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Review Article

Iron Supplementation in Oncology Patients: Interdisciplinary Expert Group Position Paper

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Abstract

Initial clinical and laboratory optimalization of the patient general health status before primary cancer treatment appears to be one of the key aspects in the management of malignancy and should be continued during cancer therapy. The purpose of this strategy is to prepare the patient for oncology treatment, secure its optimal tolerance, reduce risk of complications, and improve quality of life on every stage of cancer management. It can be achieved with dietary intervention, physiotherapy, psychology support, as well as comorbidity control, including iron deficiency, especially resulting in anemia. Appropriate laboratory investigations are essential and iron replenishment started if required. The aim of this position paper is to discuss principles of iron supplementation in this specific group of patients.

Keywords: Iron Deficiency; Anemia; Chemotherapy-Induced Anemia; Cancer; Iron Supplementation; Intravenous Iron; Hypophosphatemia; Hepcidin; Transferrin Saturation.

Introduction

Initial clinical and laboratory optimalization of the patient general health status before primary cancer treatment appears to be one of the key aspects in the management of malignancy and should be continued during cancer therapy. The purpose of this strategy is to prepare the patient for oncology treatment, secure its optimal tolerance, reduce risk of complications, and improve quality of life on every stage of cancer management. It can be achieved with dietary intervention, physiotherapy, psychology support, as well as comorbidity control, including iron deficiency, especially resulting in anemia. Appropriate laboratory investigations are essential and iron replenishment started if required, preferentially intravenously. The aim of this position paper is to discuss principles of iron supplementation in this specific group of patients.

Physiology of Iron Metabolism

The human body contains 3-5 g of iron, with 70% bound to hemoglobin and myoglobin, 15-20% stored in the hepatocytes and macrophages, and the remaining portion accumulated in the bone marrow. Iron is an indispensable component of both hemoglobin and myoglobin, as it mediates in tissue oxidation processes. Being a critical constituent of the electron transport chain enzymes, it is responsible for energy production, controls activity of various enzymes involved in the elimination of free radicals, as well as immunology molecules.

In the human body iron forms relatively stable, although rather small bioavailable plasma pool (<0.2%) bound to transferrin. This transport protein is supplied on daily basis with iron absorbed from the gastrointestinal tract (GI) in amounts of approximately 1-2 mg (up to 5%) and further 20 mg (up to 95%) comes from hemoglobin decomposed by macrophages in the spleen as a result of aging erythrocyte degradation process. This total pool is reduced daily by approximately 20 mg of iron utilized for hematopoiesis and around 2 mg lost due to the GI epithelium shedding and microbleeds.

Reduced dietary iron ions (Fe+2) are absorbed by the duodenal enterocytes via specific transport channels and finally oxidated (Fe+3) after enzymatic reduction. In the enterocytes iron is stored in a complex form bound to ferritin. Iron transportation to the bloodstream and its binding to transferrin is facilitated by ferroportin, transmembrane transport channel protein, localized in the enterocytes close to capillaries.

Ferroportin is also found in the splenic, hepatocyte, bone marrow, as well as macrophage cell membranes. It is considered a key protein regulating iron bioavailability and circulation in the human body. These cells contain iron bound to ferritin.

Ferroportin expression in the cell membranes of tissues responsible for iron absorption, storage, or utilization is regulated by hepcidin that reacts with ferroportin and promotes its degradation.

Hepcidin is synthetized in the liver and macrophages and its overexpression is caused essentially by factors responsible for reducing iron absorption and bioavailability, like inflammation, bacterial infection, and high iron and hemoglobin level. On the other hand, tissue hypoxia and low hemoglobin can exert an opposite effect increasing amount of ferroportin in the cell membranes that subsequently facilitates iron absorption and release from the tissue stores (Figure 1).

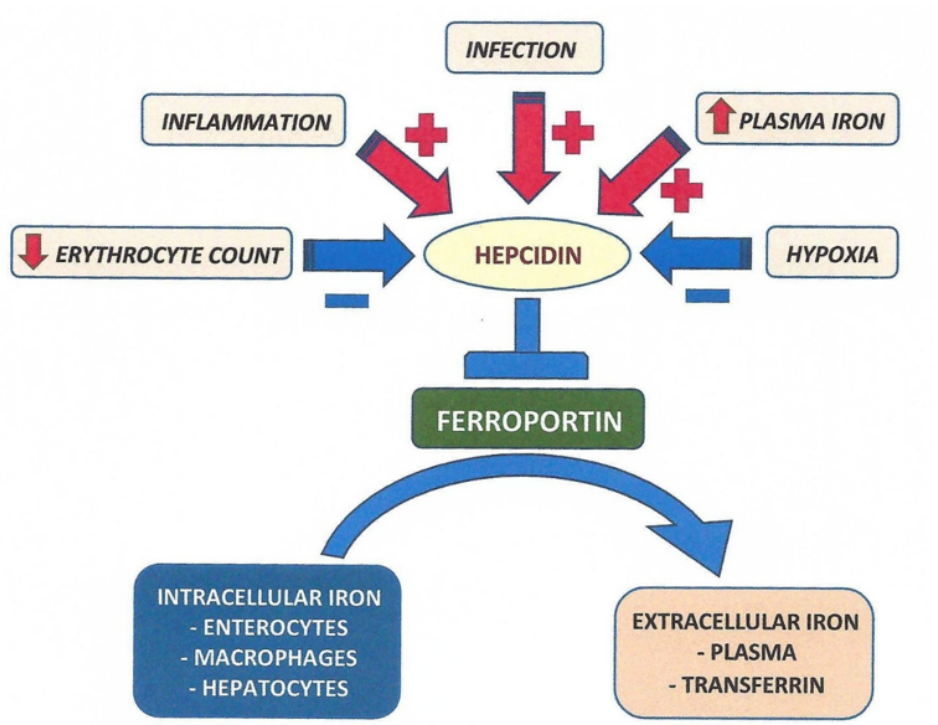


Figure 1: Hepcidin synthesis regulation scheme.

Iron Deficiency Types

The background of insufficient iron availability is dual. Firstly, it can be associated with the absolute deficiency of this element related to low storage tissue content and low circulating pool of transferrin-bound iron.

Secondly, it is a result of a relative functional deficiency when iron bioavailability is impaired by hepcidin inhibition of iron transportation mechanism in the GI tract, as well as iron release from the tissue stores. Although iron stores are repleted, the circulating iron pool is still low. Each type of the two can be isolated or is accompanied by anemia.

