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Anemia in cancer patients — Expert Group recommendations. Revision 2020

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ABSTRACT

Anemia is a common feature in about 40% of patients at the moment of cancer diagnosis and in more than half of patients on anticancer therapy. Therapeutic alternatives in cancer patients with anemia include substitution of lacking agents, red blood cell transfusions, and erythropoiesis-stimulating agents (ESAs). The advantages of red blood cell transfusions are rapid increase of hemoglobin concentration and effectiveness independent of the cause of anemia. However, several adverse reactions may occur after blood component transfusion. ESAs act through stimulation of erythropoietin receptors. Use of ESAs reduces the need for red blood cell transfusions, decreases the risk of post-transfusion adverse reactions, and improves the quality of life of cancer patients with chemotherapy-induced anemia. In accordance with registered indications, ESA may be administered in non-myeloid cancer patients with chemotherapy-induced anemia. Thromboembolic events and arterial hypertension are known risks of ESA treatment. If ESAs are used in accordance with currently approved indications and are not administered when hemoglobin (Hb) concentration is 12 g/dL or above, there is no observed unfavorable effect on survival or thromboembolic risk. The administration of RBC transfusions without delay is justified in patients with Hb under 7–8 g/dL and/or severe anemia-related symptoms (even at higher Hb levels) and the need for immediate Hb and symptom improvement. The goal of ESA treatment is maintenance of the lowest hemoglobin concentration needed to avoid red blood cell transfusion. ESAs may be used in patients with symptomatic chemotherapy-induced anemia and Hb concentration at 10 g/dL or below. There is no indication for ESAs in patients who are not receiving chemotherapy or who are receiving radiotherapy.

Key words: anemia, chemotherapy induced anemia, cancer, blood transfusion, erythropoiesis stimulating agents

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Anemia — morbidity, etiology, classification

Anemia (Lat. *anaemia* — comes from the Greek name *anaimia*, meaning lack of blood) is a reduction of blood's ability to deliver oxygen to tissues and its oxygen-carrying capacity. Anemia very often accompanies cancers, disturbs the anticancer treatment and adversely impact on the patients' quality of life (QoL).

Anemia occurs in approximately 40% of patients at cancer diagnosis and in more than half of patients undergoing anticancer treatment. The influence of anemia on malaise and quality of life has been described since the 1970s, so it is very important to treat all symptomatic patients [1].

Table 1. Reference values of the red cell system

	Women	Men
Hemoglobin level	12.5–15.5 g/dL	13,5–17,5 g/dL
RBC count	4.2–5.4 T/L	4,6–6,2 T/L
Hematocrit	37–47%	40–54%
MCV	80–94 fL	
MCHC	32–38 g/dL	
MCH	27–32 pg	
Reticulocyte percentage	5–15‰ (28–100 G/L)	
RDW*	11.5–14.5%	

*Red blood cell volume variation (anisocytosis); MCV — mean corpuscular volume; MCHC — mean corpuscular hemoglobin concentration; MCH — mean corpuscular hemoglobin; RBC — red blood count; RDW — red cell distribution width

In the prospective European Cancer Anaemia Survey (ECAS) [2], more than half of the 15,367 patients from 24 European countries developed anemia during anticancer treatment. A similar observational POLCAS study [3] involving 999 patients from 13 Polish oncology centers provided almost identical results — anemia was found in more than half of the patients after treatment completion (most often cancer of the female reproductive system, lung cancer and testicular cancer). A decrease in hemoglobin (Hb) levels correlated with a decline in performance status (PS), but only one-third of anemic patients received treatment, the most frequently red cell concentrates (RCC) transfusion.

Abnormal hematopoiesis or too fast red blood cells breakdown, as well as, acute or chronic blood loss lead to decreased Hb level and the number of erythrocytes (red blood cells, RBCs) in the peripheral blood below the normal values (Table 1) [4, 5].

Depending on Hb level, anemia is classified as: mild (Hb > 10 g/dL, but below the normal value), moderate (Hb 8–10 g/dL), severe (Hb 6.5–7.9 g/dL) and life-threatening (Hb < 6.5 g/dL).

