

Iron deficiency in gastrointestinal oncology

Kristof Verraes, Hans Prenen

University Hospitals Leuven, Belgium

Abstract

Anemia is a very common condition in patients with gastrointestinal tumors, with a negative impact on mortality, morbidity and quality of life. The underlying causes are blood loss, chemotherapy-induced myelosuppression and iron deficiency. Yet, anemia and more specifically iron deficiency remains undertreated in daily clinical practice, mainly because many clinicians are not familiar with using intravenous iron products to treat iron deficiency. Many aspects of the pathophysiology of iron deficiency are now better understood. This review focuses on the mechanisms of iron deficiency in cancer patients and summarizes the approach to successfully treating it.

Keywords Anemia, iron deficiency, digestive oncology

Ann Gastroenterol 2015; 28 (1): 19-24

Introduction

Anemia is a common finding in cancer patients, both at time of diagnosis and during antineoplastic treatment [1]. It is multifactorial and can be patient-, disease- or treatment-related (Table 1).

Specific attention for anemia in cancer patients is important, as it is linked to a poorer prognosis [2], physical symptoms [3], and a poorer quality of life (QoL) [4,5]. Anemia can be corrected in different ways depending on the clinical setting, including transfusions, erythropoiesis stimulating agents (ESA) and iron supplementation. Still, anemia in cancer patients is undertreated with a treatment rate of 38.9% (ESA 17.4%, transfusions 14.9% and iron substitution 6.5%) and mean hemoglobin (Hb) to initiate treatment of 9.7 g/dL [1]. A recent European observational study showed that, despite growing evidence, the recognition and therapy of anemia and iron deficiency (ID) is still not optimal with a substantial variation across Europe [6].

In patients with anemia, the main goal is to improve QoL (especially fatigue) with limited toxicity and a good pharmacoeconomic profile. However, treatment of anemia solely for fatigue is not sufficient, suggesting that chemotherapy-induced fatigue is multifactorial and management should be multidisciplinary [4].

As red blood cell (RBC) transfusions are expensive (300-500 € per transfused unit) and can be complicated

by procedural problems, such as iron overload, viral and bacterial infections, and immune injury, other methods for anemia correction were needed [7]. ESA are effective in correcting chemotherapy-induced anemia and reducing the need for transfusions [8]. Following international guidelines, ESA could be started in symptomatic anemic (i.e. Hb <10.0 g/dL) cancer patients receiving chemotherapy with a palliative intention [9-11].

A recent Cochrane review [12] concluded that ESA significantly reduces the need for RBC transfusion (RR 0.65), the amount of transfusions needed (on average 0.98 unit less per patient) and induces a hematological response in a greater portion of patients (RR 3.93) in combination with a better QoL. However, ESA possibly increase mortality during the study period (HR 1.17), and there is some evidence that there is a decrease in overall survival (HR 1.05). There was also a higher risk for thromboembolic events (RR 1.52), hypertension (RR 1.3), thrombocytopenia/hemorrhage (RR 1.21), and no evidence to support an effect of ESA on tumor response (RR 1.02).

As the cost per quality-adjusted life-year is estimated to be 208,000 €, ESA therapy should be seen as an expensive therapy

Table 1 Causes of anemia in cancer patients

Patient-related	Disease-related	Treatment-related
Nutritional deficiencies	Bone marrow infiltration	Chemotherapy-induced bone marrow toxicity
Thalassemia	Hemolysis	Renal toxicity
Hemoglobinopathy	Chronic blood loss	Drug induced hemolysis
	Hypersplenism	Extensive radiotherapy
	Anemia of chronic disease	

Digestive Oncology, University Hospitals Leuven and Department of Oncology, KU Leuven, Belgium

Conflict of Interest: None

Correspondence to: Hans Prenen, MD, PhD, University Hospitals Leuven, Department of Gastroenterology, Digestive Oncology Unit, Herestraat 49, B3000 Leuven, Belgium, Tel.: +32 16 34 42 18, Fax: +32 16 34 44 19, e-mail: hans.prenen@uzleuven.be

Received 18 July 2014; accepted 12 August 2014

that profoundly increases healthcare costs [13]. Depending on the studies, the target Hb was only reached in 25-73% of patients treated with ESA [14-18].