Iron Metabolism in Malignancy

Multiple factors can impair iron metabolism in malignancy, including:

- low iron supply (diet, drug interference, anorexia)
- reduced absorption (cancer of GI, hepcidin expression induced by inflammation, infection, or cancer treatment complications)
- hepcidin-induced, enhanced tissue sequestration associated with impaired bioavailability
- excessive loss (bleeding, surgery)

Iron deficiency/anemia burden and clinical importance in malignancy

Iron deficiency, in majority of cases associated with anemia, is reported in 32%-60% cancer patients [1] and depends on the type of malignancy. In one of studies it was found in 63.2%, 52.2%, and 51.3% patients suffering from pancreatic, colon, or lung cancer, respectively. There is a strong correlation between iron deficiency and anemia prevalence in most types of solid tumors [2]. Iron deficiency and anemia levels are related to malignancy stage. For example, iron deficiency prevalence raised from 35.4% to 45.2% and 53.6% in stages I–II, III, and IV, respectively, while anemia prevalence increased from 18.4% to 29.8%, and 41.2% in the most advanced stage IV patients [2].

In lymphoma or myeloma patients anemia prevalence is very high, up to 72.9% and 67.7%, respectively, and also correlates with the disease stage [3]. In 39.1% of cases it is iron deficiency anemia [4].

Unlike in solid tumor patients, in hematological malignancy iron deficiency prevalence shows no correlation with cancer stage [2] and the frequency of absolute iron deficiency is 3-4-fold lower than of functional deficit.

In cancer patients iron deficiency without anemia is found in almost 1 out of 5 patients [5] and is associated with less favorite clinical outcome [6].

Moreover, in cancer patients with concomitant iron deficiency immunotherapy response is often poorer [7]. Iron deficiency development results in anemia and impaired effectiveness of immune-checkpoint inhibitor (ICI) and chimeric antigen receptor T-cell (CAR-T) therapy [8]. Iron deficiency is also associated with increased fatigue, reduced quality of life and decreased physical performance.

Clinical trials analyzing iron supplementation in deficient patients as a strategy of malignancy outcome improvement showed this intervention alleviates anemia symptoms, leading occasionally to hemoglobin normalization [9]. Moreover, iron supplementation can enhance immunology response, i.e. improve ICI therapy efficiency due to higher ability of the immunology system to fight against malignancy [7].

Clinical Presentation of Iron Deficiency

Bearing in mind that iron function far exceeds its role in hemoglobin and myoglobin biosynthesis, a wide variety of deficiency symptoms is not surprising. The most frequent are fatigue, drowsiness, lower physical performance levels, reduced cognitive function (attention, memory), lower mood, emotional lability, loss of libido, headache, and abnormal sleep pattern. Aforementioned manifestations may be associated with tissue hypoxia. Further symptoms are more likely caused by impaired other functions related to inadequate iron bioavailability, including bluish sclera (Osler's sign) provoked by abnormal collagen synthesis followed by thinning of the sclera wall and subsequently the choroid becoming more clearly visible underneath [10], dystrophy and deformation of the nail plates (koilonychia, brittle nails, ridges, splitting) in response to abnormal cell proliferation [11], smooth and shiny tongue with distorted taste as a result of atrophic glossitis, difficulty swallowing and speaking, trismus, all related to oral cavity submucosal fibrosis [12], dry and pale skin, immunodeficiency, recurrent infections, eating of non-consumable items (pica), like chalk, soil, or stones as a consequence of the buccal and glossal mucosa abnormalities, high appetite for ice-cold food (pagophagia), and restless legs syndrome.

Laboratory Investigations

According to World Health Organization anemia is defined as hemoglobin level <13 g/dL in males and <12 g/dL in females. Iron deficiency is manifested by abnormal erythrocyte biomarkers, including Mean Corpuscular Volume (MCV) <80 fL, Mean Corpuscular Hemoglobin (MCH) <27 pG, or Mean Corpuscular Hemoglobin Concentration (MCHC) <33 g/dL. A variety of other parameters may be diagnostically helpful, although not standardized yet, and they involve Red Cell Distribution Width-Coefficient of Variation (RDW-CV), high proportion of erythrocytes with low hemoglobin concentration, or reduced mean reticulocyte hemoglobin content.

Evaluation of body iron status requires testing of a directly bioavailable iron pool aimed at body functioning related to iron, as well as a storage pool. Stored iron is bound to ferritin, so ferritin level reflects storage pool volume. Direct iron bioavailability is measured based on transferrin saturation (TSAT) representing level of saturation with iron. TSAT calculation requires serum iron and Total (TIBC) or Unsaturated Iron Binding Capacity (UIBC):

$$TSAT = \frac{Fe\ concentration}{TIBC}\ x\ 100\ \%\ \textbf{or}$$

$$TSAT = \frac{Fe\ concentration}{UIBC + Fe\ concentration}\ x\ 100\ \%$$

TSAT shows the proportion of transferrin iron-binding capacity that is available, i.e. iron-free. Based on these measurements, it is possible to diagnose:

- absolute iron deficiency, if ferritin <100 ng/mL,
- functional iron deficiency, if ferritin >100 ng/mL and TSAT <20%.

Although in healthy individuals lower limit of norm for ferritin is 30 ng/mL, it should be underlined that in malignancy or chronic inflammatory conditions ferritin levels below 100 ng/mL are already evidence of insufficient iron storage pool, keeping in mind that it is an acute phase protein [13].

Treatment

In cancer patients hepcidin concentration is frequently raised [1] and is further increasing after oral iron supplementation so its effectiveness is limited [14]. Oral iron supply in these patients is insufficient and requires adequate diet for several months to improve efficiency what might be problematic in oncology patients. Moreover, it is associated with some risk. Two meta-analyses including thousands of patients taking a reduced form of iron salts (Fe+2) orally showed GI adverse events in 30–70% of patients [15]. Most frequent adverse effects were: dysgeusia, abdominal

pain, heartburn, nausea, vomiting, or constipation. Compared to oral formulation, intravenous iron results in faster hematopoietic response, as well as similar or more prominent hemoglobin increase, and is associated with lower number of doses (1 to 4) [16]. Intravenous iron more effectively reduces fatigue than oral formulation (Functional Assessment of Cancer Therapy-Fatigue, FACIT-F). Moreover, intravenous iron seems to be better tolerated than oral. PROFOUND trial showed ferric derisomaltose therapy was associated with 3-fold lower prevalence of adverse events than ferrous sulphate which resulted in more frequent discontinuation of oral therapy due to drug intolerance or lack of response [16].

In consequence, currently there are no guidelines on iron therapy in cancer patients that would recommend against (or ban) oral iron supplementation.

Intravenous iron formulations differ in maximal dose, time of infusion, and safety profile (Table 1).

