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Anaemia in cancer patients — Expert Group recommendations

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Oncology in Clinical Practice

2017, Vol. 13, No. 5, 202–210

DOI: 10.5603/OCP.2017.0023

Translation: dr n. med. Dariusz Stencel

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ISSN 2450–1654

ABSTRACT

Anaemia 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 anaemia 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 haemoglobin concentration and effectiveness independent of cause of anaemia. However, several adverse reactions may occur after blood component transfusion. ESAs act through stimulation of erythropoietin receptors. Use of ESA reduces the need for red blood cell transfusions, decreases the risk of post-transfusion adverse reactions, and improves quality of life of cancer patients with chemotherapy-induced anaemia. In accordance with registered indications, ESA may be administered in non-myeloid cancer patients with chemotherapy-induced anaemia. Thromboembolic events and arterial hypertension are known risks of ESA treatment. If ESA are used in accordance with currently approved indications and are not administered when Hb concentration is 12 g/dL or above, there is no observed unfavourable effect on survival or thromboembolic risk. The goal of red blood cell transfusions in asymptomatic anaemia is maintenance of a haemoglobin concentration of 7–9 g/dL. The goal of red blood cell transfusions in symptomatic anaemia is a haemoglobin increase to the concentration needed for recovery of symptoms, but not higher than 8–10 g/dL. The goal of ESA treatment is maintenance of the lowest haemoglobin concentration needed to avoid red blood cell transfusion. ESA may be used in patients with symptomatic chemotherapy-induced anaemia and Hb concentration at 10 g/dL or below. There is no indication for ESA in patients who have Hb concentration 12 g/dL or above, or who are not receiving chemotherapy or who are receiving radiotherapy.

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

Oncol Clin Pract 2017; 13, 5: 202–210

Anaemia — incidence, aetiology, classification

Anaemia (Lat. *anaemia* — derived from the Greek word *anaimia*, which means lack of blood) consists of a lowered ability to carry oxygen in the blood and is

very often associated with cancer. Anaemia affects the course of treatment, having a negative impact on the patient's quality of life.

Anaemia occurs in app. 40% of patients at cancer diagnosis and in more than half of patients undergoing anticancer therapy. Since the 1970s, the effects of anaemia

mia on fatigue and quality of life have been described; therefore, it is very important to treat all symptomatic patients [1].

In a prospective European Cancer Anaerobic (ECAS) study [2], more than half of 15,367 patients from 24 European countries developed anaemia during treatment of cancer. A similar observational study, POLCAS [3], with 999 patients from 13 Polish oncological centres, provided nearly identical results — anaemia was reported in more than half of the patients after treatment (most often — female genital cancers, lung cancer, and testicular cancer). Low haemoglobin (Hb) levels correlated with worsening of performance status (PS), but only one-third of patients with anaemia received treatment (most frequently transfusion of red blood cell concentrate).

Defective haematopoiesis or overly rapid disintegration of red blood cells (RBC), as well as acute or chronic loss of blood, result in lowering of Hb concentration and RBC counts below the values considered normal (Tab. 1) [4, 5].

Depending on Hb concentration, the following types of anaemia are distinguished: mild (Hb > 10 g/dL, but below normal), moderate (Hb 8–10 g/dL), severe (Hb 6.5–7.9 g/dL), and life-threatening (Hb less than 6.5 g/dL).

The most important causes of anaemia include:

- deficiency of:
 - iron following bleeding from tumour into its interior, or after surgery,
 - folic acid due to malnutrition,
 - vitamin B₁₂ associated with malabsorption syndromes (e.g. after gastrectomy or in gastrointestinal tumours);
- immunological haemolysis (lymphomas, chronic lymphocytic leukaemia, glandular carcinoma) and non-immunological (e.g. microangiopathic in tumours that produce mucus or prostate cancer — usually reticulocytes below 2‰);
- myelosuppression after systemic use of cytotoxic drugs (especially nephrotoxic drugs) or after irradiation of more than 20% of the bone marrow);
- inhibition of erythropoiesis caused by cancerous bone marrow infiltration;
- erythrophagocytosis in histiocytic lymphomas;
- suppression of erythropoiesis due to suppression of production of endogenous erythropoietin (e.g. by cytokines) or abnormal iron utilisation (the most common cause), i.e. so-called functional iron deficiency, which leads to a clinical picture of anaemia of chronic disease (ACD).