The most important reason for ESA-refractory anemia is ID [19]. ID in cancer patients is very common. A recent prospective trial reported an ID rate of 42.6% in cancer patients, most common in patients with pancreatic, colorectal and lung cancer (63.2%, 52.2% and 51.3% respectively). ID was correlated with grade of anemia, tumor stage, time of last anticancer treatment (<12 weeks before), persistent and progressive disease status and Eastern Cooperative Oncology Group status 2-4 [20].

In this review, we will discuss the pathogenesis of ID, as well as the approach to treating it, since there are currently no clear guidelines available.

Iron homeostasis

Normal iron homeostasis

In a healthy person, iron metabolism is strictly regulated to meet the needs of the body and the bone marrow in particular, about 20-30 mg/day. The total body iron is about 50 mg/kg with iron distributed within RBC Hb (65%), in enzymes and cytochromes in myoglobin and other tissues (10%). The remainder is stored in the liver (5%), reticuloendothelial system (15%) and bone marrow (5%). The total body iron in premenopausal women is around 250-300 mg lower than in men. A normal Western diet contains 15-25 mg iron, of which only 1-2 mg/day is absorbed. Iron is lost from the human body via sloughed enterocytes, menstruation and other blood loss.

There is no substantial physiologic mechanism to regulate the iron loss. Accordingly, iron homeostasis is dependent on regulatory feedback between body iron needs and intestinal iron absorption. Iron absorption depends on the body's iron stores, the level of erythropoietic activity in bone marrow, the blood Hb concentration, the blood oxygen content, and the presence or absence of inflammatory cytokines [21-23].

Iron homeostasis in cancer patients

In cancer patients, the iron metabolism is influenced by high levels of hepcidin (Fig. 1). Hepcidin is a 25 amino-acid peptide, produced by the liver and is the major regulator of iron homeostasis by inhibiting iron transport across the gut mucosa thereby maintaining normal iron levels within the body. It also inhibits iron transport out of macrophages. The production of hepcidin is upregulated by inflammation (IL-6), and down regulated by ID and erythropoietic activity (by mechanisms that are not well understood). Cytokine-induced synthesis of hepcidin plays a critical role in macrophage iron retention which underlies anemia of chronic disease; however little evidence is available about the relation of hepcidin levels and iron metabolism in chronically ill patients.

Hepcidin affects ferroportin, a major iron exporter located on the enterocytes, hepatocytes and macrophages, in two ways. First, by its direct binding to ferroportin, hepcidin forces its internalization and degradation [24]. Furthermore, hepcidin formation is inversely correlated with the expression of ferroportin [25].

ID in cancer patients

ID is generally divided in 3 groups: Absolute ID (AID), functional ID (FID), and iron sequestration (Fig. 2). AID is the most common group. AID is the absence of storage iron because of nutritional deficiencies, malabsorption or blood loss. Its therapy is focused on repletion of iron stores. FID occurs when the bone marrow needs are higher than the possible iron supply. It can be seen during intense stimulation of the bone marrow by endogenous erythropoietin or treatment with ESA. FID can occur in the presence of storage iron and/or oral iron supplementation. This is demonstrated by the 50% reduction of serum ferritin and transferrin saturation (TSAT) in individuals under ESA. Finally, iron sequestration is the immobilization of the available storage pools [26].

Diagnostic tools in ID

It is important to differentiate which mechanism is the most important in the particular patient to guide treatment, as FID, AID, and iron sequestration can be present in cancer patients [26].

Serum ferritin is commonly assessed as the reflection of the iron stores status, while transferrin saturation <20%, percentage of hypochromic red cells >5%, and Hb content of reticulocytes (CHr) <26 pg reflect the availability of iron in the body. Furthermore, serum ferritin is an acute-phase protein and can be elevated in inflammatory states (e.g. cancer) and liver injury. Hence, normal or elevated ferritin levels in patients with a chronic disease such as cancer do not necessarily indicate sufficient iron stores [27].

