Anemia in patients with head and neck cancer – current guidelines and literature review

Niedokrwistość u chorych z nowotworami głowy i szyi – aktualne wytyczne oraz przegląd literatury

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ABSTRACT: Anemia is one of the most common comorbidities among patients qualified for surgical treatment. The number of those that is even greater in the group that underwent oncological treatment, both for chemotherapy and radiotherapy. Anemia is associated with higher risk of perioperative complications and decrease overall survival. Directed diagnostics let for patient general condition evaluation and finding causes of anemia development, which is crucial for introducing aimed therapy. Implementation of effective therapy support the improvement of patients’ quality of life and the results of oncological treatment in this group of patients.

KEYWORDS: anemia, cancer, head and neck cancer

EPIDEMIOLOGY OF ANEMIA

Anemia is one of the most common comorbidities in patients with cancer. As defined by the World Health Organization (WHO), anemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is inadequate to meet basic physiologic needs that vary with age, gender, and health status. Symptomatic anemia is manifested by: fatigue, weakness, dizziness and shortness of breath. WHO's global database on anemia provides information on the prevalence of anemia worldwide. WHO allows both Red Blood Cell (RBC) count and hemoglobin concentration as criteria for the diagnosis of anemia:

1. RBC <4.3 ×10¹²/l in women and <4.8 ×10¹²/l in men
2. hemoglobin concentration <12 g/dL in women and <14 g/dL in men [1].

In The European Cancer Anemia Survey (ECAS), anemia was found in 39.3% of patients treated for malignant tumors. Mild anemia predominated (29.3%). The occurrence of moderate and
severe anemia was significantly less frequent (8.7% and 1.3% of patients, respectively). The study noted that patients with lung cancer and cancers of the reproductive system were the most likely to develop anemia. In the group of patients with tumors located in the head and neck region, the percentage of patients with mild anemia is the highest compared to other locations of primary tumors (>75% of the group with anemia) [2].

The Polish Cancer Anemia Survey (POLCAS) has shown that anemia is present in 31% of patients starting oncological treatment, and this percentage increases to 54% among those who have completed it [3].

Studies evaluating the relationship between anemia and head and neck cancer have shown that its presence is associated with poor prognosis [4]. The study by Baumaister et al. confirmed that both preoperative anemia and the need for preoperative transfusion of blood products significantly decreased the overall survival of patients. In addition, it was emphasized that the need for blood rolling worsened the prognosis regardless of the patients’ age and tumor stage [5], but it is the degree of anemia, not the fact of transfusing blood products, that should be considered a factor worsening the prognosis [4].

**CAUSES OF ANEMIA INDEPENDENT OF NEOPLASTIC DISEASE**

The causes of anemia are varied and often result from the course of other chronic diseases, leading to progressive impairment of erythropoiesis. Coexistence of multiple diseases, as well as acute conditions, leads to a faster deterioration of blood count parameters and increases the symptoms associated with anemia, resulting in the development of symptomatic disease (Tab. II.).

Chronic inflammation is recognized as one of the more common causes of anemia in hospitalized and chronically ill patients. It is associated with prolonged immune activation usually resulting from infections and autoimmune diseases. Recently, the list of chronic conditions leading to the development of anemia by an inflammatory mechanism has been expanded to: chronic kidney disease, congestive heart failure, chronic lung disease and obesity. Cytokines induced by persistent inflammation and hepcidin (which is an inflammatory protein and also a regulator of iron transport) block intestinal absorption and cause its retention in reticuloendothelial cells, leading to reduced erythropoiesis. Furthermore, shortened erythrocyte half-life, inhibition of the erythropoietin response to anemia, and inhibition of erythroid cell differentiation by inflammatory mediators contribute to disease progression [6].

Thyroid disorders leading to disturbances of normal production of thyroid hormones can also lead to disturbances of iron absorption from the gastrointestinal tract and development of secondary anemia, which requires implementation of supplementation therapy with thyroid hormones and iron preparations [7].