A healthy individual has enough iron reserves for up to twice the increase in erythropoiesis. Blood loss or impaired iron absorption leads to real iron deficiency with ferritin concentration below 30 ng/mL and trans-

Table 1. Reference values of red blood system

	F	M
Haemoglobin concentration	12.5– –15.5 g/dL	13.5– –17.5 g/dL
Erythrocytes count	4.2–5.4 T/L	4.6–6.2 T/L
Haematocrit	37–47%	40–54%
MCV	80–94 fL	
MCHC	32–38 g/dL	
MCH	27–32 pg	
Percentage of reticulocytes	5–15‰ (28–100 G/L)	
RDW*	11.5–14.5%	

*Index of red cell volume differentiation (anisocytosis); MCV — mean corpuscular volume; MCHC — mean corpuscular haemoglobin concentration; RDW — red cell distribution width

ferrin saturation below 15%. Incorrect values of the mentioned parameters are classic indications for iron supplementation. It should be highlighted that cancer patients often experience functional deficiency of iron (ferritin — 800 ng/mL or less, transferrin saturation — less than 20%) [5].

Based on assessment of mean corpuscular volume (MCV), the following anaemia types can be distinguished:

- microcytic (MCV < 80 fL) — with elevated RDW most often due to iron deficiency in chronic bleeding or sideroblastic anaemia, 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), following bone marrow infiltration, acute bleeding, early stage of iron deficiency anaemia, mixed vitamin deficiency, renal disease, hypothyroidism;
- macrocytic (MCV > 100 fL) — in haemolysis (often in lymphoproliferative diseases — late autoimmune haemolysis, after fludarabine, after transfusion with ABO incompatible blood), due to vitamin B₁₂ and/or folic acid deficiency, in myelodysplastic syndromes, multiple myeloma, liver diseases, hypothyroidism, sideroblastic anaemia, and haematopoietic regeneration after chemotherapy.

In addition to low MCV values, abnormal laboratory parameters in case of iron deficiency include:

- RDW — increased;
- number of hypochromic erythrocytes — increased;
- reticulocyte haemoglobin content — decreased;
- iron concentration — decreased;
- ferritin concentration — low;
- ferritin saturation — low (Fe/TIBC < 20%);
- soluble transferrin receptor (sTfR) concentration — increased;
- total iron binding capacity (TIBC) — increased.

The consequences of anaemia in cancer patients

Anaemia in cancer patients:

- worsens the quality of life;
- hinders and/or delays the onset of chemo- or radiotherapy;
- reduces curability after irradiation;
- is a negative prognostic factor;
- correlates with higher mortality (especially in patients with lymphomas, head and neck tumours, lung cancer, cervical cancer, prostate cancer).

Treatment

In the treatment of patients with cancers with anaemia the following can be used:

- substitution of deficiency (iron, vitamin B12, folic acid), which is not covered by these recommendations;
- transfusions of red blood cell concentrates;
- erythropoiesis stimulating agents (ESA).

A transfusion of red blood cell concentrates

Preparations containing red blood cells include:

- red blood cell concentrate;
- leukocyte-depleted red blood cell concentrate;
- irradiated red blood cell concentrate;
- irradiated leukocyte-depleted red blood cell concentrate;
- washed red blood cell concentrate.

The advantages of RBC concentrates include:

- rapidly increased haemoglobin levels in patients with anaemia;
- efficacy regardless of the cause of anaemia.