Soluble transferrin receptor levels, suggested to differentiate patients needing therapy with iron, ESA or the combination, rather reflects the erythropoietic activity than the iron status and cannot be assessed as iron status parameter when erythropoiesis is stimulated, as with ESA [28].

Recently, a diagnostic plot was suggested for the differentiation between the different mechanisms to guide therapy, based on iron stores (reflected as the ratio of soluble transferrin receptor to log ferritin) and iron demand (reflected as the Hb content of the reticulocytes) [28] (Fig. 3). As the ratio of soluble transferrin receptor to log ferritin and CHr are not routinely measured, the plot is difficult to use in a day-to-day clinical practice. In routine clinical practice, serum ferritin levels below 100 ng/mL probably indicate insufficient iron stores in patients with cancer, and the combination of low TSAT (<20%) and normal or even elevated serum ferritin may indicate FID.

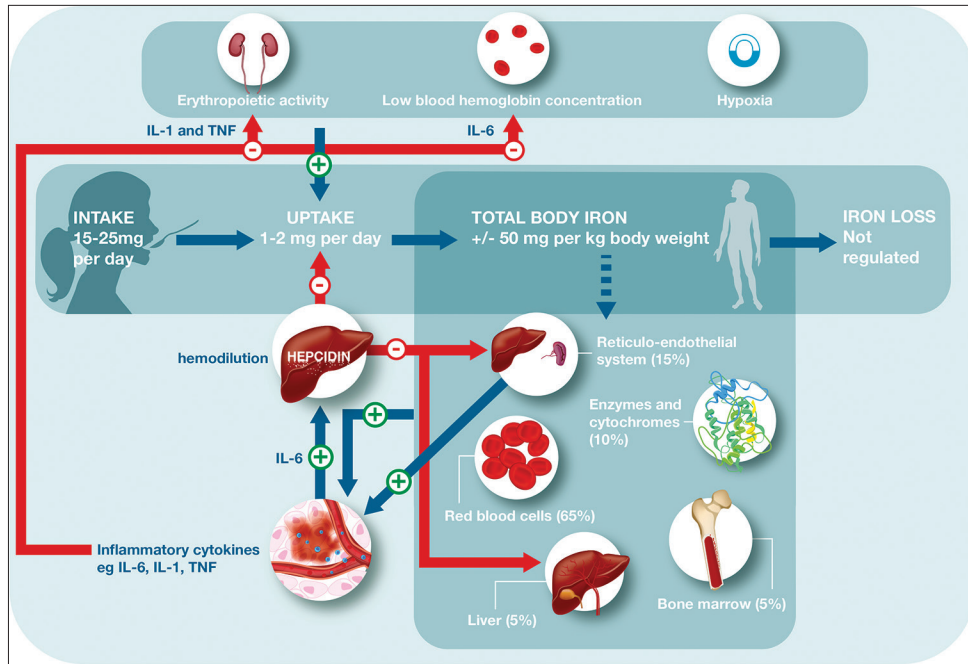


Figure 1 Overview of iron homeostasis in cancer patients. Cytokine-induced hepcidin production results in inhibition of iron uptake and promotion of iron sequestration. Inflammatory cytokines also directly inhibit erythropoietic activity and cause low blood hemoglobin concentration (by hemodilution) thus further worsening anemia in cancer patients
IL, interleukin; TNE, tumor necrosis factor