Iron formulation	Maximal single dose	Minimal infusion time	Hypo-phosphatemia risk
Complex ferric oxyhydroxide (III) with sucrose (Venofer)	>70 kg, 500 mg; ≤70 kg, 7 mg/kg	3.5 h	No risk signals
Complex ferric oxyhydroxide (III) with dextran	100-200 mg or full dose infusion up to 20 mg/kg	100 ml over 30 min[2]	No risk signals
(CosmoFer)		Full dose infusion over 4-6 h[2]	
Ferric derisomaltose	20 mg/kg	≤1000 mg over 15 min;	No risk signals
(Monover)		>1000 mg over 30 min	
Ferric derisomaltose	200 mg	Bolus injection or direct injection to venous access of dialysis machine	No risk signals
(Diafer)[3]			
Ferric carboxymaltose	1000 mg	≤500 mg over 6 min;	Serum phosphate levels should be monitored[4]
(Ferinject)		>500-1000 mg over 15 min	

[1]Based on Summary of Product Characteristics.
[2]Each time first 25 mg to be infused over 15 minutes.
[3]This product is dedicated to chronic renal insufficiency patients on dialysis.
[4]In patients receiving multiple high doses or on long-term treatment, as well as in patents at risk of hypophosphatemia.

Table 1: Comparison of intravenous iron formulations.

In general, novel intravenous iron formulations are preferred, as they are associated with potentially less adverse events, can be administered in higher maximal single doses, and are more effective than formulations brought earlier on the market.

Iron should be provided when absolute deficiency is detected, as well as in case of functional deficiency due to increased requirement as result of enhanced erythropoiesis (post-hemorrhagic anemia, chemotherapy, erythropoiesis-stimulating medication) (Figure 2).

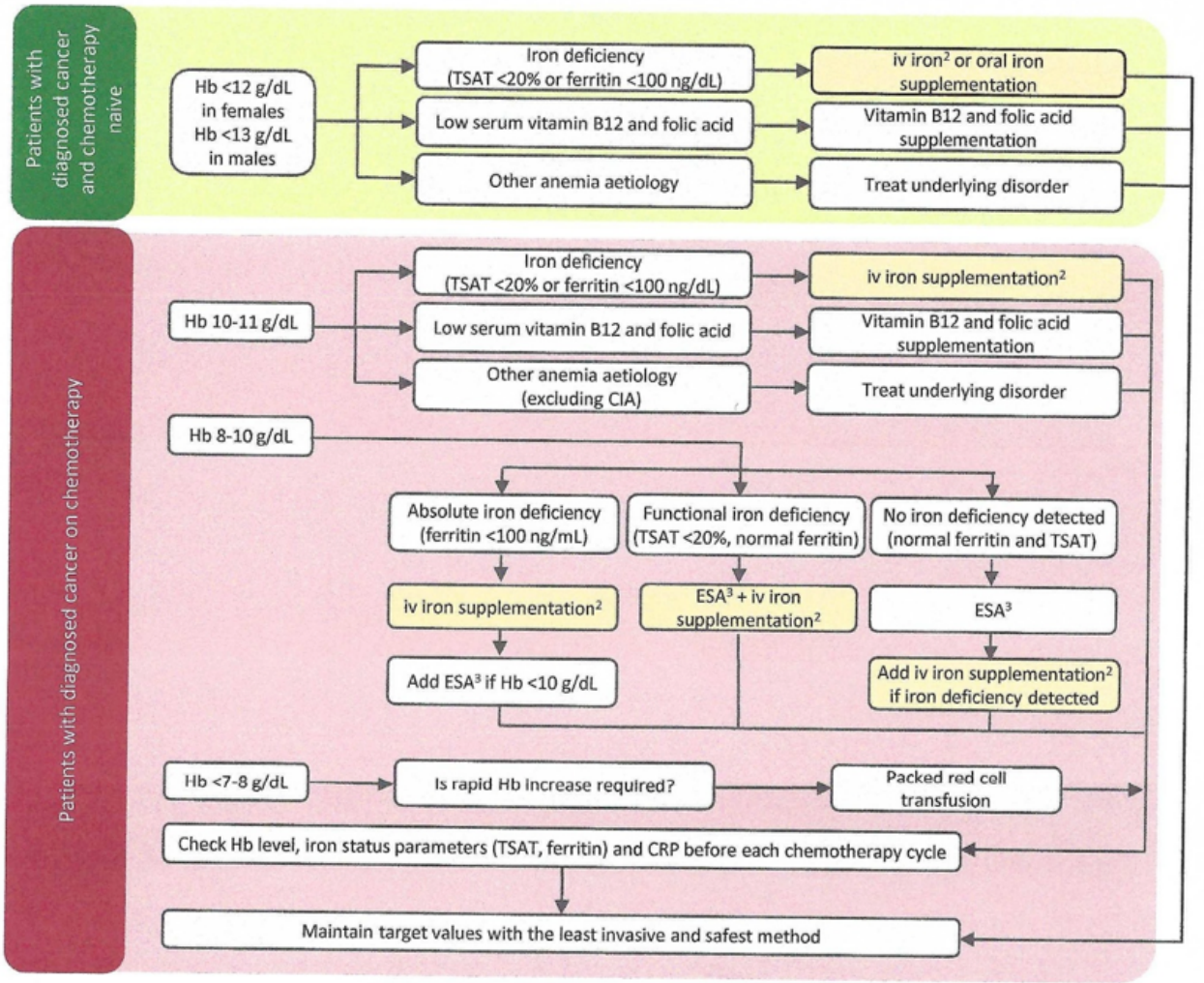


Figure 2: Anemia management in cancer patients (flowchart). 1) Cancer patients who are not on chemotherapy (For example, patients before oncology treatment or receiving other types of anticancer management.) and present rapid hemoglobin drop (>2 g/dL), patients prioritized for quality of life improvement and stabilization, patients scheduled for major surgery. 2) Doses should be calculated individually based on Summary of Product Characteristics. 3) ESA dosage should be in agreement with approved Summary of Product Characteristics. ESA dose escalation or switch to another ESA in patients non-responding to treatment within 4–8 weeks is not recommended and ESA treatment should be discontinued. ESA can only be used in patients on chemotherapy.