In cancer patients undergoing transfusions of blood components the correlations were found with:

- shorter overall survival time [6–10];
- earlier onset of tumour recurrence [10–12];
- higher mortality due to relapse of cancer [11, 13];
- higher number of postoperative complications (including infection) [14–17];
- prolonged hospitalisation time [18];
- higher risk of lymphoma [19];
- higher risk of thromboembolic complications.

The causes of negative effects of blood component transfusions could be:

- changes occurring during storage of erythrocytes;
- immunogenicity of blood cells;
- thrombogenicity of blood components;
- presence of pathogens and/or leukocytes in blood components;
- human error;

Table 2. Post-transfusion immune-mediated adverse reactions

Posttransfusion immune-mediated adverse reactions	
Early	Delayed
Acute haemolytic transfusion reaction (AHTR)	Delayed haemolytic transfusion reaction (DHTR)
Transfusion-related acute lung injury (TRALI)	Transfusion-associated graft versus host disease (TA-GvHD)
Febrile non-haemolytic transfusion reaction	Post-transfusion thrombocytopenic purpura
Anaphylactic reaction	Alloimmunisation to RBC antigens
Urticaria	Immunomodulation

RBC — red blood cell

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

Posttransfusion non-immune-mediated adverse reactions	
Early	Delayed
Non-immunological haemolysis	Haemosiderosis
Transfusion-associated circulatory overload (TACO)	Transmission of viral and bacterial infection and protozoal infestation
Sepsis	Transmission of prions
Air embolism	
Citrate intoxication	

- use of less safe components due to lower costs.

A number of adverse reactions may occur after transfusion of blood components (Tab. 2 and 3).

Due to the significant number of adverse reactions associated with the presence of leukocytes in blood components and their possible effects (including fatal complications), relevant prevention is indicated by reduction of leukocytes in blood components and/or irradiation with ionising rays.

Absolute indications for the use of leukocyte-depleted red blood cell concentrate include [19]:

- transfusions in patients with non-haemolytic febrile reactions;
- transfusion in patients in whom TRALIs have occurred;
- transfusions in patients who have been found to have anti-HLA antibodies or are suspected of having these antibodies;
- prophylaxis of immunisation with erythrocyte antigens — multiple recipients (in the course of haematological malignancies or chronic renal failure);

- prophylaxis of immunisation with HLA antigens;
 - febrile non-haemolytic transfusion reaction,
 - platelet refractoriness;
- cytomegalovirus (CMV) infection prevention.

Leukodepletion of blood components does not prevent the onset of TA-GvHD, for donor lymphocytes are responsible. To reduce the risk of TA-GvHD it is necessary to irradiate red blood cell concentrates.

Irradiated red blood cells concentrates are absolutely indicated in case of [19]:
- consanguinity (first and second degree) of donor and recipient;
- compatibility of blood components in the HLA system;
- immune system failure (especially with severe T-cell deficiency);
- transfusion of granulocyte concentrates;
- recipients of haematopoietic stem cell transplants
 - from the beginning of conditioning chemo and/or radiotherapy to the completion of prophylaxis of transplantation-related GvHD, usually for about three months (autologous transplantation) or six months (allogeneic transplantation) following transplantation or to the blood lymphocyte count above $10^9/L$;
- chronic GvHD;
- collection of autologous hematopoietic cells and up to seven days before collection;
- immunosuppressive treatment;
- Hodgkin's lymphoma (HL);
- treatment with purine analogues (e.g. fludarabine, cladribine, deoxycytosine) or purine antagonists (bendamustine, clofarabine);
- treatment with alemtuzumab (anti-CD52).

Erythropoiesis-stimulating agents (ESA)

Erythropoiesis-stimulating agents include:

- epoetin (alfa, beta, theta);
 - darbepoetin alfa.
- ESA work by stimulating receptors for erythropoietin.

Objective of ESA treatment

The use of ESA reduces the number of transfusions required, decreases the risk of post-transfusion adverse reactions, and improves the quality of life of patients with chemotherapy-induced anaemia. The Hb level during ESA treatment should not exceed 12 g/dL.