The most important causes of anemia are:

— deficiencies of:
  - iron following bleeding in and out of the tumor or following surgery,
  - folic acid due to malnutrition,
  - vitamin B12 associated with malabsorption disorders (e.g. after gastrectomy, in gastrointestinal neoplasms);
— immune (lymphomas, chronic lymphocytic leukemia, adenocarcinomas) and non-immune hemolysis (e.g. microangiopathic hemolytic anemia [MAHA] in mucus-producing tumors or prostate cancer — usual reticulocytes below 2‰);
— bone marrow suppression after systemic use of cytotoxic drugs (especially nephrotoxic) or after irradiation > 20% of the bone marrow volume);
— erythropoiesis inhibition due to tumor infiltration of bone marrow;
— erythrophagocytosis in histiocytic lymphomas;
— erythropoiesis inhibition due to suppression of endogenous erythropoietin production (e.g. by cytokines) or inappropriate iron utilization [the most common cause, i.e. functional iron deficiency, which gives a picture of anemia of chronic disease (ACD)].

A healthy person has enough iron stores for up to 2-fold increase of erythropoiesis. Blood loss or impaired absorption leads to true iron deficiency with ferritin levels 30 ng/mL and transferrin saturation below 15%. Abnormal values of the above parameters are standard indications for iron preparations use. It should be remembered that in cancer patients, functional iron deficiency is often observed, with ferritin level 800 ng/mL or less and transferrin saturation below 20% [5].

Based on the mean corpuscular volume, anemia could be classified as:

— microcytic (MCV < 80 fL) — with increased red cell distribution width (RDW), most often due to iron deficiency in chronic bleeding or sideroblastic anemia, with normal RDW in the course of ACD and spherocytosis;
— normocytic (MCV 80–100 fL) in the course of ACD (most often), after chemotherapy or irradiation (iatrogenic), as a result of bone marrow infiltration, acute bleeding, in the initial stage of iron deficiency anemia, in mixed vitamin deficiencies, in kidney diseases, hypothyroidism;
— macrocytic (MCV > 100 fL) in hemolysis (often in lymphoproliferative diseases — late autoimmune hemolysis, after fludarabine, after incompatible blood transfusion), due to vitamin B12 and/or folic acid deficiency, in myelodysplastic syndromes, multiple myeloma, liver diseases, hypothyroidism, sideroblastic anemia and during the regeneration of the hematopoietic system after chemotherapy.

In addition to a low MCV, abnormal laboratory parameters in iron deficiency include:

— RDW — increased;
— number of hypochromic erythrocytes — increased;
— reticulocytes Hb content — decreased;
— iron concentration — reduced;
— ferritin concentration — low;
— transferrin saturation — low (Fe/TIBC < 20%);
— concentration of soluble transferrin receptors (sTfR) — increased;
— total iron binding capacity (TIBC) — increased.

Consequences of anemia in cancer patients

Anemia in cancer patients:

— worsens the quality of life;
— precludes the maintenance of the chemotherapy regimen, which directly affects the effectiveness of the therapy;

— reduces radiation-curability;
— has a negative prognostic impact;
— correlates with higher mortality (in particular in patients with lymphomas, head and neck cancers, lung cancer, cervical cancer, prostate cancer).

Diagnostics

Depending on patient's general condition, before deciding on the treatment method, the tests should be performed to determine the etiology of anemia and to enable causative treatment and/or therapy with the lowest risk of adverse reactions.

The following diagnostic tests are recommended:
— complete blood count;
— a reticulocyte count;
— iron concentration;
— TIBC;
— transferrin saturation;
— ferritin concentration;
— folic acid concentration;
— vitamin B12 concentration
— fecal occult blood test (FOBT);
— parameters assessing renal function.

Additional tests could be performed if clinically justified:
— erythropoietin concentration;
— TSH level;
— direct antiglobulin test (CLL, lymphomas, prior autoimmune disease);
— testing for hemoglobinopathy.

When the cause of anemia in cancer patient is not determined, it is classified as cancer induced anemia (CIA).