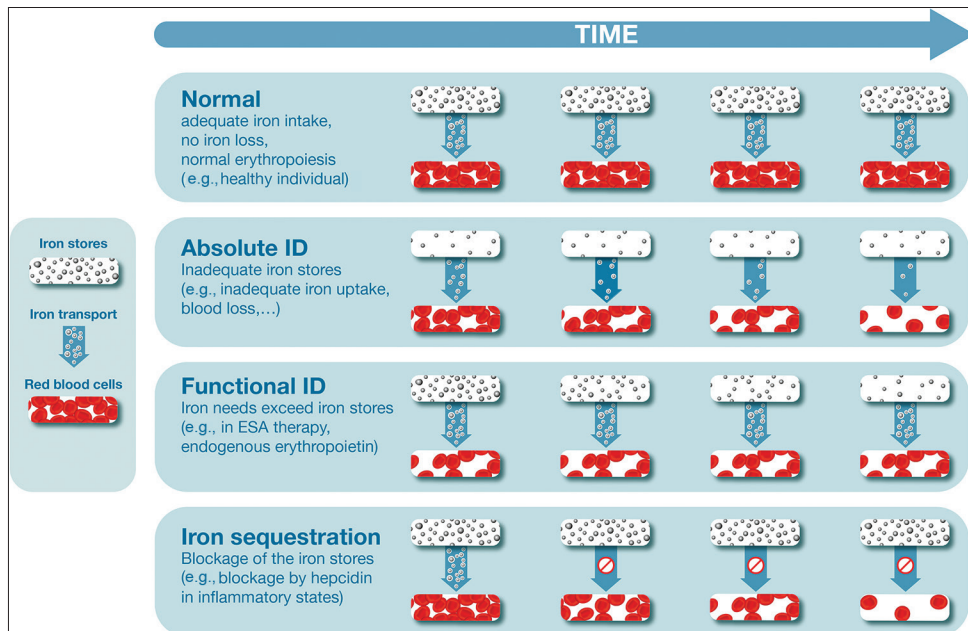


Figure 2 Types of iron deficiency (ID) in cancer patients
ESA, erythropoiesis stimulating agents

Iron therapy in cancer patients

Oral iron therapy

Theoretically, oral iron could be used in cancer patients with AID, who are not receiving ESA and do not have

inflammation. But we believe that, although still commonly prescribed [6], there is no place for oral iron supplementation in cancer patients as they are highly susceptible for low iron intake, low iron absorption, and higher portion of blood loss. Even in addition to ESA, oral iron has no role in anemia treatment [14,15].

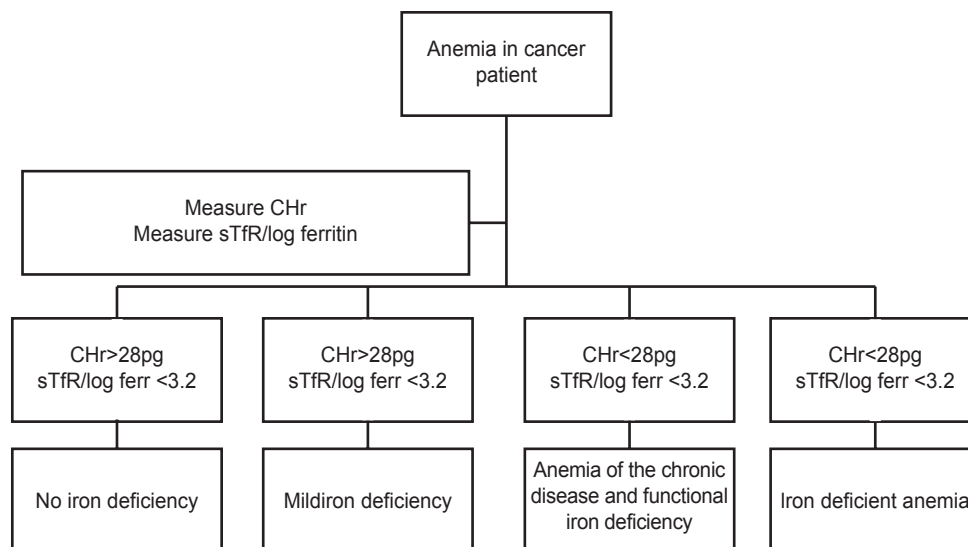


Figure 3 Diagnostic plot in anemia (in patients with CRP >5 mg/L, the cut-off for STFR/LOG FERR is 2.0). CHr, Hemoglobin concentration in reticulocytes; sTfR/log ferritin, Ratio of soluble transferrin receptor to log ferritin [28]