According to registered indications, ESA could be used in patients with non-myeloid cancer with chemotherapy-induced anaemia (CIA). Use of ESA in patients with hypersensitivity to the drug and uncontrolled hypertension is not recommended.

All meta-analyses confirmed the efficacy of ESAs in decreasing the frequency of blood transfusions, which is the main goal of ESA treatment in patients with CIA.

The risk associated with use of ESA includes the occurrence of:

- thromboembolic complications — ESA increases the risk of thromboembolic complications independently of Hb concentration — especially in patients with concomitant thrombosis risk factors (including thrombophilia, elevated platelets number, hypertension, treatment with steroids, longer immobilisation, status after recent operation, some types of hormonal therapy) [7, 8, 10, 13, 14].
 - hypertension — patients with chronic renal failure are particularly vulnerable;
 - cancer progression and shortening of overall survival. Cancer progression and shorter overall survival time were observed in meta-analyses that included clinical trials with ESA in patients with cancer and Hb concentration above 12 g/dL or during radiotherapy and in patients with active cancer, who did not receive radiotherapy or chemotherapy (Tab. 4).
- If ESA are used according to currently recommended indications and are not used in patients with Hb concentration of 12 g/dL or higher, no unfavourable impact on overall survival and/or disease progression is observed [20, 23, 26, 27, 32, 33].

More than 90 studies evaluating ESA value were performed in cancer patients, but in most trials no overall survival analysis was planned. In addition, many studies have evaluated off-label use of ESA (e.g. higher than recommended initial and/or target Hb levels, use during radiotherapy, and treatment of anaemia in cancer patients who did not receive chemotherapy). Benefit-risk assessment was difficult due to the large variety of available results of studies on ESA, which justified performing several meta-analyses. Meta-analyses summarise the data from many clinical trials and cover large groups of patients. The results of the most important meta-analyses are summarised in Table 4 and 5.

Recommendations

1. Indications to start treatment of anaemia

In most cases of normovolaemic anaemia with Hb concentration above 7 g/dL, proper tissue oxygenation is provided without the need for adaptive mechanisms, unless normal physical activity is performed without the need for more physical effort. Transfusion of red blood cells in most people with Hb concentration higher than 7 g/dL does not increase the amount of oxygen delivered to the organs. Patients with clinical symptoms of anaemia (symptoms of coronary heart disease, tachycardia, dyspnoea, orthostatic hypotension, fatigue) are advised to transfuse red blood cells when Hb concentration is lower than 8 g/dL. Most patients, even in severe condition, tolerate well Hb levels in the range of 7–10 g/dL [41]. There is not a higher mortality rate in the perioperative period in patients with Hb

Table 4. Effect of ESA on time to disease progression (based on [34])

Meta-analysis	Number of studies (number of patients)	Treatment type	Effect on disease progression
Hedenus et al. 2005 [35]	4 (1129)	4 chemotherapy	HR for PFS = 0.92 (95% CI: 0.78–1.07)
Boogaerts et al. 2006 [36]	3 (454)	3 chemotherapy	No tumour progression risk was identified for ESA use
Seidenfeld et al. 2006 [37]	5 (688)	3 chemotherapy 2 radiotherapy alone	Relative risk for complete response = 1.00 (95% CI: 0.92–1.10)
Ludwig et al. 2009 [20]	6 (2122)	6 chemotherapy	HR for disease progression = 0.92 (95% CI: 0.82–1.03) HR for PFS = 0.93 (95% CI: 0.84–1.04)
Aapro et al. 2009 [38]	12 (2297)	9 chemotherapy 2 surgery 1 radiotherapy alone	HR for disease progression = 0.85 (95% CI: 0.72–1.01)
Glaspay et al. 2010 [23]	26 (9646)	21 chemotherapy 1 radiotherapy, 4 radiotherapy alone	OR for disease progression = 1.01 (95% CI: 0.90–1.14)