Treatment

In the management of anemia in cancer patients, causal treatment should be used when available and the diagnosed deficiencies should be corrected first (iron, vitamin B12, folic acid). If deficiencies correction does not bring the expected results and the anemia does not improve despite the anticancer treatment, ESA administration may be considered. RBC transfusions are reserved for the following situations: deficiencies correction has not brought the expected results, there are no indications for ESA, and the level of anemia does not allow the initiation or continuation of anticancer treatment or causes significant symptoms.

Iron supplementation

Criteria for starting iron supplementation are as follow:
— anemia ($8 < Hb < 10$ g/dL) or
— absolute iron deficiency (ferritin < 100 ng/mL and transferrin saturation < 20%);
— relative iron deficiency (ferritin > 100 ng/mL and transferrin saturation < 20%) — iron should be administered before starting ESA.

While using ESA, iron levels should be monitored and supplemented as needed.

Contraindications to iron supplementation — active infection, treatment with drugs with cardiotoxicity related to the generation of free oxygen radicals (anthracyclines, alkylating drugs and *Vinca* alkaloids).

Administration route

Due to frequently reduced iron absorption from the gastrointestinal tract in cancer patients, iron preparations should be administered intravenously.

Dosage
— 1000 μg once or in divided doses, depending on the type of drug.

Red blood cells concentrates transfusion

Preparations containing red blood cells are:
— red cell concentrate (RCC) (packed red cells);
— leukocyte-depleted RCC;
— irradiated RCC;
— irradiated leukocyte-depleted RCC;
— washed RCC.

The advantages of RBC transfusions are that:
— they rapidly increase hemoglobin levels in patients with anemia;
— they are effective regardless of anemia etiology.

Cancer patients receiving a transfusion of blood components are found to have:
— shorter overall survival time [6–10];
— the earlier occurrence of tumor relapse [10–12];
— higher mortality due to recurrence of the neoplastic disease [11, 13];
— a higher number of postoperative complications (including infections) [14–17];
— prolonged hospital stay [18];
— higher risk of developing lymphomas [19];
— higher risk of thromboembolic complications.

The reasons for the adverse effects of blood components transfusions may be:
— changes that occur during the RBC storage;
— immunogenicity of blood cells;
— thrombogenicity of blood component;
— presence of pathogens and/or leukocytes in blood components;
— immunomodulation;
— human error;
— using less safe blood concentrates due to lower costs.

Table 2. Post-transfusion immune-mediated adverse reactions

Post-transfusion immune-mediated adverse reactions	
Early	**Delayed**
Acute hemolytic transfusion reaction (AHTR)	Delayed hemolytic transfusion reaction
Transfusion-related acute lung injury (TRALI)	Transfusion-associated graft versus host disease (TA-GvHD)
Febrile non-hemolytic transfusion reactions (FNHTR)	Post-transfusion purpura (PTP)
Anaphylactic reaction	Alloimmunization to blood cell antigens
Urticaria	Immunosuppression

Due to the increasingly common use of immunotherapy with immune checkpoint inhibitors in cancer patients, the impact of blood component transfusions on the immune system should be taken into account. Cytokine release (including IL-6, IL-8, IL-10) induced by transfusion of blood components has proven pro-inflammatory and immunosuppressive effects, and, its clinically significant interaction with a mechanism of action of immunomodulating drugs cannot be excluded [20].

Therefore, RBC transfusions should not be used as a universal method of treating anemia in cancer patients and should be limited only to situations in which they are the only effective way to raise hemoglobin levels or are indications for immediate elimination or relief of anemia symptoms.

In addition, 2020 has already brought an additional problem in many countries (including Poland) related to a significant reduction in the availability of blood and its components due to the rapidly spreading SARS-CoV-2 pandemic and the need for their rational use.

Due to the possibility of a number of post-transfusion adverse reactions, including fatal ones (Tables 2 and 3), and taking into account that the majority of them are caused by the presence of leukocytes in blood components, it is advisable to use prophylaxis by leukocyte depletion in blood components and/or X-ray irradiation.

