VIA MEDICA

NOWOTWORY Journal of Oncology
2023, volume 73, number 5, 309–316
DOI: 10.5603/njo.96928

ISSN: 0029–540X, e-ISSN: 2300-2115
www.nowotwory.edu.pl

Review article

Clinical nutrition in oncology

Anemia in cancer patients: addressing a neglected issue – diagnostics and therapeutic algorithm

Konrad Tałasiewicz[1], Aleksandra Kapała[1, 2]

[1]*Department of Oncology Diagnostics, Cardio-Oncology and Palliative Medicine, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*
[2]*Department of Clinical Nutrition, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland*

Cancer-related anemia (CRA) continues to be a critical concern despite advancements in oncology treatments. The prevalence of anemia varies from 30% to 90%, impacting the quality of life and prognosis of cancer patients. While CRA is often attributed to antineoplastic therapies, it can also result from the disease itself. Inflammation and the iron regulatory hormone hepcidin play significant roles in CRA pathogenesis. Treatment-induced anemia caused by chemotherapy, tyrosine kinase inhibitors (TKIs) and immunotherapy, pose additional challenges. Intravenous (IV) iron has emerged as an effective treatment option for CRA, overcoming limitations associated with oral iron supplementation. Combining IV iron and ESAs enhances treatment outcomes. Future directions involve exploring ESA safety and their immunomodulatory effects. Transfusions provide quick relief but might impact prognosis and immune response. Other considerations include incorporating physical activity and exploring hepcidin-directed therapy. In conclusion, CRA management necessitates a multifaceted approach to address deficiencies, optimize therapies and improve patient outcomes.

Key words: anemia, cancer, hepcidin, erythropoiesis-stimulating agents, blood transfusions

Introduction

Although modern oncology drugs employ mechanisms distinct from classical 20th-century cytotoxic therapies, cancer-related anemia (CRA) remains an underestimated issue. It is not always solely a consequence of antineoplastic treatments. The prevalence of anemia, varying from 30% to 90%, depends on factors such as neoplasm type, disease progression, or treatment method [1–4]. Anemia ranges from causing mild, persistent symptoms like fatigue to life-threatening conditions, especially for individuals with concurrent chronic diseases. Without a doubt, it significantly impairs quality of life (QOL) for cancer patients [5–6].

General definitions

According to the World Health Organization (WHO), anemia is a state where hemoglobin levels or red blood cell counts fall below the lower limits of normal (women <12 g/dl, men <13 g/dl) [7]. Cancer-related anemia (CRA) can result from cancer treatment (chemotherapy-induced anemia [CIA]) or the disease itself. Neoplasms can affect red blood cell (RBC) production (erythropoiesis), RBC breakdown (hemolysis), and blood loss (bleeding). For anemia resulting from oncological therapy, the Common Terminology Criteria for Adverse Events (CTCAE) grading system is used [8]. However, there are inconsistencies between WHO values and those of CTCAE (tab. I).

How to cite:
Tałasiewicz K, Kapała A. ***Anemia in cancer patients: addressing a neglected issue – diagnostics and therapeutic algorithm.*** *NOWOTWORY J Oncol* 2023; 73: 309–316.

Table I. Comparison of the values proposed by the World Health Organization and adapted by the Common Terminology Criteria for Adverse Events (CTCAE)

Severity of anemia	WHO (Hb)		CTCAE	CTCAE level
	women	men		
normal level	≥12 g/dl	≥13 g/dl	up to lower limit of normal (LLN)	0
mild	10–11.9 g/dl	10–12.9 g/dl	10 g/dl – LLN	1
moderate	8–9.9 g/dl	8–9.9 g/dl	8–9.9 g/dl	2
severe	6.5–7.9 g/dl	6.5–7.9 g/dl	<8 g/dl	3
life-threating	<6.5 g/dl	<6.5 g/dl	life-threating consequences	4

Pathogenesis and diagnostic approach

Anemia diagnosis must consider the intricate interplay of RBC production and usage across various organs (the intestines, liver, spleen, kidney, bone marrow) [9]. In most cases, CRA is primarily attributed to two causes – iron deficiency and concurrent antineoplastic therapy. Key indicators in CRA diagnosis are serum ferritin (SF) and transferrin saturation (TSAT; serum iron/total iron binding capacity x 100). Other iron-related parameters are often influenced by external factors and are unreliable predictors (e.g., MCV, soluble transferrin receptor) or are not routinely available (e.g., zinc protoporphyrin or hepcidin levels).