ESA — erythropoiesis stimulating agents; Hb — haemoglobin; AoC — anaemia of cancer; CIA — chemotherapy-induced anaemia; CI — confidence interval; OR — odds ratio; HR — hazard ratio

Table 5. Effect of ESA on overall survival time in cancer patients (based on [23])

Meta-analysis	Number of studies	Number of patients	Statistics	95% CI
Glaspay et al. 2010 [23]	60	15 323	1.06 OR	0.97–1.15
Studies with chemotherapy	47	12 108	1.03 OR	0.93–1.13
Mean baseline Hb concentration < 10 g/dL	16	3265	0.99 OR	0.80–1.22
Mean baseline Hb concentration 10–12 g/dL	13	3661	0.91 OR	0.77–1.08
Mean baseline Hb concentration > 12 g/dL	13	4522	1.13 OR	0.94–1.36
Studies with AoC	9	1901	1.09 OR	0.87–1.36
Studies with radiotherapy	4	1314	1.18 OR	0.95–1.47
Bohlius et al. 2006 [39]	42	8167	1.08 OR	0.99–1.18
All studies, mean baseline Hb concentration < 10 g/dL	20	3765	1.01 OR	0.89–1.15
All studies, mean baseline Hb concentration 10 – < 12 g/dL	8	1712	0.98 OR	0.82–1.16
All studies, mean baseline Hb concentration > 12 g/dL	7	1696	1.27 OR	1.05–1.54
Studies in patients undergone chemotherapy	30	6282	1.02 OR	0.90–1.15
Studies in patients with AoC	3	276	1.14 OR	0.56–2.31
Studies in patients undergone radiotherapy	8	1187	1.27 OR	1.05–1.5
Seidenfeld et al. 2006 [37]	39	7891	1.08 Peto OR	0.98–1.18
All studies, mean baseline Hb concentration < 10 g/dL	17	3489	1.01 Peto OR	0.89–1.15
All studies, mean baseline Hb concentration 10–12 g/dL	8	1712	0.98 Peto OR	0.82–1.16
All studies, mean baseline Hb concentration > 12 g/dL	7	1696	1.27 Peto OR	1.05–1.54
Ross et al. 2006 [40]	17	2895	1.14 OR	0.90–1.45
Studies in patients with CIA, baseline Hb concentration < 11 g/dL	11	2014	0.99 OR	0.72–1.36
Studies in patients without CIA	6	881	1.39 OR	0.96–2.00
Bennett et al. 2008 [25]	51	13 611	1.10 HR	1.01–1.20
Studies in patients undergone chemotherapy or radiotherapy	45	11 522	1.09 HR	0.99–1.19
Studies in patients with AoC	6	1800	1.29 HR	1.00–1.67

ESA — erythropoiesis stimulating agents; Hb — haemoglobin; AoC — anaemia of cancer; CIA — chemotherapy-induced anaemia; CI — confidence interval; OR — odds ratio; HR — hazard ratio