Formulations of intravenous (IV) iron

There are 4 formulations of IV iron available: low molecular weight iron dextran, iron gluconate, iron sucrose and iron ferric carboxymaltose (FCM). They all have an iron-oxyhydroxide core (FeOOH) and a carbohydrate coat, resembling ferritin which protects the organism against the toxicity of unbound inorganic ferric iron (Fe³⁺). Although they have the same basic structure, each formulation differs in core size, shell and global particle size. Due to these biochemical differences, serum clearance rate differs, with plasma half-lives from 30-60 h for iron dextran, 5.3 h for iron sucrose, 1 h for iron gluconate, and 7-12 h depending on dose for FCM [29].

Historically, there is some concern about the possible side effects of IV iron anaphylactic reactions, chronic iron overload, and possible stimulation of cancer cells. To our knowledge, in more than 50 years of IV iron use, no manifestations of chronic iron overload have been described when the agents were used at recommended doses and indications under frequent monitoring. Furthermore, although it is mostly seen in high molecular weight iron dextran [30], the most feared complication of parenteral iron still remains anaphylactic reactions. Fletes *et al* [31] showed a low overall risk for serious adverse events related to iron dextran infusion in clinical practice; globally in 20 cases per 100,000 doses admitted and mostly related to high molecular weight iron dextran. There are no clinical prospective data available about the oncogenic risk. Human data and animal models do show that chronic iron overload does increase cancer risk and promote tumor growth. However, epidemiological and non-clinical studies often show conflicting data and in absence of long-term safety studies, extrapolation to a clinical setting remains difficult [32].

IV iron in combination with ESA

According to the current evidence, it is recommended to optimize the available iron stores with IV iron before or during therapy with ESA [14-19] (Table 2).

In contrast to studies mentioned in Table 2, Steensma *et al* [33] did not find any difference in hematopoietic response rate, ESA dose requirements, transfusion needs, and QoL in 502 patients receiving darbepoetin every 3 weeks randomized to the combination with oral placebo, oral ferrous sulfate 325 mg per day and ferric gluconate 187.5 mg every 3 weeks. The negative results might be explained by the low dose of ferric gluconate, which was about 50% of the recommended single dose.

Overall, the available studies are heterogeneous in study design (different oncologic profiles, different iron formulations, different prevalence in ID and different endpoints), which makes the generalization of the results complicated. In general, there is compelling evidence that the response to ESA is better when IV iron is added.

IV iron as monotherapy

A body of evidence shows that IV administration of iron routinely in absence of ESA is favorable. Kim *et al* [34] showed in cervical cancer patients treated with chemoradiotherapy that giving iron sucrose every chemotherapy cycle reduces the need for transfusion (40% vs. 64% of the patients, and fewer units needed: 1.87 vs. 3.58 units). Dangsuwan [35] showed a significant reduction in transfusion need in the next chemotherapy cycle by giving iron sucrose in comparison to oral iron (22.7% vs. 63.6%).

A large German prospective, non-interventional 12-week study [36] showed that patients with baseline Hb up to

Table 2 Overview of the available studies with IV iron in combination with ESA. Hematopoietic response was defined as Hb increase ≥ 2 g/dL, Hb ≥ 11 g/dL, Hb ≥ 12 g/dL or Hb ≥ 13 g/dL in the different studies