Functional and absolute iron deficiency

Typically, CRA patients exhibit normocytic anemia accompanied by iron deficiency (TSAT < 20%) and normal or elevated SF > 100 ng/ml [10–13]. This condition is referred to as functional iron deficiency anemia (FIDA). Another situation arises when TSAT is <20% and ferritin is <100 ng/ml, leading to absolute iron deficiency anemia (AIDA) [14]. These two clinical scenarios have distinct underlying causes. AIDA is usually linked to blood loss or inadequate iron intake/malabsorption. FIDA, on the other hand, arises due to iron sequestration driven by chronic inflammation (involving hepcidin) [15], and/or iron-restricted erythropoiesis prompted by endogenous erythropoietin production or erythropoiesis-stimulating agents [16].

Role of inflammation and hepcidin

Inflammation is a hallmark of cancer [17], impacting erythropoiesis *via* cytokines like IL-1, IL-6, IL-10, IFN-γ, TNF-α, and raising reactive oxygen species (ROS) levels. The levels of these cytokines can predict hemoglobin concentrations [18]. Hepcidin, a liver-produced iron regulatory hormone, is affected by both inflammatory cytokines and ROS. Hepcidin inhibits iron release to erythropoiesis from macrophages and hepatocytes, and also influences iron absorption in enterocytes. This hormone binds to ferroportin, an iron exporter, causing its degradation [19–20]. Consequently, oral iron absorption is limited in cancer patients, reducing its availability for dietary supplementation.

Treatment-induced anemia

In the past five years, over 200 cancer drugs have been approved, with 14% surpassing the prior standard of care [21]. Chemotherapy-induced anemia remains a significant concern, as it is still widely used, especially in neoadjuvant and adjuvant settings for solid tumors. Up to 90% of solid tumor patients experience anemia during chemotherapy [22], with incidence varying by regimen, tumor type and stage.

New agents like tyrosine kinase inhibitors (TKIs), small molecules and immunotherapy (ICI) can induce or exacerbate preexisting anemia differently from traditional cytotoxic agents. TKIs often lead to hematological toxicities [23], with mechanisms varying. Some TKIs, such as sunitinib, imatinib and pazopanib, can cause macrocytosis, which may serve as a predictor of patient survival [24–26]. The mechanism might relate to c-KIT inhibition [26]. Rarely do drugs like alectinib induce hemolytic anemia [27].

Immunotherapy can also lead to anemia via autoantibody-induced hemolysis, requiring treatment with steroids and rituximab [28]. In extremely rare cases, lethal aplastic anemia has been described [29].

CRA treatment

Three main strategies address CRA, either individually or in combination. Correcting deficiencies (iron, vitamin B_{12}, folate) is paramount. Erythropoiesis-stimulating agents (ESAs) and red blood cell concentrates (transfusions) follow.

Iron treatment

While oral iron is standard for general iron deficiency anemia treatment, it has limitations in cancer patients due to gastrointestinal (GI) intolerance. GI symptoms often accompany cancer treatments, making oral supplementation difficult [30]. Moreover, heightened hepcidin levels impair proper iron utilization. Studies suggest alternating dosing schedules could decrease hepcidin levels and enhance iron absorption [31–32]. Intravenous (*iv*) iron is preferred for CRA patients due to its more direct delivery and bypassing GI issues [33–34]. Intravenous iron, alone or with ESA, effectively treats chemotherapy-induced anemia, saves costs and improves QOL [35–38]. Intravenous iron suits both functional and absolute iron deficiency scenarios.

Intravenous iron treatment

Intravenous iron formulations have been utilized in human medicine for nearly a century; however, some physicians continue to harbor unnecessary concerns reminiscent of the early days of its introduction [39]. The prospective European ECAS study, conducted at the beginning of the 21st century to gather data on the prevalence and treatment of anemia, revealed that only 6.5% of patients received iron treatment [40]. These concerns likely stem from apprehensions about potential side effects.

Safety and side effects of intravenous iron supplementation

Contemporary iron products (as outlined in table II) all possess an iron core enveloped by a carbohydrate shell, a feature that distinguishes them from one another. Intravenous iron infusions seldom lead to hypersensitivity reactions, and although such reactions can be life-threatening, severe anaphylactic-type reactions are exceedingly rare [41]. High molecular weight iron dextrans, previously used, had significantly higher rates of serious adverse drug events, leading to their discontinuation. The new formulations are designed to be safer. A comprehensive systemic review that evaluated the safety of intravenous iron across randomized clinical trials established that intravenous iron is not correlated with an increased risk of serious adverse events [42]. The European Medical Agency has issued recommendations for managing allergic reactions associated with intravenous iron-containing medications, concluding that the benefits of these medications outweigh the associated risks [43]. As a result, administering a test dose with these new formulations is no longer advised.