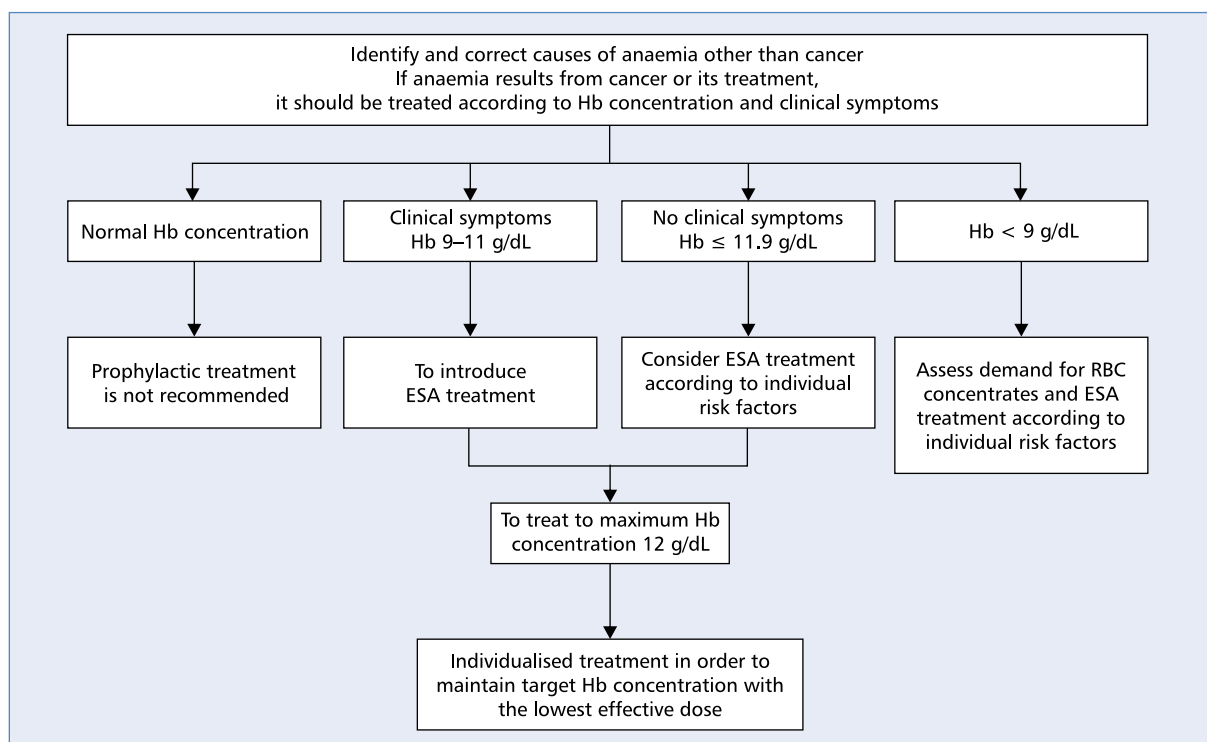


Figure 1. Algorithm for treatment of anaemia in cancer patients [43]

between 6 and 10 g/dL prior to surgery as compared to patients with Hb above 10 g/dL. Furthermore, there are reports indicating that liberal red blood cell transfusion strategy (Hb level below 10 g/dL) is associated with a higher mortality rate as compared to a restriction strategy where RBC concentrate is only given after a decrease of Hb concentration below 7–8 g/dL [42].

Figure 1 presents the recommended algorithm for the treatment of anaemia in cancer patients [43].

Other potential causes of anaemia (e.g. iron deficiency, bleeding, nutritional deficiencies, or haemolysis) should be analysed and removed prior to ESA treatment.

In patients with Hb concentration below 9 g/dL transfusion of RBC concentrate should be considered to rapidly relieve symptoms of anaemia, and ESAs may be considered in further treatment.

Patients receiving chemotherapy should be given with ESA at Hb concentration in range of 9–11 g/dL if symptoms associated with anaemia are present.

The use of ESA could be considered in selected patients without clinical symptoms of anaemia undergoing chemotherapy at Hb concentration in range of 11–11.9 g/dL, if further decline is expected.

ESA treatment is not recommended for prevention of anaemia in patients with normal Hb concentration before chemotherapy.

There is no clear evidence that transfusions of leukocyte-depleted red blood cell concentrate has a more favourable effect on clinical cancer course than RBC

without leukocyte depletion. However, due to the higher risk of post-transfusion adverse reactions associated with leukocytes in concentrates (febrile non-haemolytic transfusion reaction, TRALI, immunisation, CMV transmission), it is advisable to use leukocyte-depleted red blood cell concentrate in patients with expected multiple blood transfusions.

2. Aim of anaemia treatment

Treatment of patients with anaemia is conducted to:

- reduce or eliminate the symptoms of anaemia;
- allow anti-cancer treatment;
- have better quality of life.