Absolute indications to leukocyte-depleted RCC include [19]:
— transfusions in patients with previous non-hemolytic febrile reactions;
— transfusions in patients with previous TRALI;
— transfusions in patients with or suspected to have anti-HLA antibodies;
— prophylaxis of immunization with erythrocyte antigens — multiple recipients (in the course of hematopoietic malignancies or chronic renal failure);
— prophylaxis of immunization with HLA antigens;
  • non-hemolytic febrile reactions,
  • platelet transfusion refractoriness;
— prophylaxis of cytomegalovirus (CMV) infection.

Table 3. Post-transfusion non-immune-mediated adverse reactions

Post-transfusion non-immune-mediated adverse reactions	
Early	**Delayed**
Non-immune hemolysis	Hemosiderosis
Transfusion associated circulatory overload (TACO)	Transmission of viral, bacterial, protozoal infections
Sepsis	Transmission of prions
Air embolism	
Citrate intoxication	

Leukocyte depletion in blood components does not prevent transfusion-associated graft *versus* host disease (TA-GvHD) which is caused by donor lymphocytes. In order to reduce the risk of TA-GvHD, irradiation of RBC concentrates is necessary.

Absolute indication to irradiated RCC include [19]:
— relatedness (1st and 2nd degrees) between donor and recipient;
— HLA compatible blood components;
— immunodeficiency (especially with severe T-cell deficiency syndrome);
— transfusion of granulocyte concentrates;
— hematopoietic cell transplant recipients — from the initiation of conditioning chemotherapy and/or radiotherapy to completion of GvHD prophylaxis related to the transplant, usually for about 3 months (autologous transplant) or 6 months (allogeneic transplant) after the transplant or until the blood lymphocyte count is above 10^9/L;
— chronic GvHD;
— autologous hematopoietic cells collection and within 7 days prior to collection;
— immunosuppressive treatment;
— Hodgkin's disease;
— treatment with purine analogues (e.g. fludarabine, cladribine, deoxycoformicin) or purine antagonists (bendamustine, clofarabine);
— treatment with alemtuzumab (anti-CD52).

Erythropoiesis stimulating agents (ESA)

Erythropoiesis stimulating agents (ESAs) include:
— epoetin (alpha, beta, theta);
— darbepoetin alfa.

ESAs work by stimulating the receptors for erythropoietin.

Aim of ESA treatment

The use of ESA reduces the number of necessary transfusions, reduces the risk of post-transfusion adverse reactions, and improves the quality of life of patients with chemotherapy-induced anemia.

The target hemoglobin level, which obviates the need for RBC transfusion is approximately 12 g/dL. When using ESA a Hb level of 12 g/dL should not be exceeded.

According to the registered indications, ESAs can be used in patients with non-myeloid neoplasms with chemotherapy-induced anemia (CIA). In line with the ESMO recommendations, ESA can also be used in patients with myelodysplastic syndrome [21].

The use of ESA in patients with hypersensitivity to the drug and uncontrolled hypertension is not recommended.

All meta-analyses confirmed the effectiveness of ESA in reducing the frequency of blood transfusions, which is the main goal of ESA use in patients with CIA.

It is worth noting that ESA, unlike RBC concentrate, has a positive effect on the immune system. Among other things, ESA reduces the expression of pro-inflammatory cytokine genes (IL-1β, IL-6, IL-10, TNF-α), lowers the concentration of IL-1α and IL-6 and causes a decrease in the number of suppressive cells (CD8+CD152+) [22–25].

Risk related to the use of ESAs

Using ESA increases the risk of:

1. Thromboembolic complications

It should be highlighted that many factors may contribute to the increased risk of thromboembolic complications in cancer patients. The most important of them are: high hematocrit, advanced patient's age, prolonged immobilization, major surgery, multiple injuries, a history of thromboembolism, chronic heart failure and cancer type [26]. Remarkably higher risk of thromboembolic events occurs in pancreatic and gastric cancer, and in multiple myeloma during immunomodulatory treatment [27, 28]. However, there is no convincing clinical evidence that the use of ESA further increases the risk of thromboembolic events in patients treated with lenalidomide or thalidomide. [29, 30].