In the course of diabetes, especially with persistently high glycemic values, a gradual damage of organs, including kidneys, and secondary erythropoietin deficiency are observed. In a study by Bosman et al. it was shown that among patients treated for diabetes with concomitant anemia, blood erythropoietin levels were significantly lower than the cut-off values [8]. In addition, patients in this group are particularly at high risk of developing cardiovascular disease, which increases the risk of anemia [9].

Anemia is a common comorbidity in patients undergoing ongoing gastroenterological care for: chronic inflammatory bowel disease, peptic ulcer disease and liver failure of various etiologies. In this group, bleeding episodes, malabsorption syndrome and chronic inflammation play the most important role in the context of its development. Anemia can significantly contribute to increased morbidity and mortality due to the underlying disease, as well as significantly reduce: quality of life, exercise capacity and cognitive function [10].

**THE MOST COMMON CAUSES OF ANEMIA IN PATIENTS WITH HEAD AND NECK CANCER**

Anemia that develops in association with the course of malignancy, regardless of the immediate cause, is called Cancer-Related Anemia (CRA). It is estimated that CRA occurs in 58% of patients with solid tumors and 84% with lymphoid malignancies [11].

The development of anemia in malignant diseases may be direct, associated with chronic inflammation, micro- and macro-nutrient deficiencies, and secondary, due to bleeding episodes leading to rapid anemization of patients [12].

Deficiencies of nutrients crucial for proper erythropoiesis result, in patients with tumors of the head and neck region, from gradual development of dysphagia and odynophagia, which forces the patient to change the type of food intake, its form and quantity (Fig. 1.). In addition, tumors located in the gastrointestinal tract can lead to local food malabsorption, which increases the rate of disease progression due to deficiencies of key elements, vitamins, and compounds [13]. Iron deficiency is estimated to contribute to the development of anemia in 29–60% of cases in patients with malignancies [14], and up to 63% of oncology patients with anemia have transferrin saturation and ferritin levels below population reference levels. This has a significant impact on the impairment of erythropoiesis [15].

An equally important factor in the development of anemia is vitamin B12 and folic acid deficiency. In the study by Raval et al. it was found that a decrease in their plasma concentrations correlates with

<table>
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<tr>
<th>ANEMIA</th>
<th>HAEMOGLOBIN VALUE (g/dl)</th>
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<tbody>
<tr>
<td>Males</td>
<td>Females</td>
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<tr>
<td>Mild</td>
<td>10.0–13.5</td>
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<tr>
<td>Moderate</td>
<td>9.9–9.0</td>
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<tr>
<td>Severe</td>
<td>7.9–6.5</td>
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<td>Life-threatening</td>
<td>&lt;6.5</td>
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**Tab. I. Distribution of severity of anemia according to WHO guidelines.**
a higher frequency of precancerous lesions in the oral cavity and cancer progression. In the group of patients with advanced lesions, the values of vitamin B12 and folic acid concentrations were significantly lower than in other patients included in the study [16]. Similar findings were published by Nacci et al. in a study showing a relationship between decreased plasma folate levels and laryngeal cancer progression [17]. The results suggest the potential importance of these deficiencies in the development and progression of head and neck cancers, in addition to their involvement in the development of CRA.

Furthermore, as tumor mass increases and abnormal vascularization develops as a result of neoangiogenesis, episodes of massive bleeding from the tumor surface and into the tumor are observed. This translates into rapid loss of circulating blood and erythrocyte mass. In cases of massive bleeding, it is necessary to secure an open airway and stop the bleeding as quickly as possible. Interventional radiology procedures, which allow obliteration of vessels feeding the tumour, enable to control the bleeding and protect the patient against its recurrence. Such procedures allow minimally invasive treatment improving the comfort and quality of life of patients, especially in the group with advanced lesions disqualified from surgery or as part of palliative management aimed at improving the quality of life [18]. Thus, they are superior to methods of stopping the bleeding and achieving haemostasis using classical surgical techniques (tamponade, tumescence, electrocoagulation).