Prevention and management protocols for infusion reactions have been well-delineated and align with approaches used in managing other infusion-related reactions observed in the field of oncology [44, 45]. There is contradictory data concerning cardiotoxicity and the risk of exacerbating infections when using intravenous iron [42, 46, 47]. Consequently, intravenous iron administration should be avoided in patients with active infections and on the same day as cardiotoxic chemotherapy administration.

In conclusion, the use of more recent intravenous iron formulations is regarded as safer compared to other commonly used methods in addressing anemia among cancer patients [42]. Nonetheless, determining the optimal dosing and treatment schedule for intravenous iron remains an ongoing effort, with variations among the different available products.

Erythropoiesis-stimulating agents

Erythropoietin (EPO), a hormone produced in the kidneys and liver, increases red blood cell production in response to hypoxia. Recombinant EPO was synthesized in the 1980s, revolutionizing chronic kidney disease treatment [48]. ESAs entered oncology in the 1990s, gaining popularity but later encountering safety concerns [49]. Modern erythropoiesis-stimulating agents (ESAs) (tab. III) are indicated for adult cancer patients with non-myeloid malignancies receiving chemotherapy, aiming to raise hemoglobin from 8–10 g/dl to no more than 12 g/dl. ESA treatment necessitates reevaluation after 4–6 weeks, adjusting doses based on response or cessation if no response is observed.

ESAs concerns

The most common side effects include allergic reactions and cardiovascular complications. Allergic reactions range from more commonly occurring mild local injection site reactions to rare but serious reactions that require prompt attention. Early reports regarding thrombotic risk [50] led to concerns about the safety of ESAs and their potential impact on the survival of cancer patients. A recent systematic review of randomized controlled trials revealed that although this type of therapy is associated with adverse cardiovascular effects, including venous thromboembolism (VTE), it does not affect patients' overall survival, and ESAs can be used safely [51]. Due to the lack of prospective trials, neither the National

Table II. Intravenous iron formulations: characteristics, dosing and comments. The information based on the summaries of product characteristics approved by the EMA and/or FDA

Preparation	Dosing	Comments
ferric carboximaltose	20 mg/kg up to 750–1000 mg intravenous infusion or single injection up to minimum 15 mins. Second dose might be administered after ≥ 7 days	may cause transient hypophosphataemia
derisomaltoze	500–2000 mg depending on the weight, infusion over 15 mins. (up to 1000 mg) and over 30 mins. (>1000 mg) or 500 mg bolus at a speed of 250 mg/min.	relatively a new product
iron sucrose	200 mg maximum dose in injection, 500 mg infusion of at least 3.5 h	commonly used in the USA
LMWID	depending on the preparation – 240–360 mins. infusion – complicated dosing (test dose recommended)	complicated dosing
ferric gluconate	125 mg in 60 mins., repeat in 2–3 weeks until a total dose of 1000 mg is obtained	associated with serious infusion reactions
ferumoxytol	510 mg in 15 mins. not available in the European Union	might influence MR results up to 3 months

LMWID – low molecular weight iron dextran; MR – magnetic resonance

Table III. Erythropoiesis-stimulating agents. The information is based on the summaries of product characteristics approved by the EMA and/or FDA

Erythropoiesis-stimulating agent (ESA)	Dosing	Dose escalation possibility
epoetin alfa	150 units/kg 3x/week or 30 000 units/week	300 units/kg 3x/week or 60 000 units/week
epoetin beta	30 000 units (450 units/kg)	60 000 units (900 units/kg/week)
epoetin theta	20 000 units/week	40 000 units/week (max. 60 000 units/week)
darbepoetin alpha	2.25 µg/kg/week or 500 µg/3 weeks	4.5 µg/kg/week

Comprehensive Cancer Network® (NCCN®) nor the European Society of Medical Oncology recommends the routine use of standard prophylactic anticoagulation in the absence of other risk factors [33, 52]. The use of validated scales predicting VTE events, such as the KHORANA scale, is strongly encouraged for patients receiving chemotherapy [53]. Another significant cardiovascular effect is arterial hypertension, which typically manifests at the beginning of therapy. The exact mechanism of this complication is not well understood. An important subgroup of patients includes those with chronic kidney disease or preexisting arterial hypertension. For these individuals, the introduction of ESAs should be cautious, and a gradual correction of anemia is advised [54].