CIA-chemotherapy-induced anemia; CRP-C-reactive protein; ESA-erythropoietin stimulating agent; Hb-hemoglobin; iv-intravenous; TSAT-transferrin saturation

Iron supplementation is contraindicated in:

- active infection requiring antibiotics,
- cardiotoxic medication associated with free radical generation (in particular, anthracyclines, alkylating agents, and Vinca alkaloids): iron should be administered at least 48 h pre-cardiotoxic therapy or if this approach is not feasible it can be provided next day (plasma half-life is 1-20 h depending on formulation).
- shock (especially septic), severe multiorgan insufficiency, critically ill patient

Dosing

Intravenous iron dose is calculated based on Ganzoni formula:

$$\textit{Total Fe dose (elemental Fe in mg)} = \textit{body weight(kg)} \; x \; \Delta Hb\left(\frac{g}{dL}\right) x \; 2.4 + 500 \; mg$$

ΔHb = target hemoglobin – real hemoglobin level (in g/dL)

A different iron dose calculation method is based on a simple scheme involving hemoglobin concentration and body weight (Table 2).

Hb (g/dL)	Body weight < 50 kg	Body weight 50–70 kg	Body weight ≥ 70 kg
≥ 10	500 mg	1000 mg	1500 mg
< 10	500 mg	1500 mg	2000 mg

Table 2: Simplified calculation scheme.

Treatment Effectiveness Assessment

A repeat hemoglobin level evaluation needs to be performed before each chemotherapy cycle. Otherwise, hemoglobin concentration should be monitored every 2–6 weeks. Lack of expected response to intravenous iron requires further diagnostic work-up to detect exact anemia etiology.

Safety

Risk of adverse events in intravenous iron supplementation is low. Adverse event prevalence, mainly immune-mediated (urticaria, itching, dyspnea, wheezing, oral/lingual/pharyngeal/whole body swelling, chest pain), is estimated to be less than 4%, and frequency of reactions requiring vasoactive agents is 0.006% [17]. A vast majority of reported serious post-intravenous iron adverse events are not allergic (IgE-mediated sensitivity) and seem to be of pseudo-allergic background (mediated by complement activation) in reaction to poorly bound iron atoms before they are absorbed by transferrin. Pseudo-allergic reactions occur in initial phase of infusion, are often self-limiting, and not life-threatening [18].

According to European Medicines Agency (EMA) regulations there is no need to start either from a test dose or routine anti-histaminic premedication pre-iron infusion [19].

To control safety hazards in intravenous iron therapy, it is recommended to:

1. Assess risk of potential reaction.
2. Chose a type of formulation enabling full dose provision in a single infusion.
3. Avoid intravenous iron supplementation in the first trimester of pregnancy.
4. Keep at least 30 min intervals between iron administration and other medications known to trigger allergic reactions (including chemotherapy and monoclonal antibodies).
5. Take precautions when intravenous iron is prescribed for patients with known allergy, atopy, or systemic inflammatory disease; it is prudent to initiate infusion starting with a reduced flow rate.
6. Keep target ferritin level at 50 ng/mL (100 ng/mL in malignancy) [19].

As majority of adverse events are non-allergic, their occurrence after first dose of given iron supplementation agent is not a contraindication for another dose of the same formulation [20].

Ferric carboxymaltose can induce fibroblast growth factor 23 (FGF23) secretion leading to higher urinary phosphate excretion, followed by often asymptomatic severe phosphate deficiency [21, 22].

In view of possible hypophosphatemic osteomalacia, it is recommended to monitor serum phosphate in patients with risk factors or receiving long-term or repeat high dose infusions of this formulation [23]. Particular attention should be paid to cancer patients with frequent abnormal phosphate status and associated hypophosphatemia resulting in serious complications and poor outcome, as well as reduced treatment effectiveness [24].

Hypophosphatemia risk factors and underlying mechanisms are showed in Table 3.

When hypophosphatemia risk is high ferric carboxymaltose should be avoided and a different iron formulation must be considered

	Risk factors	Mechanism
1	Oncology treatment	Chemotherapy (cisplatin, ifosfamide) → renal tubulopathy with urinary phosphate loss. Tyrosine kinase inhibitors (imatinib, dasatinib) → phosphate status impairment. Immunotherapy (immune checkpoint inhibitors, CAR-T) → autoimmune kidney injury
2	Parenteral nutrition without phosphate supplementation	Suboptimal phosphate supply in undernutrition or low-protein diet. Diuretics or excessive fluids → dilution and/or phosphate loss
3	Tumour lysis syndrome	Initial hyperphosphatemia evolving into hypophosphatemia in consequence of aggressive fluid therapy and diuretics
4	Bone metastases	Osteoblast hyperactivity or osteoclast stimulation can impair Ca-P status
5	Infections and general disorders in cancer patients	Sepsis, undernutrition, massive transfusions, respiratory alkalosis → higher intracellular phosphate consumption
6	Impaired phosphate absorption	Chronic GI disorders, including inflammatory bowel disease, coeliac disease, irritable bowel syndrome as a cause of abnormal phosphate absorption. Persistent vomiting or diarrhoea: fluid and electrolyte loss can result in phosphate deficiency
7	Long-term medication	Acid-neutralising agents (aluminium salts), some diuretics, as well as some phosphate-binding medication can reduce phosphate absorption
8	Refeeding syndrome	Food re-introduction in chronically undernourished patients can result in sudden phosphate shift into intracellular space

Table 3: Hypophosphatemia risk groups.

Management algorithm in adverse events that are likely to be related to intravenous iron supplementation is showed in Figure 3 [25, 26].

ESA and Iron Supplementation

The effectiveness of erythropoiesis-stimulating agents (ESA) depends on amount of iron available for hematopoiesis. An increased iron requirement is observed during ESA therapy. Several published studies on concomitant treatment with ESA and iron suggest that intravenous iron added to ESA therapy effectively improves hematology response parameters (higher Hb levels) [28-34].

In conclusion, it is advised to (Figure 2):

1. Check iron status before ESA initiation [27].

2. In case of absolute iron deficiency with low transferrin saturation (<20%) and low ferritin, and/or high proportion of hypochromic erythrocytes (>5%) iron supplementation needs to be provided intravenously before ESA treatment initiation [27].

3. If functional iron deficiency (TSAT <20% and serum ferritin >100 ng/mL) is detected iron supplementation should be started before or simultaneously with ESA [13].

4. If iron deficiency is not confirmed iron status needs to be monitored during ESA therapy and supplemented on as-required basis.

Previously published studies including gynecological cancer [35, 36] or lymphoma patients [37], as well as prospective observational studies [38, 39] showed that some patients benefit from intravenous iron supplementation even without simultaneous ESA therapy (higher Hb, reduced requirement for blood transfusion) but these findings warrant confirmation in larger randomized controlled trials [13].