3. Treatment

3.1. Elimination of causes (Fe supplementation, stopping the bleeding, blocking the haemolytic reaction)

3.2. RBC concentrate transfusion

3.2.1. Disadvantages and limitations

Risk of post-transfusion adverse reactions, including life-threatening, risk of progression of cancer, need for hospitalisation.

3.2.2. Advantages

Highly effective treatment of anaemia. Rapid action — eliminating the symptoms of anaemia.

3.3. Use of ESA

3.3.1. Disadvantages and limitations

Long time needed for action, risk of thromboembolic events, hypertension, limit of Hb concentration of 12 g/dL, which must not be exceeded during ESA administration.

3.3.2. Advantages

Ability of outpatient administration, long dosing intervals, ability to maintain a relatively steady Hb concentration, reduced need for red blood cell transfusions, improved quality of life.

Aim of red blood cell transfusions

The aim of red blood cell transfusions in asymptomatic anaemia is to maintain Hb concentration in range 7–9 g/dL.

The aim of red blood cell transfusions in symptomatic anaemia is to increase Hb concentration to the level necessary to eliminate the symptoms, but not higher than 8–10 g/dL.

When ordering red blood cell transfusions, safer blood components (such as leukocyte-depleted or irradiated red blood cell concentrates) should be considered.

Aim of treatment with ESA

The aim of ESA treatment is to maintain, in patients with anaemia accompanied by chemotherapy, the lowest Hb concentration that does not require red blood cell transfusions.

The results of meta-analyses of the effect of ESA on overall survival time and progression-free survival are contradictory, mainly due to the inclusion of studies that allowed use of ESA in patients with Hb concentration above 12 g/dL. Therefore, they result in cautiously formulated recommendations for ESA use in patients treated with cure intention (primarily because of the risk of thromboembolic complications).

The European Medicines Agency (EMA) allows the use of ESA in symptomatic chemotherapy-induced anaemia in the following manner:

- in patients undergoing chemotherapy with Hb concentration of 10 g/dL or less, ESA treatment could be considered to increase Hb by more than 2 g/dL or avoid further Hb decrease;
- in patients not undergoing chemotherapy there are no indications for ESA treatment, and administration of ESA in order to achieve Hb concentration of 12–14 g/dL could be associated with increased risk of death;
- in patients treated with cure intention ESA should be used with caution.

It should be emphasised that in early cancer stages a statistically significant positive correlation was observed between RBC concentrate transfusion and shorter overall survival and higher mortality rate. According to the authors of these recommendations, there

is a risk of anaemia treatment with RBC concentrate transfusions in early stage of malignancy. This is most likely due to the immunomodulating effect of transfused blood components, which inhibits the recipient's immune system and weakens its function of controlling the development of cancer.

It is recommended that patients be informed in detail about intended use of ESA, together with comprehensive information provided on the purpose and potential adverse reactions associated with this treatment (especially thromboembolic complications). It is also advisable to inform the primary care physician about the use of ESA.

Dosage of ESA

Initial ESA dose is as follow:

- epoetin — 150 U/kg 3 ×/week or 30,000 U/week;
- darbepoetin — 2.25 µg/kg/week or 500 µg/3 weeks.

Initial pre-evaluation of iron metabolism is necessary, and ESA should be introduced only after compensating for any deficiencies. It is advisable to monitor haemoglobin and iron concentrations during treatment, and in the case of iron deficiency, supplementation is necessary, but only intravenously.

In case of lower than expected haemoglobin level increase, ESA dose can be increased to:

- epoetin — 300 U/kg 3 ×/week or 60,000 U/week;
- darbepoetin — 4.5 µg/kg/week.

ESA doses should be reduced by approximately 25–50% if the haemoglobin concentration increases to a level that allows transfusion of red blood cells to be avoided, or increases by more than 2 g/dl within four weeks.

ESA should be discontinued after a maximum of four weeks (epoetin) or nine weeks (darbepoetin alfa) in the case of lack of efficacy, and up to four weeks after chemotherapy cessation. Discontinuation of ESA is also recommended if ESA neutralising antibodies occur.

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