ESAs and possible stimulation of cancer growth

Increased EPO signaling has been observed on cancer cells, particularly in the hypoxic regions of various tumors [55]. This observation led to the hypothesis of potential cancer growth stimulation. Early trials suggested inferior overall survival among patients receiving ESA during chemotherapy [56–57]. However, all trials that raised such concerns targeted hemoglobin levels above 12 g/dl. When ESAs are used within registered indications among patients receiving chemotherapy for non-myeloid cancers with hemoglobin levels below 10 g/dl and a target range up to 12 g/dl, no impact on overall survival was confirmed [51, 58–61]. Recent randomized, double-blinded, placebo-controlled studies focusing on this strategy appear to confirm the safety of ESAs and their lack of impact on overall survival (OS) and progression-free survival (PFS) for patients with solid tumors [62].

Combining intravenous iron and ESAs

Given the recommendation for correcting all deficiencies prior to initiating ESA treatment, a question arises about the combination of *iv* iron formulations and ESAs. This treatment approach should be administered on a regular daily basis, as demonstrated in a randomized controlled trial that showed significant improvements in both quality of life (QoL) and hemoglobin levels [16]. This combination also leads to a reduction in the need for transfusions when compared to the use of ESAs alone [63].

ESA future directions

Further research, particularly randomized controlled trials focused on the safety of ESAs, is necessary. With the growing interest in the potential immunomodulatory effects of erythropoietin (EPO) and its derivatives (given that ESAs might exhibit anti-inflammatory effects) [64], additional studies are required to determine the viability of their use in conjunction with modern treatment modalities like immunotherapy.

Transfusions

RBC transfusions are commonly used, because they provide quick relief, but come with risks like immune modulation [65, 66]. Transfusions negatively impact cancer patients, affecting progression-free and overall survival, recurrence and perioperative morbidity [67–74]. Some negative effects stem from immune activation, impacting oncology treatments [75–76]. Recent trials found decreased immunotherapy response rates with transfusions [77].

Considerations for optimizing RBC use in cancer patients

Although the precise hemoglobin (Hb) level or timing for blood transfusions in relation to the type of cancer treatment or disease stage has yet to be definitively established, there is existing data regarding different approaches to red blood cell (RBC) utilization.

Recognizing the adverse effects of transfusions on cancer patients at various stages of therapy, many healthcare professionals underscore the importance of adopting a more cautious approach to RBC transfusions. This approach is founded on the use of a lower Hb concentration as the threshold for initiating transfusions (typically around 7–8 g/dl), in contrast to a more liberal threshold (around 9–10 g/dl). Restrictive RBC transfusion strategies (Hb < 7–8 g/dl) align with reduced morbidity and mortality [78–79].

Foliate and vitamin B_{12} deficiency

Megaloblastic anemia stemming from deficiencies in vitamin B_{12} and folate is less frequent among cancer patients compared to iron deficiency. Such deficiencies may be linked to

disease progression and malnutrition, as well as increased cellular turnover, particularly in cases of lymphomas and leukemias. Individuals who have undergone gastrectomy or have experienced significant infiltration of the intestine may also experience such deficiencies due to the altered absorption of these vitamins in these parts of the digestive system. Certain cytotoxic drugs, commonly employed in cancer treatment such as 5-fluorouracyl, methotrexate and hydroxycarbamide, can induce megaloblastic anemia by interfering with DNA synthesis [80].

Additional considerations for the treatment of cancer-related anemia

While the primary modalities of addressing cancer-related anemia (ESA, iron supplementation and transfusions) form the foundation of management, there are several other noteworthy aspects to be taken into account. These encompass lifestyle interventions and a range of supplementary approaches.

Physical activity

Compelling evidence underscores the pivotal role of exercise and various forms of physical activity in cancer prevention and treatment, notably in enhancing patients' quality of life (primarily alleviating fatigue). Of all cancer-related fatalities worldwide, approximately 35% can be attributed to environmental factors, including sedentary lifestyles [81]. Different types of exercise have proven highly effective in mitigating cancer-related fatigue during treatment [82], as well as potentially improving overall cancer survival rates [83]. Given the key role inflammation plays in the development of cancer-related anemia, the potential anti-inflammatory effects of physical activity are noteworthy. Moreover, physical activity may influence hepcidin levels. Emerging data suggests that engaging in exercise can lead to improvements in hemoglobin levels in patients undergoing chemotherapy while using ESAs [84], in breast cancer patients during radiotherapy [85], and in breast cancer patients undergoing chemotherapy [86–87]. Nonetheless, an optimal type and intensity of physical activity has yet to be definitively established.

Hepcidin-directed therapy

Given the often-elevated levels of hepcidin in cancer patients, therapeutic approaches involving monoclonal antibodies that neutralize these proteins have gained attention. This form of treatment holds the potential to enhance ferroportin expression in enterocytes and macrophages, thereby facilitating the release of stored iron and promoting effective erythropoiesis. Initial clinical trials assessing the safety of such antibodies in addressing cancer-related anemia have yielded promising results [88]. Subsequent research in this domain is warranted, as it could potentially introduce another avenue for targeted treatment of cancer-related anemia.