Due to the lack of prospective randomized clinical trials (RCTs) proving that anticoagulation treatment reduces the risk of thromboembolic events in patients receiving ESA, and the conclusions from meta-analyzes showing a relatively low risk of thromboembolic complications in patients treated with ESA according to the currently recognized indications, routine thromboprophylaxis during treatment with ESA alone is not recommended [31].

Table 4. Model of risk assessment of thromboembolic complications in outpatients

Risk factors	Points
Gastric cancer, pancreatic cancer	2
Lung cancer, bladder cancer, testicular cancer, kidney cancer, lymphoma	1
Platelet count before chemotherapy ≥ 350,000/μL	1
Hemoglobin level < 10 g/dL **or ESA use**	1
Leukocyte count before chemotherapy > 11,000/μL	1
BMI ≥ 35 kg/m^2	1

High risk — total points ≥ 3
Intermediate risk — total points = 1–2
Low risk — total points = 0

Table 5. Model of risk assessment of thromboembolic complications in in patients treated stationary (authors modification)

Risk factors	Points
Active malignant tumor	3
History of thrombosis (excluding superficial thrombosis)	3
Mobility restrictions	3
Thrombophilia	3
Recent (up to a month) trauma or surgery	2
Age ≥ 70 years	1
Heart and/or lung failure	1
Myocardial infarct and/or ischemic stroke	1
Acute infection and/or rheumatological disease	1
BMI ≥ 30 kg/m^2	1
Current hormone treatment	1
ESA use	1

High risk — total points ≥ 4

However, other risk factors for thromboembolic complications in cancer patients should be considered and the administration of ESA should be included when assessing individualized risk for each patient. The algorithms for calculating the risk indices for outpatients (example in Table 4 [32]) or hospitalized patients (example — Table 5 [33]) may be helpful.

2. Hypertension — patients with chronic renal failure are particularly at risk

When ESAs are used in accordance with the registration and based on recommendations for the treatment of chemotherapy-induced anemia and are not used

when the Hb level is 12 g/dL or higher, then no adverse effect on overall survival is observed, and there is no evidence from clinical trials (neither single studies nor meta-analyzes) of a stimulating effect of ESAs on cancer progression or relapse [34–53].

Recommendations

1. Indications for the initiation of anemia treatment

In most cases of normovolemic anemia with Hb concentration above 7 g/dL, proper oxygenation of tissues is ensured without the need to activate adaptive mechanisms, provided that normal life activities are performed and do not require greater physical effort. Red blood cell transfusion in most people with Hb levels higher than 7 g/dL does not increase the amount of oxygen delivered to the organs. In patients with symptoms of severe anemia (symptoms of ischemic heart disease, tachycardia, dyspnea, orthostatic hypotension, fatigue), red blood cell transfusion is indicated when the Hb concentration is lower than 8 g/dL. Majority of patients — even in a severe general state — tolerate Hb levels in the range of 7–10 g/dL well [54]. In general, the perioperative mortality rate in patients with preoperative Hb levels between 6 and 10 g/dL is not increased compared to patients with Hb levels above 10 g/dL. Moreover, there are reports that a liberal red blood cell transfusion strategy (Hb concentration < 10 g/dL) is associated with higher mortality compared to a restrictive strategy, in which the use of RBC is ordered only after the Hb concentration drops below 7–8 g/dL [55].

It should be emphasized that in the early stages of neoplastic disease, a statistically significant positive correlation was observed between RBC transfusion and shorter overall survival and higher mortality. According to the authors of these recommendations, there is a risk associated with RBC transfusions in the treatment of anemia in early-stage cancers. This is most likely due to the immunomodulatory effect of the transfused blood component, which suppresses the recipient's immune system and weakens its cancer-controlling function.

If the Hb level is above 6 g/dL and there are no symptoms of severe anemia requiring urgent RBC transfusion, it is recommended to diagnose the cause(s) of anemia and apply the procedures appropriate to the diagnosis (e.g., correct iron deficiency, stop bleeding, stop hemolysis). If the above procedure does not bring the expected results (increase in Hb level above 8 g/dL), the use of ESA can be considered (Figure 1). In patients receiving chemotherapy or combined chemoradiotherapy, ESA should be started at Hb levels < 10 g/dL if there are symptoms related to anemia. The use of ESA may be considered in selected asymptomatic patients receiving chemotherapy with Hb levels < 8 g/dL.