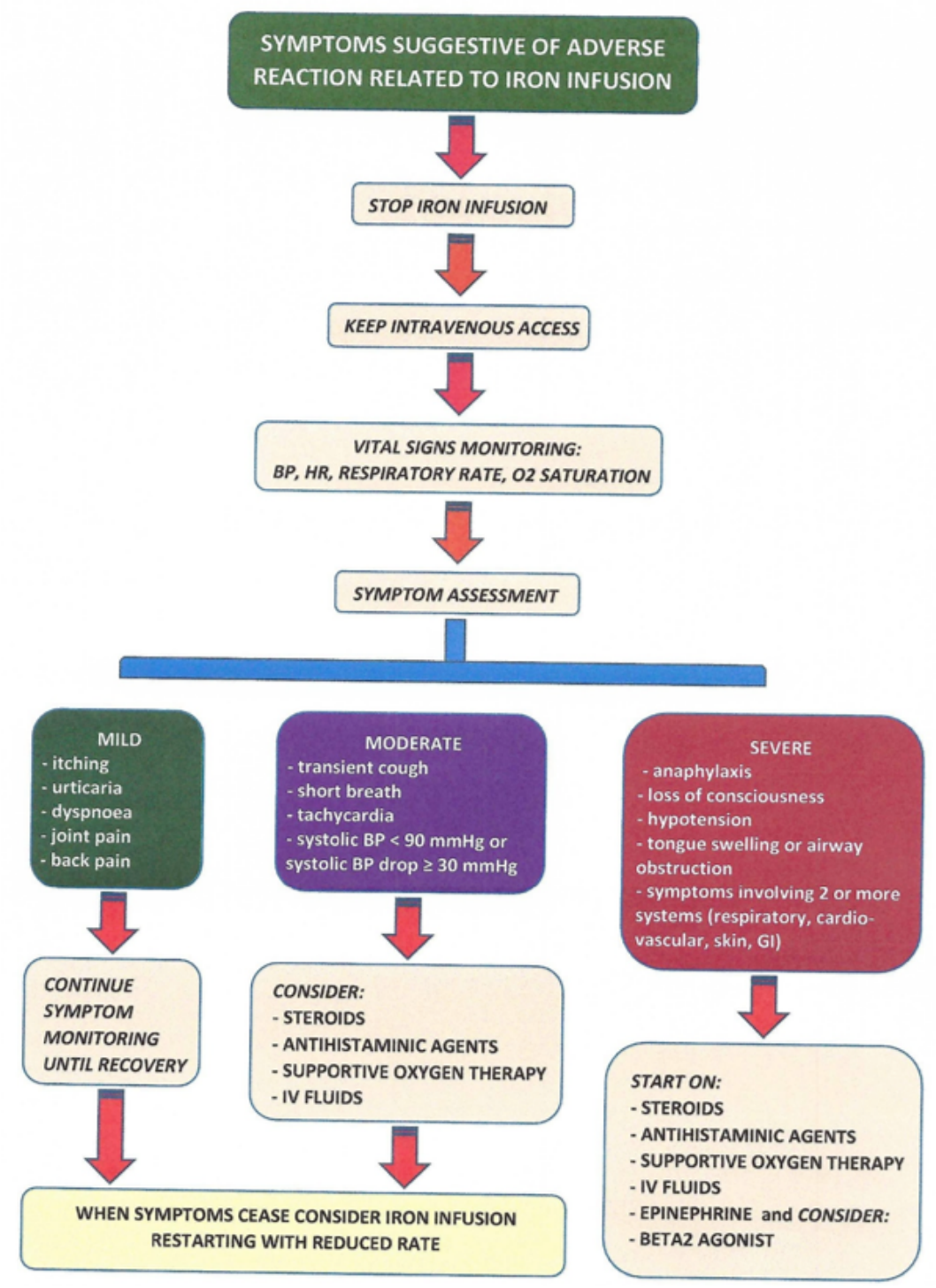


Figure 3: Management algorithm in adverse events related to intravenous iron supplementation.

Iron Overload

Iron overload risk related to supplementation suggests need to closely monitor therapy and underlines the importance of personalized treatment [40]. Both in preclinical and clinical setting, it was showed that iron overload promotes tumor growth and reduces the effectiveness of anticancer therapy. Mouse models in preclinical studies revealed iron overload stimulates tumor progression through generation of free radicals that contribute to gene mutations and drive malignant cell proliferation. These models also showed iron overload compromises immune response, mainly due to change in CD8+ T cell function and promotion of immunosuppressive polarization of M2 macrophages. Iron overload considerably raises the risk of carcinogenesis, including hepatocellular cancer in hereditary haemochromatosis and in patients receiving frequent blood transfusions. Moreover, abnormal iron metabolism is observed in many other tumors and plays a key role in disease progression. For example, breast cancer cells present enhanced hepcidin expression that attenuates ferroportin activity and results in intracellular iron accumulation promoting tumor growth. Inhibition of changes in iron metabolism effectively blocks colorectal cancer growth. Glioma cells absorb iron what helps them survive hypoxia.

Clinical trials also showed that patients with high iron levels present poorer response to chemotherapy and immunotherapy; in this setting tumors are more resistant to treatment mode of action based on oxidative stress promotion and malignant cell necrosis. Regardless of this risk, the study involving patients with advanced metastatic cancer revealed that individuals with higher serum iron (>1036 µg/L) had better response to ICI than with lower iron levels. This unexpected discovery suggests complex role of iron status in oncology treatment, when both deficiency and overload can produce contradictory results depending on circumstances [40]. Hence, iron status checks should be performed in 1-3 month intervals.

Epidemiology data suggest correlation between some cancer types and increased iron exposure or overload. Non-clinical models were inconclusive in terms of cancerogenic impact of iron [41]. It was also found out chronic iron overload (e.g., in hereditary haemochromatosis; TSAT >45%, serum ferritin >1000 ng/mL suggestive of cirrhosis) escalates tumor risk [41].

Long-term intravenous iron (iron sucrose) and darbepoetin (DA) safety were assessed in patients with lymphoid malignancy who received autologous hematopoietic cell transplantation (n=127). Patients with pre-transplant iron overload developed post-transplant infection more frequently but infection parameters were similar in all 3 groups suggesting 900 mg intravenous iron infusion post-transplant is fairly safe. In conclusion, DA and intravenous iron therapy post-autologous hematopoietic cell transplant have no influence on long-term safety, disease outcomes, and survival [42].