Zinc deficiency

Zinc deficiency is prevalent in many countries and frequently coexists with iron deficiency. Among adults afflicted with chronic diseases, zinc deficiency has been associated with anemia [89]. While some recent analyses among non-cancer anemic patients have suggested a correlation between zinc levels and hemoglobin concentration [90], evidence in the context of cancer patients remains limited.

Conclusions

CRA's impact is significant, but awareness and treatment approach vary. There are three main pillars guide treatment: correcting deficiencies, using ESAs and transfusions. Intravenous iron addresses iron deficiency more effectively. ESAs have associated concerns but remain valuable. Transfusions provide relief but may affect prognosis. Future research focuses on enhancing interventions and combining treatments to optimize CRA management.

Article information and declarations

Author contributions

Konrad Tałasiewicz – conceptualization, visualization, writing – original draft, writing – reviewing and editing.
Aleksandra Kapała – conceptualization, supervision, writing – reviewing and editing.
All authors discussed and commented on the manuscript.

Funding

None declared

Conflict of interest

None declared

Konrad Tałasiewicz
Maria Sklodowska-Curie National Research Institute of Oncology
Department of Oncology Diagnostics, Cardio-Oncology and Palliative Medicine
ul. Roentgena 5
02-781 Warszawa, Poland
e-mail: konrad.talasiewicz@nio.gov.pl

Received: 12 Aug 2023
Accepted: 6 Sep 2023

References

1. Wojtukiewicz MZ, Sierko E, Rybaltowski M, et al. The Polish Cancer Anemia Survey (POLCAS): a retrospective multicenter study of 999 cases. Int J Hematol. 2009; 89(3): 276–284, doi: 10.1007/s12185-009-0273-x, indexed in Pubmed: 19343481.
2. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 2004; 116 Suppl 7A: 11S–26S, doi: 10.1016/j.amjmed.2003.12.008, indexed in Pubmed: 15050883.
3. Harrison L, Shasha D, Shiaova L, et al. Prevalence of anemia in cancer patients undergoing radiation therapy. Semin Oncol. 2001; 28(2 Suppl 8): 54–59, doi: 10.1016/s0093-7754(01)90214-3, indexed in Pubmed: 11395854.
4. Xu H, Xu L, Page JH, et al. Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clin Epidemiol. 2016; 8: 61–71, doi: 10.2147/CLEP.S89480, indexed in Pubmed: 27186078.