The development of anemia also occurs in an indirect mechanism related to the activation of inflammatory mediators disturbing the process of erythropoiesis and iron absorption from the gastrointestinal tract [12]. The production of cytokines by the primary tumor and as an element of the immune system response, particularly by monocytes, results in disturbance of the erythropoiesis process (inhibition of precursor cells formation, decreased erythropoietin production) and decreased ability to absorb iron from food. The most frequently mentioned cytokines negatively affecting erythrocyte synthesis include interferon γ, tumor necrosis factor (TNF) and interleukins 1 and 6 [19]. The applied oncological treatment, leading to tumor breakdown and release of toxic compounds and inflammatory mediators, is not indifferent to the development of anemia [4].

Additionally, as a result of activation of the immune system defense response and production of proinflammatory cytokines and decreased osmotic resistance of erythrocytes, a higher risk of developing hemolytic anemia is observed, which may occur in advanced stages of cancer. It is observed much more frequently in patients undergoing biologic treatment with inhibitors: CTLA4, PD-1 and PD-L1 [20].

**DIAGNOSIS OF ANEMIA IN PATIENTS WITH HEAD AND NECK CANCER**

Diagnosis of anemia in the course of cancer should be based on the assessment of typical parameters of peripheral blood count: hemoglobin concentration, hematocrit, erythrocyte saturation with hemoglobin, and reticulocyte count. Further diagnostic evaluation of iron balance, vitamin B12 and folic acid concentrations provides information on the possible need for complex supplementation therapy. In case of rapidly progressive or symptomatic anemia, the patient should be qualified for urgent gastrointestinal endoscopy (gastroscopy and colonoscopy) and upper respiratory tract endoscopy (e.g. nasofiberoscopy).

Diagnosis of iron deficiency anemia should begin when a decreased hemoglobin level is found with an associated decrease in reticulocyte count, red blood cell volume, and hemoglobin saturation (microcytic anemia). In addition, increased anisocytosis with the appearance of microcytes of different shape is observed. The basic parameters that can be evaluated to confirm the diagnosis include the assessment of reticulocyte hemoglobin saturation, soluble transferrin receptor concentration, and Total Iron Bounding Capacity (TIBC), which remains the diagnostic standard. The most sensitive indicator of iron deficiency in the body and its sequelae is decreased ferritin concentration, but this parameter may be falsely negative in patients with active inflammation because it belongs to the group of acute inflammatory phase proteins.

If hemolytic anemia is suspected, bilirubin, lactate dehydrogenase, and haptoglobin should also be measured. Useful in differentiating between hemolytic anemia from autoimmunity and nonimmune hemolytic anemia is the Coombs test and evaluation of IgG, IgM, and IgA autoantibodies to determine the causative treatment regimen.
IRON SUPPLEMENTATION AND QUALIFICATION FOR BLOOD PRODUCT THERAPY

The goal of iron preparation therapy is to safely and effectively correct the observed anemia in oncology patients with total iron deficiency (transferrin saturation < 20%; ferritin < 30 ng/mL) or functional iron deficiency (transferrin saturation 20–50%; ferritin 30–800 ng/mL) [21, 22].

Depending on the degree of iron deficiency, supplementation with oral or para-enteral preparations should be considered (especially in patients requiring rapid compensation of blood count values). Large availability of supplements in the form of tablets, syrups and orally administered solutions allows to choose a preparation convenient for use also in patients with dysphagia resulting from the presence of tumors in the oral cavity, pharynx and larynx. The use of complex preparations containing additionally folic acid, vitamin B12 and ascorbic acid in the treatment allows for comprehensive patient-friendly supplementation management (reduction of the number of drugs taken and doses) (Tab. III.).

The use of injectable iron has historically been associated with a high risk of serious adverse events (including anaphylactic reaction and shock) due to the use of macromolecular iron dextran formulations. Currently, commercially available formulations show high safety of use, with lower reaction rates than penicillin [23]. Recent studies show fewer adverse reactions than orally administered iron. The most commonly reported include headache, numbness in the extremities, fainting, palpitations, dyspnea, nausea, diarrhea or constipation, and the occurrence of allergic skin lesions [24]. It remains good clinical practice to administer a bolus dose of 25 mg as a slow infusion. In the absence of adverse reactions, the infusion is continued to the standard dose of 100 mg of iron. Subsequent injections are repeated at 7-day intervals until a total dose of 1000 mg iron is achieved.