In patients with normal Hb levels before chemotherapy prophylactic use of ESA is not recommended.

There is no clear evidence that leukocyte-depleted RBC concentrate transfusions have a more favorable impact on the course of the neoplastic disease than blood cells without a reduced number of leukocytes. However, due to the higher risk of post-transfusion adverse reactions related to the presence of leukocytes in concentrates (febrile non-hemolytic transfusion reactions, TRALI, immunization, CMV transmission), it is advisable to use leukocyte-depleted RBC concentrate in cancer patients who are expected to receive multiple transfusions of blood components.

2. Aim of anemia treatment

The aims of anemia treatment include:

— improvement or resolution of anemia symptoms;

— enabling anticancer treatment;

— improvement of quality of life, taking into account a patient's life expectancy.

This goal should be achieved with the least invasive and safest treatment methods. Table 6 presents a comparison of the advantages and risks related to specific treatment methods.

3. Drug dosing

Iron dosage

Due to very common elevated levels of hepcidin blocking the ferroportin responsible for the iron transport from enterocytes into the blood in cancer patients, orally administered iron will not be effective. In these patients, iron should only be administered intravenously. Currently used iron preparations are safe and, in accordance with the recommendations of the European Medicines Agency, do not require a trial dose administration [56]. When choosing an iron preparation, the deficiency stage and the duration of infusion should be taken into account (Table 7). The recommended dose is 1000 mg as a single or divided dose.

ESA dosage

The starting dose for ESA is:

— epoetin — 150 U/kg three times per week or 30,000 U/week;

— darbepoetin — 2.25 μg/kg/week or 500 μg/3 weeks.

A preliminary evaluation of iron balance is necessary and the use of ESA should only be started after any deficiencies have been corrected. It is advisable to monitor hemoglobin levels and iron stores during treatment [57]. In the case of iron deficiency, appropriate supplementation is necessary, but only by the intravenous route.