General Recommendations

1. Patients on chemotherapy with anemia (Hb ≤ 11 g/dL) and absolute iron deficiency (serum ferritin <100 ng/mL) need intravenous iron supplementation to reduce deficit (See: table/graph).
2. Cancer patients who experience rapid hemoglobin drop (>2 g/dL), patients prioritized for quality of life improvement and stabilization, as well as patients scheduled for major surgery require intravenous iron supplementation to reduce deficit associated with anemia (Hb ≤ 12 g/dL in females and Hg <13 g/dL in males) and absolute iron deficiency (serum ferritin <100 ng/mL).
3. In functional iron deficiency (serum ferritin >100 ng/mL and TSAT <20%) intravenous iron supplementation should be commenced before and/or during ESA therapy if ESA treatment is considered.
4. In some functional iron deficiency patients (serum ferritin >100 ng/mL and TSAT <20%) intravenous iron supplementation without ESA may be considered.
5. Intravenous iron dose should be calculated individually based on individual patient needs.
6. It is preferred to use iron formulation that can be administered in full single dose.
7. Intravenous iron supplementation can be provided with chemotherapy on the same day, unless it is cardiotoxic, but chemotherapy goes first.
8. Iron status needs to be monitored in 1-3 month intervals.

Management of certain clinical conditions in relation to tumor type and patient characteristics is discussed below.

Iron supplementation in cardiac insufficiency related to oncology treatment

Joint risk factors make malignancy and cardiac insufficiency (CI) coexist. Malignancy treatment results in heart injury not only directly due to cardiotoxicity and contractility reduction induced by some oncology treatment but also through promotion of well-known risk factors, including hypertension, dyslipidemia, hyperglycemia, and thromboembolic complications. It is estimated cardiotoxic oncology drugs can provoke reduction of the left ventricular ejection fraction by at least 10% in almost half of treated patients. In this patient cohort the risk of CI development presenting with an abnormal left and also right ventricular ejection fraction is very high [43].

Radiotherapy, particularly with chest area involvement and performed in certain circumstances with limited ability to focus

radiation to tumor location, is associated with heart injury. In this setting the risk of CI with preserved left ventricular ejection fraction is mostly raised [44].

Iron deficiency/anemia prevalence in these specific CI etiology subgroups is unknown. Global iron deficiency prevalence in CI patients vary between 50% and 75%, depending on phenotype and diagnostic criteria [45]. On the other hand, anemia prevalence is estimated between 30% and 50% [46].

Available guidelines developed by European Society of Cardiology and various American associations do not diversify management based on CI etiology [47, 48].

Recommendations:

1. Iron metabolism diagnostic work-up in all patients with CI.
2. Intravenous (but not oral) iron supplementation with ferric carboxymaltose or ferric derisomaltose in all symptomatic patients who manifest cardiac insufficiency with ejection fraction <50% (but not in case of preserved ejection fraction where treatment benefit and safety data are lacking), if TSAT <20% and ferritin < 300 ng/mL, regardless of either presence or absence of anemia [49, 50].

Gynecological Cancer

Optimization of general health status and clinical (metabolic) parameters is crucial in oncology treatment. It is very important when various therapy options are engaged to gain projected clinical outcomes but there is also a concurrent risk of adverse event intensification. It is encountered in gynecological cancer management setting.

Swedish long-term study showed a clear beneficial effect of iron supplementation in patients managed surgically for ovarian cancer. Patients received a single intravenous dose of ferric derisomaltose (1000 mg or 1500 mg, based on body weight) in combination with tranexamic acid 1000 mg. Meantime, more restrictive blood transfusion guidelines were being introduced that recommended Hb threshold <7 g/dL for patients with no comorbidity and Hb <8 g/dL for patients with comorbidities. Intravenous iron therapy was provided between week 3 and day 1 pre-surgery and during post-operative in-hospital period. Transfusion rate was reduced by 31%. Although the prevalence of mild, Clavien-Dindo classification (CD) grade 1 or 2, post-operative complications was slightly increased, severe complication (CD ≥ 3a) rate was stable. Hospitalization period was reduced and no delays in chemotherapy were reported [51].

Similar ongoing studies are aimed at confirming pre-surgery iron supplementation effectiveness, including Swiss Tranafer-Stud trial [52] and joint Canadian and Swedish FORGE trial [53].

A potential way of iron provision is intra-operative intravenous administration, especially if not performed during pre-surgery period. Benefits of this strategy are showed in a sub-section with recommendations for patients undertaking surgery. Irrespective of whether surgery is a first line therapy or follows systemic treatment, intravenous iron administration is always beneficial for patients. A good timing for iron supplementation is neoadjuvant chemotherapy. Patients suffering from advanced ovary cancer who received three or four systemic chemotherapy cycles with paclitaxel and carboplatin (occasionally in combination with bevacizumab) and followed by surgery are good candidates. This approach provides 9-12 week period for prehabilitation procedures involving intravenous iron supplementation. Iron is supplied together with subsequent systemic treatment cycles (every 3 weeks). Certainly chemotherapy can produce in itself simultaneous adverse events requiring iron supplementation. It seems necessary to provide supplementation in grade 1 anemia (Hb 10-12 g/dL), and beyond any doubt in grade 2 (Hb 8-9.9 g/dL). Similar rules can be implemented during post-operative supplementary chemotherapy and supportive treatment.

Next group of patients with frequent occurrence of hematology complications, e.g. anemia, includes females receiving radiotherapy, chemoradiotherapy, or combination of classic chemotherapy with ionizing energy-based treatment, as well as more and more common immunotherapy. It refers to patients diagnosed with endometrial, cervical, or vulva cancer.

In combined treatment options (chemotherapy/radiotherapy or chemoradiotherapy), where systemic therapy plays a role of neoadjuvant therapy, hematology complications, including grade ≥ 2 anemia, emerge in radiotherapy week 4. [54] In patients receiving chemoradiotherapy in combination with immunotherapy anemia (all grades) develops in approximately 23%, and grade ≥ 3 in 9.3% treated patients [55].

Abovementioned changes occur especially in advanced cervical cancer patients. Radiotherapy, a basic treatment modality in cervical cancer, particularly in combination with chemotherapy, has a direct myelosuppressive impact on bone marrow function. The pelvis, a location of active hemopoiesis, is often being radiated during treatment with dose-dependent erythrocyte progenitor suppression. Chemotherapy based on cisplatin is effective in tumor control but augments suppression effect through toxicity to haemopoietic stem cells. Cumulative influence of various therapy modalities can lead to severe and progressive hematocrit and hemoglobin drop during treatment. Moreover, abnormal kidney function can add on to anemia development in some patients. Chronic disease and dehydration can impair renal function and, in consequence, reduce erythropoietin biosynthesis, an essential

hormone for erythrocyte production. Furthermore, less highlighted reason, like hemolysis, can develop in immune-mediated manner or as a result of mechanical destruction of erythrocytes, especially in advanced malignancy with blood vessel involvement [56].

