid environment and increases absorption of exogenous iron [36,43,44]. Clinical evidence supports oral SI iron as a valid option for ID treatment, with a higher efficacy and tolerability than oral iron salts. Indeed, this new formulation has shown to be devoid of the common side effects of conventional oral iron supplementation, such as stomach pain, nausea, constipation, discoloration of the mucous and feces. Moreover, sucrosomial iron supplementation advantages are based on its higher safety profile compared to IV formulations, and on an easy patient management and lower costs, since IV infusions require specific facilities and dedicate personnel. Indeed, IV iron can only be performed in authorized centers equipped with emergency and intensive care professionals, and for this reason physicians and patients are often discouraged from supplementation. Interestingly, Mafodda et al recently published the results of a retrospective study evaluating the efficacy of oral sucrosomial iron supplementation in patients suffering from chemotherapy-related anemia featuring neither FID nor AIDand receiving darbepoetin, in comparison with IV iron supplementation.In particular, authors examined the ability of sucrosomial iron versus intravenous iron in increasing hemoglobin as well as safety, need of transfusion, and quality of life (QoL). The study showed no difference in the Hb response rate between the two treatment arms, as well as in the requirement of red blood cell transfusions and improvement in QoL. More important, sucrosomial oral iron formulation was better tolerated since it did not show the risks of IV iron [37]. Overall, performance of oral sucrosomial iron was comparable to that of IV iron and produced comparable advantages for patients in terms of quality of life and Hb levels together with higher safety, suggesting a potential benefit also in reducing the need for transfusions for such patients. Recent study analyzed the cost-effectiveness of intravenous sodium ferrigluconate vs oral sucrosomial iron in patients with iron deficiency anemia refractory/intolerant to oral iron sulfate without other interfering factors on iron absorption. The study showed a better quality of life and wellness perception was recorded in the SI group. Nevertheless, appropriately sized randomized control trials are needed to confirm the promising results obtained with oral SI supplementation in anemic oncologic patients [45].

Conclusion

Iron deficiency (ID) is usually treated with oral iron salts, however this approach is very usually accompanied by gastrointestinal side effects, which consequently reduce the compliance with treatment. On the other hand, intravenous (IV) iron formulations are increasingly safe, but there is still a risk of hypersensitivity reactions and the need for venous access and infusion monitoring. Interestingly a recent paper showed that intravenous iron may be a more appropriate therapy to limit adverse microbial outcomes, compared to oral iron in anaemic Colorectal Cancer Patients [38]. In this scenario, the innovative oral iron formulation, Sucrosomial® Iron (SI), represent a valid option for ID treatment, which is more efficacious and tolerable than oral iron salts. SI has also demonstrated a similar effectiveness, with lower risks, than IV iron. Actually, oral SI represents a valid and promising choice of treatment of ID, especially for patients with intolerance to iron salts or no-responders to ion salts. Moreover, SI should also be considered as an alternative to IV iron for initial and/or maintenance treatment in different patient populations.

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