Study	No of patients	Treatment	Hematopoietic response (%)	Remarks
Auerbach 2004	157	ESA+no iron	25	IV iron group had more energy, activity level and QoL score; short-term study (6 weeks); no difference in transfusion rates
		ESA+oral iron	36	
		ESA+iron dextran IV	68	
Henry 2007	187	ESA+no iron	41	No difference in transfusion rate; observation for 12 weeks (8 weeks therapy); no difference in mortality and infection rates
		ESA+oral iron	45	
		ESA+ferric gluconate	73	
Hedenus 2007	67	ESA+no iron	53	IV iron use decreased ESA dose
		ESA+iron sucrose	57	
Bastit 2008	396	ESA+no iron	73	Lower transfusion need in IV iron group; no difference in QoL
		ESA+iron sucrose/ sodium ferric gluconate	86	
Pedrazolli 2008	149	ESA+no iron	62	High dropout during study; even without iron deficiency, IV iron induces better results with ESA
		ESA+ferric gluconate	77	
Auerbach 2010	242	ESA+no iron	63	
		ESA+iron dextran	82	

ESA, erythropoiesis stimulating agents; IV, intravenous; QoL, quality of life; Hb, hemoglobin

11.0 g/dL and serum ferritin up to 500 ng/mL benefited from FCM treatment (stable Hb ≥ 11.0 g/dL). Also patients with ferritin >500 ng/mL but low transferrin saturation benefited from FCM treatment. FCM was well tolerated, 2.3% of patients reported putative drug-related adverse events.

Concluding remarks

Anemia and ID in cancer patients are a major cause of cancer morbidity. Nevertheless, it still remains an underestimated problem and sensitization of physicians caring for cancer patients is necessary. It is important to differentiate between FID and AID as it implies the potential response on ESA and the possible need for iron supplements in patients receiving ESA. In general, most studies showed benefit from IV iron versus oral iron or no iron supplements with a good tolerance. However, these studies are very heterogeneous in their design (observational vs. per protocol; transfusion threshold; IV iron formulations and dosage regimen; and length of study) and study population, so it is difficult to estimate the expected effect on a particular patient with a particular IV iron formulation.

Iron overload can be prevented by strict follow up of the iron parameters during therapy, although there are no good clinical endpoints available so far. There are no good data available about the oncologic risk when IV iron is properly used, but there are some data suggesting an increased risk in chronic iron overload. Since ID has a negative impact on the outcome and QoL, aiming for a normal iron status with a TSAT target ranging from 20-50% seems to be reasonable in cancer patients.

As mentioned before, there are no specific studies or guidelines available for gastrointestinal cancer patients. But

in general, based on the studies in general oncology patients (with heterogeneous study populations), we advise to be vigilant about ID in cancer patients in order to prevent anemia, anemia-related symptoms, and treatment with expensive ESA and transfusion. IV and not oral iron should be started when ferritin levels are <100 ng/mL and/or transferrin saturation is below 20%, independently from Hb level. Good clinical endpoints are lacking, but targeting TSAT between 20 and 50%, Hb levels above 10 g/dL, and absence of fatigue in combination with good QoL seem reasonably achievable. However, we need new prospective trials to investigate the optimal tailored iron therapies in the future in cancer patients, both in curative and palliative settings.

References

- Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anemia in cancer patients. *Eur J Cancer* 2004;**40**:2293-2306.
- Clarke H, Pallister CJ. The impact of anaemia on outcome in cancer. *Clin Lab Haematol* 2005;**27**:1-13.
- Ludwig H, Strasser K. Symptomatology of anemia. *Semin Oncol* 2001;**28**:7-14.
- Holzner B, Kemmler G, Greil R, et al. The impact of hemoglobin levels on fatigue and quality of life in cancer patients. *Ann Oncol* 2002;**13**:965-973.
- Lind M, Vernon C, Cruickshank D, et al. The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. *Br J Cancer* 2002;**86**:1243-1249.
- Ludwig H, Aapro M, Bokemeyer C, et al. A European patient record study on diagnosis and treatment of chemotherapy-induced anaemia. *Support Care Cancer* 2014;**22**:2197-2206.
- Schrijvers D. Management of Anemia in cancer patients: transfusions. *Oncologist* 2011;**16**:12-18.