Therapeutically, low hematocrit and hemoglobin are associated with poorer oxidation of the tumor, with direct consequences for radiotherapy effectiveness which is fundamental in cervical cancer treatment [56]. It was noted that hemoglobin level significantly dropped post cisplatin cycle 4 (radiation week 4) [54], and median time between therapy initiation and hemoglobin nadir was 36 days. It was found hemoglobin nadir (<9 g/dL) was significantly associated with poor local disease control, i.e. earlier local relapse. Blood transfusion was necessary in 44.9% patients. Significant negative correlation was showed between blood transfusion prevalence and overall survival time [57].

In view of reported facts, iron supplementation during radiotherapy and especially in combination with chemotherapy is warranted. It is very important to initiate it before treatment week 4, when hematology parameters, including red cells, reach the lowest values. It helps to avoid blood transfusion and treatment delays. Delphi consensus introduced restricted indications for blood transfusion during radiotherapy in cervical cancer patients. It was stated that the indication for transfusion is Hb level <8 g/dL during tele-radiotherapy, and <7 g/dL during brachytherapy. The therapeutic target is Hb level ≥ 9 and <12 g/dL [58].

Recommendations:

3. Pre-operative intravenous iron supplementation in patients scheduled for gynecological cancer surgery needs to be considered as an effective mode of post-operative anemia prevention limiting transfusion requirements and reducing period of convalescence. It promotes earlier initiation of supplementary therapy.
4. In particular, intravenous iron supplementation should considered before neoadjuvant chemotherapy.
5. During radiotherapy or its combination with chemotherapy intravenous iron supplementation may help in maintaining Hb level >9 g/dL what plays a key role in treatment continuity, as well as improves prognosis, especially in cervical cancer patients.

Oncology Patients with Chronic Kidney Disease

Erythropoietin doses used in oncology are much higher than for anemia treatment in chronic kidney disease (CKD) patients. Usually they are between 4000 and 6000 IU subcutaneous erythropoietin alpha weekly or >500 μg darbepoietin alpha three weekly. ASCO/ASH guidelines recommend for erythropoietin therapy in patients with post-myelosuppresive treatment anemia only, recommend against ESA therapy in anemia resulting from other reasons, and suggest iron supplementation even when evidence of deficiency is lacking [59]. It seems they do not apply to oncology patients with CKD. It is well known that in all these diseases higher erythropoietin requirement correlates with higher mortality. However, high quality clinical trials where anemia treatment in oncology patients with CKD is evaluated are lacking and highly reliable guidelines are unavailable. KDIGO recommends to avoid hemoglobin levels <9 g/dL in CKD patients and suggests ESA treatment initiation if Hb level is 9-10 g/dL, clearly following iron deficiency replenishment [60].

It needs to be underlined that iron supplementation, both oral or intravenous, is beneficial for anemia control in patients with renal insufficiency and cancer. It was confirmed in patients on ESA, 5 HIF-PHI (e.g., roxadustat), as well as not receiving this medication. Physicians should remember that in CKD patients, regardless of cancer comorbidity, an important cause of iron deficiency is high hepcidin level so intravenous iron formulation is more effective than oral. Iron supplementation is not contraindicated in oncology patients, except for some types of renal cell carcinoma.

According to 2019 ASCO/ASH guidelines ESA therapy needs to be discontinued in patients who do not respond within 6-8 weeks (Hb increase less than 1-2 g/dL or no transfusion requirement reduction) [61].

Recommendations:

6. Anemia treatment with intravenous iron agents is beneficial (except for some types of renal cell carcinoma) and needs to be commenced before ESA or 5 HIF-PHI therapy initiation.
7. Iron supplementation can be contemplated when serum ferritin is less than 500 ng/mL and transferrin saturation does not exceed 30%.
8. If TSAT during iron supplementation exceeds 50% or ferritin level raises above 800 ng/mL, iron supply should be discontinued.
9. Serum ferritin interpretation in CKD patient needs to be careful, especially in dialyzed individuals who often have subclinical infection. Ferritin is an acute phase protein and uremia is associated with inflammation. Serum ferritin <30 ng/mL always reflects a severe iron deficit and lack of bioavailable iron in the bone marrow.
10. In advanced CKD, particularly in dialyzed patients, intravenous iron supplementation is more beneficial than oral supply because of high hepcidin level that inhibits GI iron absorption.
11. In renal cell carcinoma patients malignant cells need to be assessed for iron affinity (biopsy staining) before iron supplementation is initiated; iron supplementation does

not seem to be contraindicated in any other cancer type.

12. During maintenance iron supplementation its serum level, TSAT, as well as serum ferritin all should be monitored. Supplementation needs to be continued until TSAT and ferritinemia results qualify.
13. One of goals for iron supplementation is to reduce blood transfusion rate or ESA exposure.

Oncology Patients Scheduled for Surgery

It should be highlighted that many patients have no anemia investigation done pre-operatively, some of surgical procedures are urgent, as well as persistent tumor bleeding may lead to anemia development or progression shortly before surgery. Surgical treatment itself is associated with blood loss, its volume is often substantial and may predict potential post-operative deficit with no indication for emergency transfusion. Intraoperative iron administration is recognized as one of options that can improve clinical course of the disease, as well as promote and accelerate erythropoiesis in post-operative period. It is worth underlying that procedure-induced inflammation enhances hepcidin biosynthesis which subsequently reduces iron bioavailability via inhibition of GI iron absorption and blockage of iron release from the body stores. It ultimately leads to low iron blood levels and limits erythropoiesis, even when iron reservoirs are filled up [62]. Intravenous iron supplementation is an easily available source of this element, inducing 5-fold higher erythropoietic response in blood loss anemia than post-operative oral supply. In the onco-surgery context a good safety profile should be also addressed; not only did clinical trials show lack of negative impact of intravenous iron supplementation on prognosis but it is clear iron supplementation reduces transfusion requirement which is a proven factor of poorer cancer treatment outcomes (immunosuppression, infection, transfusion-related reaction). From clinical practice perspective it should be underlined that decision-making process regarding blood transfusion need (intra- or postoperative) should not exclude indications and intravenous iron supplementation demand. Not infrequently, blood transfusion is an essential treatment option, but being a provisional mode of therapy associated with many potential consequences it fails to rebuild iron stores, as well as has no long-term impact on erythropoiesis.

In terms of broadly understood prehabilitation process or preparing patients for surgery, pre-operative intravenous iron supplementation seems to be an optimal management modality.