5. Cella D, Kallich J, McDermott A, et al. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol. 2004; 15(6): 979–986, doi: 10.1093/annonc/mdh235, indexed in Pubmed: 15151958.
6. Barca-Hernando M, Muñoz-Martin AJ, Rios-Herranz E, et al. Case-Control Analysis of the Impact of Anemia on Quality of Life in Patients with Cancer: A Qca Study Analysis. Cancers (Basel). 2021; 13(11), doi: 10.3390/cancers13112517, indexed in Pubmed: 34063886.
7. Cappellini MD, Motta I. Anemia in Clinical Practice-Definition and Classification: Does Hemoglobin Change With Aging? Semin Hematol. 2015; 52(4): 261–269, doi: 10.1053/j.seminhematol.2015.07.006, indexed in Pubmed: 26404438.
8. National Cancer Institute, Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50 (24.07.2023).
9. Gilreath JA, Rodgers GM. How I treat cancer-associated anemia. Blood. 2020; 136(7): 801–813, doi: 10.1182/blood.2019004017, indexed in Pubmed: 32556170.
10. Ludwig H, Müldür E, Endler G, et al. Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia. Ann Oncol. 2013; 24(7): 1886–1892, doi: 10.1093/annonc/mdt118, indexed in Pubmed: 23567147.
11. Park S, Jung CW, Kim K, et al. Iron deficient erythropoiesis might play key role in development of anemia in cancer patients. Oncotarget. 2015; 6(40): 42803–42812, doi: 10.18632/oncotarget.5658, indexed in Pubmed: 26517509.
12. Naoum FA. Iron deficiency in cancer patients. Rev Bras Hematol Hemoter. 2016; 38(4): 325–330, doi: 10.1016/j.bjhh.2016.05.009, indexed in Pubmed: 27863761.
13. Gluszak C, de Vries-Brilland M, Seegers V, et al. Impact of Iron-Deficiency Management on Quality of Life in Patients with Cancer: A Prospective Cohort Study (CAMARA Study). Oncologist. 2022; 27(4): 328–333, doi: 10.1093/oncolo/oyac005, indexed in Pubmed: 35380718.
14. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood. 2010; 116(23): 4754–4761, doi: 10.1182/blood-2010-05-286260, indexed in Pubmed: 20826717.
15. Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol. 2014; 89(2): 203–212, doi: 10.1002/ajh.23628, indexed in Pubmed: 24532336.
16. Auerbach M, Ballard H, Trout JR, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol. 2004; 22(7): 1301–1307, doi: 10.1200/JCO.2004.08.119, indexed in Pubmed: 15051778.
17. Hanahan D. Hallmarks of Cancer: New Dimensions. Cancer Discov. 2022; 12(1): 31–46, doi: 10.1158/2159-8290.CD-21-1059, indexed in Pubmed: 35022204.
18. Macciò A, Madeddu C, Gramignano G, et al. The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. Haematologica. 2015; 100(1): 124–132, doi: 10.3324/haematol.2014.112813, indexed in Pubmed: 25239265.
19. Goodnough LT. Iron deficiency syndromes and iron-restricted erythropoiesis (CME). Transfusion. 2012; 52(7): 1584–1592, doi: 10.1111/j.1537-2995.2011.03495.x, indexed in Pubmed: 22211566.
20. Ganz T. Anemia of Inflammation. N Engl J Med. 2019; 381(12): 1148–1157, doi: 10.1056/nejmra1804281.
21. Benjamin DJ, Xu A, Lythgoe MP, et al. Cancer Drug Approvals That Displaced Existing Standard-of-Care Therapies, 2016-2021. JAMA Netw Open. 2022; 5(3): e222265, doi: 10.1001/jamanetworkopen.2022.2265, indexed in Pubmed: 35289858.
22. Xu H, Xu L, Page JH, et al. Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clin Epidemiol. 2016; 8: 61–71, doi: 10.2147/CLEP.S89480, indexed in Pubmed: 27186078.
23. Barber NA, Afzal W, Akhtari M. Hematologic toxicities of small molecule tyrosine kinase inhibitors. Target Oncol. 2011; 6(4): 203–215, doi: 10.1007/s11523-011-0202-9, indexed in Pubmed: 22127751.
24. Kucharz J, Giza A, Dumnicka P, et al. Macrocytosis during sunitinib treatment predicts progression-free survival in patients with metastatic renal cell carcinoma. Med Oncol. 2016; 33(10): 109, doi: 10.1007/s12032-016-0818-9, indexed in Pubmed: 27573381.
25. Schallier D, Trullemans F, Fontaine C, et al. Tyrosine kinase inhibitor-induced macrocytosis. Anticancer Res. 2009; 29(12): 5225–5228, indexed in Pubmed: 20044640.