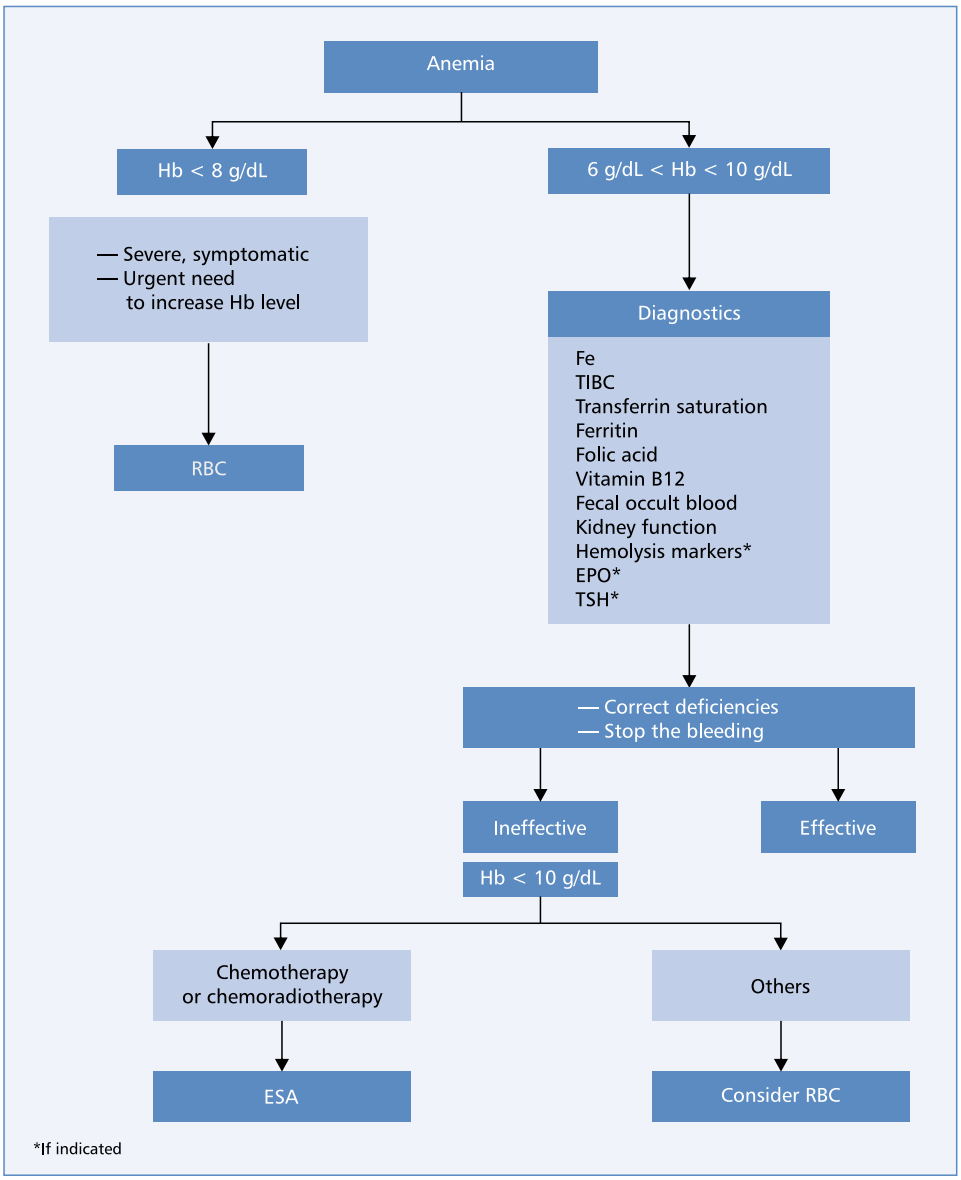

Figure 1. Algorithm for management of anemia in cancer patients. Hb — hemoglobin; ESA — erythropoiesis stimulating agent; RBC — a concentrate of red blood cells

Table 6. Advantages and risks related to specific methods of anemia treatment

	Advantages	Risks and limitations
RBC transfusions	Quickly reduces the symptoms of anemia, regardless of its cause, and increases the Hb level	Can cause many adverse reactions, including fatal ones
		Require pre-transfusion tests
		The necessity of hospitalization
		Hb concentration cannot be kept on stable level
		Adverse effect on the immune system (immunosuppression, possible interaction with immunotherapy)
ESA	Possibility of outpatient treatment	Increased risk of thromboembolic complications
	Stable Hb levels during treatment	The time required to achieve a treatment effect
	Beneficial effect on the immune system	Indications limited to the group of patients receiving chemotherapy or chemoradiotherapy
	Improving patients' quality of life	May be ineffective in some patients

Table 7. Dosages and minimum infusion time for iron preparations.

Iron preparation	Maximum dose	Minimum infusion time
Gluconate	125 mg	60 min
Saccharide	200–500 mg	30–210 min
Dextran	Different	240–360 min
Derisomaltoside	20 mg/kg	15 min (for a dose ≤ 1000 mg)
Carboxymatoside	20 mg/kg to 1000 mg	15 min

ESA doses should be reduced by approximately 25–50% if the hemoglobin concentration rises to levels preventing red blood cell transfusions or increases by more than 2 g/dL within 4 weeks.

It is recommended to thoroughly inform patients about the planned use of ESA together with comprehensive information on the purpose and potential adverse reactions associated with the treatment (especially thromboembolic complications). It is also recommended to inform the primary care physician about the use of ESA.

Except patients receiving epoetin theta (deliberately administered at a low initial dose), increases in ESA doses and changes to other ESA preparation in unresponsive patients within 4–8 weeks are not recommended. ESA treatment should be discontinued in patients who have not demonstrated at least initial Hb response after this period.

ESA discontinuation is also recommended after a maximum of 4 weeks after chemotherapy completion and in the case of the appearance of neutralizing anti-ESA antibodies.

Conflicts of interest

The authors declare to have no conflict of interest.

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