If low haemoglobin values persist despite maximum doses of intravenous preparations, treatment must be discontinued for 4 weeks after a total dose of 1000 mg has been reached. Re-initiation of treatment with iron preparations can be considered only after this period.

In a selected group of patients requiring intensive hemoglobin equalization prior to planned oncologic treatment, the use of Erythropoiesis Stimulating Agents (ESAs) in conjunction with iron supplementation treatment may be considered.

Available meta-analyses do not clearly define the safety of ESA. Older studies demonstrate an increased risk of thromboembolic complications and higher mortality associated with the implementation of such treatment. However, more recent publications suggest: good tolerability of such treatment, reduced number of necessary transfusions of blood products and improved quality of life [25, 26].

Eligibility for treatment with human erythropoietin analogues is still controversial in patients with CRA, but the National Comprehensive Cancer Network (NCCN) accepts this approach for the purpose of rapid compensation of blood morphology parameters and improvement of general condition of patients. The European Society for Medical Oncology recognizes the use of ESAs only in patients undergoing chemotherapy who have hemoglobin levels below 10 g/dL. To reduce the risk of embolic/thrombotic complications in this group, treatment should be administered at the lowest effective dose possible until hemoglobin levels >12 g/dL are achieved. The guidelines of the American Society of Clinical Oncology are more restrictive, recommending eligibility only for patients in whom the expected benefit of avoiding blood transfusions is greater than the potential adverse effects [27].

The fastest method enabling to restore normal haemoglobin concentration values is transfusion of packed red blood cells, which is obtained from whole blood donations deprived of plasma and subjected to special preparation. One unit of the concentrate should provide the patient with an increase in haemoglobin by 1 g/dL and haematocrit by 3% [28].

However, this management should be reserved for patients in severe or life-threatening conditions due to limited availability of blood products and risk of post-transfusion complications. According to the current guidelines, patients qualified for therapy with red blood cells should have blood volume loss exceeding 30% due to haemorrhage or symptomatic anaemia (e.g. weakness, dyspnoea, dizziness) [29]. Multicentre studies recommend the use of a restrictive approach for qualification for transfusion of red blood cells (haemoglobin decrease below 7–8 g/dL) due to lack of better therapeutic outcomes in the group of patients in whom the liberal approach was implemented (haemoglobin decrease below 9–8 g/dL) [30].

The most commonly observed early post-transfusion complications include acute haemolytic reaction, allergic and anaphylactic
reaction, clotting disturbances after massive blood transfusion, fever, infection, transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI). If they occur, it is necessary to implement prompt treatment and secure the material for further laboratory tests and remnants of the transfused blood product [31].

The group of late post-transfusion complications includes the potential risk of hepatitis B and C infection, HIV, HTLV and development of symptomatic disease, despite the current transfusionology standards. Much less common complications of blood transfusion include Creutzfeldt-Jakob disease, malaria, babesiosis, and West Nile fever. In the group of patients undergoing frequent transfusions of red blood cells, iron overload syndrome may also be observed [32].

Current qualification procedures for potential donors, meticulous serological and virological diagnostics, and modern preparation allow for a significant reduction in the risk of early and late complications, which translates into increased safety of patients requiring blood transfusions.

**SUMMARY**

Anemia often accompanies cancer and requires diagnosis and treatment. Patients who have undergone previous oncological treatment are at much higher risk of developing anemia secondary to systemic treatment or radiotherapy. Before implementing the treatment of anemia associated with cancer, an in-depth diagnostics based on laboratory and endoscopic examinations is always necessary.

Patients with malignancies of the lung, reproductive tract and gastrointestinal tract are most at risk for anemia. Patients with cancers of the head and neck region, located particularly in the initial part of the gastrointestinal tract, are at risk of progressive cachexia as a result of dysphagia and odynophagia secondary to changes in lifestyle and diet.

Comprehensive treatment for anemia, aimed at equalization of hemoglobin values in a group of patients undergoing oncological treatment, allows to: significantly reduce the incidence of complications, improve therapeutic outcomes and quality of life [33].

**REFERENCES**


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