26. Kloth JSL, Hamberg P, Mendelaar PAJ, et al. Macrocytosis as a potential parameter associated with survival after tyrosine kinase inhibitor treatment. Eur J Cancer. 2016; 56: 101–106, doi: 10.1016/j.ejca.2015.12.019, indexed in Pubmed: 26841094.
27. Dores GM, Nayernama A, Cheng C, et al. Hemolytic anemia following alectinib reported to the U.S. Food and Drug Administration Adverse Event Reporting System. Am J Hematol. 2022; 97(4): E129–E132, doi: 10.1002/ajh.26454, indexed in Pubmed: 34985778.
28. Kroll MH, Rojas-Hernandez C, Yee C. Hematologic complications of immune checkpoint inhibitors. Blood. 2022; 139(25): 3594–3604, doi: 10.1182/blood.2020009016, indexed in Pubmed: 34610113.
29. Guo Q, Zhao JN, Liu T, et al. Immune checkpoint inhibitor-induced aplastic anaemia: Case series and large-scale pharmacovigilance analysis. Front Pharmacol. 2023; 14: 1057134, doi: 10.3389/fphar.2023.1057134, indexed in Pubmed: 36778017.
30. Rund D. Intravenous iron: do we adequately understand the short- and long-term risks in clinical practice? Br J Haematol. 2021; 193(3): 466–480, doi: 10.1111/bjh.17202, indexed in Pubmed: 33216989.
31. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015; 126(17): 1981–1989, doi: 10.1182/blood-2015-05-642223, indexed in Pubmed: 26289639.
32. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017; 4(11): e524–e533, doi: 10.1016/S2352-3026(17)30182-5, indexed in Pubmed: 29032957.
33. Aapro M, Beguin Y, Bokemeyer C, et al. ESMO Guidelines Committee. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018; 29(Suppl 4): iv96–iv9iv110, doi: 10.1093/annonc/mdx758, indexed in Pubmed: 29471514.
34. Radziwon P, Krzakowski M, Kalinka-Warzocha E, et al. Anemia in cancer patients — Expert Group recommendations. Oncol Clin Pract. 2017; 13: 202–210, doi: 10.5603/OCP.2017.0023.
35. Makharadze T, Boccia R, Krupa A, et al. Efficacy and safety of ferric carboxymaltose infusion in reducing anemia in patients receiving chemotherapy for nonmyeloid malignancies: A randomized, placebo--controlled study (IRON-CLAD). Am J Hematol. 2021; 96(12): 1639–1646, doi: 10.1002/ajh.26376, indexed in Pubmed: 34653287.
36. Jang JHo, Kim Y, Park S, et al. Efficacy of intravenous iron treatment for chemotherapy-induced anemia: A prospective Phase II pilot clinical trial in South Korea. PLoS Med. 2020; 17(6): e1003091, doi: 10.1371/journal.pmed.1003091, indexed in Pubmed: 32511251.
37. Luporsi E, Mahi L, Morre C, et al. Evaluation of cost savings with ferric carboxymaltose in anemia treatment through its impact on erythropoiesis-stimulating agents and blood transfusion: French healthcare payer perspective. J Med Econ. 2012; 15(2): 225–232, doi: 10.3111/13696998.2011.639823, indexed in Pubmed: 22077267.
38. Gluszak C, de Vries-Brilland M, Seegers V, et al. Impact of Iron-Deficiency Management on Quality of Life in Patients with Cancer: A Prospective Cohort Study (CAMARA Study). Oncologist. 2022; 27(4): 328–333, doi: 10.1093/oncolo/oyac005, indexed in Pubmed: 35380718.
39. GOETSCH A, MOORE C, MINNICH V. OBSERVATIONS ON THE EFFECT OF MASSIVE DOSES OF IRON GIVEN INTRAVENOUSLY TO PATIENTS WITH HYPOCHROMIC ANEMIA. Blood. 1946; 1(2): 129–142, doi: 10.1182/blood.v1.2.129.129.
40. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer. 2004; 40(15): 2293–2306, doi: 10.1016/j.ejca.2004.06.019, indexed in Pubmed: 15454256.
41. Wysowski DK, Swartz L, Borders-Hemphill BV, et al. Use of parenteral iron products and serious anaphylactic-type reactions. Am J Hematol. 2010; 85(9): 650–654, doi: 10.1002/ajh.21794, indexed in Pubmed: 20661919.
42. Avni T, Bieber A, Grossman A, et al. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015; 90(1): 12–23, doi: 10.1016/j.mayocp.2014.10.007, indexed in Pubmed: 25572192.
43. European Medicines Agency. New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/06/WC500144874.pdf (27.07.2023).
44. Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management.