8. Bohlius J, Weingart O, Treele S, Engert A. Cancer-related anemia and recombinant human erythropoietin – an updated overview. *Nat Clin Pract Oncol* 2006;**3**:152-164.
9. Rodgers GM 3rd, Becker PS, Blinder M, et al. Cancer- and chemotherapy-induced anemia. *J Natl Compr Canc Netw* 2012;**10**:628-653.
10. Rizzo JD, Brouwers M, Hurley P, et al. American Society of Hematology and the American Society of Clinical Oncology Practice Guideline Update Committee. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood* 2010;**116**:4045-4059.
11. Schrijvers D, De Samblanx H, Roila F; ESMO Guidelines Working Group. Erythropoiesis-stimulating agents in the treatment of anaemia in cancer patients: ESMO Clinical Practice Guidelines for use. *Ann Oncol* 2010;**21**(Suppl 5):v244-v247.
12. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database of Syst Rev* 2012;**12**:CD003407.
13. Wilson J, Yao GL, Raftery J, et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. *Health Technol Assess* 2007;**11**:1-202.
14. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. *J Clin Oncol* 2004;**22**:1301-1307.
15. Henry DH, Dahl NV, Auerbach M, Tchekmedyian S, Laufman LR. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. *Oncologist* 2007;**12**:231-242.
16. Hedenus M, Birgegard G, Nasman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. *Leukemia* 2007;**21**:627-632.
17. Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. *J Clin Oncol* 2008;**26**:1611-1618.
18. Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alpha. *J Clin Oncol* 2008;**26**:16919-1625.
19. Goodnough LT. Erythropoietin and iron-restricted erythropoiesis. *Exp Hematol* 2007;**35**:167-172.
20. Ludwig H, Müldür E, Endler G, Hübl W. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. *Ann Oncol* 2013;**24**:1886-1892.
21. Muñoz M, Villar I, García-Erce JA. An update on iron physiology. *World J Gastroenterol* 2009;**15**:4617-4626.
22. Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999;**341**:1986-1995.
23. Fleming RE, Bacon BR. Orchestration of iron homeostasis. *N Engl J Med* 2005;**352**:1741-1744.
24. Ganz T, Nemeth E. Heparin and iron homeostasis. *Biochim Biophys Acta* 2012;**1823**:1434-1443.
25. Theurl I, Aigner E, Theurl M, et al. Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. *Blood* 2009;**113**:5277-5286.
26. Goodnough LT. Iron deficiency syndromes and iron-restricted erythropoiesis. *Transfusion* 2012;**52**:1584-1592.
27. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol* 2006;**1**:S4-S8.
28. Steinmetz HT, Tsamaloukas A, Schmitz S, et al. A new concept for the differential diagnosis and therapy of anaemia in cancer patients. *Support Care Cancer* 2010;**19**:261-269.
29. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol* 2004;**15**:S93-S98.
30. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant* 2006;**21**:378-382.
31. Fletes R, Lazarus JM, Gage J, Chertow GM. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am J Kidney Dis* 2001;**37**:743-749.
32. Beguin Y, Aapro M, Ludwig H, Mizzen L, Osterborg A. Epidemiological and nonclinical studies investigating effects of iron carcinogenesis – a critical review. *Crit Rev Oncol Hematol* 2014;**89**:1-15.
33. Steensma DP, Sloan JA, Dakhill SR, et al. Phase III, randomized study of the effects of parenteral iron, oral iron, or no iron supplementation on the erythropoietic response to darbepoetin alfa for patients with chemotherapy-associated anemia. *J Clin Oncol* 2010;**29**:97-105.
34. Kim YT, Kim SW, Yoon BS, et al. Effect of intravenously iron sucrose on the prevention of anemia in the cervical cancer patients treated with concurrent chemoradiotherapy. *Gynecol Oncol* 2007;**105**:199-204.
35. Dangsuan P, Manchana T. Blood transfusion reduction with intravenous iron in gynecologic cancer patient receiving chemotherapy. *Gynecol Oncol* 2010;**116**:522-525.
36. Steinmetz T, Tschechne B, Harlin O, et al. Clinical experience with ferric carboxymaltose in the treatment of cancer- and chemotherapy-associated anaemia. *Ann Oncol* 2013;**24**:475-482.