In vast majority of cancer cases it takes several weeks from the tumor diagnosis to surgery. This interval perfectly fits into prehabilitation timeframe in these patients which is approximately 4-6 weeks (acceptable period 2-6 weeks), and in certain circumstances even 7-10 day period can be utilized for intervention, including intravenous iron supplementation. Prehabilitation period is used to optimize patient preparation for treatment, exerts beneficial effect on biochemical parameters, as well as patient comfort, anxiety reduction, and important feeling of being under good quality care. Important advantages of intravenous iron formulation are following:

- it leads to more rapid anemia improvement resulting in better patient comfort and clinical status,
- it induces erythropoiesis and higher hemoglobin levels more efficiently and improves patient performance what further helps or sometimes even makes possible recommended physical exercise or improves exercise tolerance,
- it facilitates pre-operative oncology management (e.g., rectal cancer chemotherapy), reduces discontinuation rates, and expedites surgery in case of disease deterioration,
- pre-operative iron supplementation as one of patient preparation plan components perfectly complements dietary recommendations, including protein supplementation, and enhances erythropoiesis efficiency,
- better tissue perfusion gained post-operatively (as a consequence of improved anemia and higher Hb levels) is beneficial for inflammation in operated tissue which is of great importance in first few days post-surgery (wound healing, especially GI anastomoses).

To optimize intravenous iron supplementation dosage, including pre-operative phase, requirement evaluation is needed (see: Treatment, Dosing).

Optimal timeframe for intravenous iron supplementation is 2-6 weeks pre-surgery but in case of urgent procedure 1 week is acceptable and helps to activate erythropoiesis before procedure.

Supplementation shortly before surgery or intraoperatively, as discussed earlier, is a feasible mode of intravenous iron supply, especially when missed in pre-operative period.

Post-operative intravenous iron supplementation, starting from post-procedure day 1, is beneficial in patients who:

- presented with anemia pre-operatively and iron supplementation, including intravenous, was not commenced,
- had a substantial blood loss intraoperatively and had no peri-operative intravenous iron supplementation,
- are scheduled for further stages of surgical treatment,
- manifest anemia in post-operative blood tests (very often of deficiency background; it should be born in mind inflammation results in raised hepcidin levels, followed by inhibition of GI iron absorption and poorer release of iron stores, leading eventually to lower iron bioavailability).

Post-operative intravenous iron supplementation in cancer patients is particularly important because further oncology treatment started generally in most of cases could impair erythropoiesis and GI iron absorption, and patient`s clinical status should be good enough to safely continue anti-tumor treatment.

Recommendations:

14. Intravenous iron administration in cancer patients scheduled for surgery who require supplementation is frequently advisable and should be always considered.
15. Intravenous iron supplementation is possible at every stage of surgical treatment (pre-, intra-, and post-operative) but optimal timeframe is 2-6 weeks pre-surgery.
16. With regard to high risk of perioperative blood loss and its negative consequences (including transfusion requirement), it is advisable to supplement iron intravenously in patients awaiting surgery, also anti-tumor treatment naive, in accordance with the criteria included in the earlier part of this position paper.

GI Cancer

Iron deficiency anemia is a common hematology complication in GI cancer as a result of both increased iron loss and reduced absorption [63]. European survey on anemia prevalence and treatment in patients suffering from various types of cancer (n=15,367) showed anemia occurrence in almost 40% of GI and colorectal cancer cases [3].

In GI cancer patients iron deficiency anemia is associated with increased mortality risk, poor response to oncology treatment, worse overall and progression-free survival, fatigue and lower quality of life. Targeted anemia therapy can improve both prognosis and quality of life in these patients [63].

Studies involving patients who suffer from various GI malignancies (mainly colorectal but also esophageal and gastric adenocarcinoma) confirmed beneficial effect of intravenous iron aiming at iron deficit and anemia improvement, including:

- higher hemoglobin levels [64-69].
- improved iron status parameters (higher ferritin level and TSAT) [9, 64, 66, 69, 70].
- reduced blood transfusion need [67-69].
- better quality of life [9, 65].
- shorter hospitalization [68, 69].

With good safety profile of iron supplementation, i.e. lack of adverse events or only mild hypersensitivity reactions. These trials evaluated 1000 to 2000 mg ferric derisomaltose or ferric carboxymaltose supplementation.

Studies also revealed that anemia can be a prognosis-worsening factor in gastric cancer patients so Hb levels can be a suitable and cost-effective prognostic marker in this patient cohort [71, 72]. These data support the British Society of Gastroenterology guidelines on iron deficiency anemia (IDA) management in adult patients and underline age, sex, Hb level, and mean corpuscular volume as independent GI cancer risk predictive factors in IDA that needs to be considered as one of complete risk assessment components. It appears that cancer risk in iron deficiency without anemia is low (quality of evidence: high, consensus: 92%, strength of recommendations: strong) [73].

Recommendations:

In GI cancer patients general recommendations should be used in accordance to management algorithm (Figure 2).

Hematologic Malignancy

Borodini et al. demonstrated that iron supplementation added to bortezomib boosts lipid damage and polyubiquitinated protein accumulation resulting in enhanced cell death induction compared to bortezomib without iron [74].

A multicenter prospective randomized trial revealed ferric carboxymaltose 1000 mg given to patients with lymphoid malignancy associated with anemia (Hb 8.5-10.5 g/dL) and functional iron deficiency (transferrin saturation <20%, ferritin >30 ng/mL [females] or >40 ng/mL [males]) lead to Hb >1 g/dL and TSAT >20% increase in all patients who received iron. In post-infusion week 8 mean Hb increase was significantly higher in iron-supplemented cohort (Hb = 2.1 g/dL vs. 1.1 g/dL) [37].

Data obtained from several published clinical trials on iron supplementation combined with ESA therapy suggest that addition of intravenous iron to ESA therapy successfully improves hematology response parameters (raised Hb level), quality of life, as well as minimizes blood transfusion rates. It is worth mentioning that in these clinical trials patients suffering from hematology malignancies were also recruited (apart from solid tumors) [29, 30, 31 42, 75].

Recommendations:

17. It is recommended to supplement iron intravenously in lymphoid malignancy patients with anemia (Hb 8.5-10.5 g/dL) and functional iron deficiency.
18. In myelodysplastic syndrome (MDS) patients iron should be administered with particular caution and exclusively when iron deficit is confirmed.
19. In MDS patients on ESA therapy intravenous iron supplementation should be considered in patients with transferrin saturation less than 20% (grade D) [76].

20. With regard to high iron overload risk in MDS patients with history of blood transfusions, it is prudent to closely monitor iron status (serum ferritin and transferrin saturation) before each iron infusion [76].

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