Haematologica. 2014; 99(11): 1671–1676, doi: 10.3324/haematol.2014.111492, indexed in Pubmed: 25420283.
45. Lim W, Afif W, Knowles S, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. Vox Sang. 2019; 114(4): 363–373, doi: 10.1111/vox.12773, indexed in Pubmed: 30937914.
46. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomised clinical trials. BMJ. 2013; 347: f4822, doi: 10.1136/bmj.f4822, indexed in Pubmed: 23950195.
47. Shah A, Fisher SA, Wong H, et al. Safety and efficacy of iron therapy on reducing red blood cell transfusion requirements and treating anaemia in critically ill adults: a systematic review with meta-analysis and trial sequential analysis. J Crit Care. 2019; 49: 162–171.
48. Lin FK, Suggs S, Lin CH, et al. Cloning and expression of the human erythropoietin gene. Proc Natl Acad Sci U S A. 1985; 82(22): 7580–7584, doi: 10.1073/pnas.82.22.7580, indexed in Pubmed: 3865178.
49. Schoen MW, Hoque S, Witherspoon BJ, et al. End of an era for erythropoiesis-stimulating agents in oncology. Int J Cancer. 2020; 146(10): 2829–2835, doi: 10.1002/ijc.32917, indexed in Pubmed: 32037527.
50. Bennett CL, Silver SM, Djulbegovic B, et al. Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. JAMA. 2008; 299(8): 914–924, doi: 10.1001/jama.299.8.914, indexed in Pubmed: 18314434.
51. Gergal Gopalkrishna Rao SR, Bugazia S, Dhandapani TP, et al. Efficacy and Cardiovascular Adverse Effects of Erythropoiesis Stimulating Agents in the Treatment of Cancer-Related Anemia: A Systematic Review of Randomized Controlled Trials. Cureus. 2021; 13(9): e17835, doi: 10.7759/cureus.17835, indexed in Pubmed: 34527499.
52. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors Version 2.2023 — March 6, 2023. © National Comprehensive CancerNetwork, Inc. 2023. All rights reserved. Accessed 27 July 2023. To view the most recent and complete version of the guideline, go online to NCCN.org.
53. Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood. 2008; 111(10): 4902–4907, doi: 10.1182/blood-2007-10-116327, indexed in Pubmed: 18216292.
54. Brar SK, Perveen S, Chaudhry MR, et al. Erythropoietin-Induced Hypertension: A Review of Pathogenesis, Treatment, and Role of Blood Viscosity. Cureus. 2021; 13(1): e12804, doi: 10.7759/cureus.12804, indexed in Pubmed: 33628672.
55. Kumar SM, Zhang G, Bastian BC, et al. Erythropoietin and erythropoietin receptor expression in human cancer. Cancer Res. 2001; 61(9): 3561–3565, indexed in Pubmed: 11325818.
56. Wright JR, Ung YC, Julian JA, et al. Randomized, double-blind, placebo-controlled trial of erythropoietin in non-small-cell lung cancer with disease-related anemia. J Clin Oncol. 2007; 25(9): 1027–1032, doi: 10.1200/JCO.2006.07.1514, indexed in Pubmed: 17312332.
57. Leyland-Jones B, Semiglazov V, Pawlicki M, et al. Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. J Clin Oncol. 2005; 23(25): 5960–5972, doi: 10.1200/JCO.2005.06.150, indexed in Pubmed: 16087945.
58. Aapro M, Moebus V, Nitz U, et al. Safety and efficacy outcomes with erythropoiesis-stimulating agents in patients with breast cancer: a meta-analysis. Ann Oncol. 2015; 26(4): 688–695, doi: 10.1093/annonc/mdu579, indexed in Pubmed: 25542926.
59. Vansteenkiste J, Glaspy J, Henry D, et al. Benefits and risks of using erythropoiesis-stimulating agents (ESAs) in lung cancer patients: study-level and patient-level meta-analyses. Lung Cancer. 2012; 76(3): 478–485, doi: 10.1016/j.lungcan.2011.12.015, indexed in Pubmed: 22277104.
60. Glaspy J, Crawford J, Vansteenkiste J, et al. Erythropoiesis-stimulating agents in oncology: a study-level meta-analysis of survival and other safety outcomes. Br J Cancer. 2010; 102(2): 301–315, doi: 10.1038/sj.bjc.6605498, indexed in Pubmed: 20051958.
61. Ludwig H, Crawford J, Osterborg A, et al. Pooled analysis of individual patient-level data from all randomized, double-blind, placebo-controlled trials of darbepoetin alfa in the treatment of patients with chemotherapy-induced anemia. J Clin Oncol. 2009; 27(17): 2838–2847, doi: 10.1200/JCO.2008.19.1130, indexed in Pubmed: 19380447.
62. Gascón P, Nagarkar R, Šmakal M, et al. A Randomized, Double-Blind, Placebo-Controlled, Phase III Noninferiority Study of the Long-Term Safety and Efficacy of Darbepoetin Alfa for Chemotherapy-Induced Anemia in Patients With Advanced NSCLC. J Thorac Oncol. 2020; 15(2): 190–202, doi: 10.1016/j.jtho.2019.10.005, indexed in Pubmed: 31629060.
63. Bastit L, Vandebroek An, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol. 2008; 26(10): 1611–1618, doi: 10.1200/JCO.2006.10.4620, indexed in Pubmed: 18375890.
64. Silva I, Alípio C, Pinto R, et al. Potential anti-inflammatory effect of erythropoietin in non-clinical studies in vivo: A systematic review. Biomed Pharmacother. 2021; 139: 111558, doi: 10.1016/j.biopha.2021.111558, indexed in Pubmed: 33894624.
65. Ludwig H, Aapro M, Bokemeyer C, et al. A European patient record study on diagnosis and treatment of chemotherapy-induced anaemia. Support Care Cancer. 2014; 22(8): 2197–2206, doi: 10.1007/s00520-014-2189-0, indexed in Pubmed: 24659244.
66. Schrijvers D. Management of anemia in cancer patients: transfusions. Oncologist. 2011; 16 Suppl 3: 12–18, doi: 10.1634/theoncologist.2011-S3-12, indexed in Pubmed: 21930830.
67. Chau JKM, Harris JR, Seikaly HR. Transfusion as a predictor of recurrence and survival in head and neck cancer surgery patients. J Otolaryngol Head Neck Surg. 2010; 39(5): 516–522, indexed in Pubmed: 20828514.
68. Anic K, Schmidt MW, Schmidt M, et al. Impact of perioperative red blood cell transfusion, anemia of cancer and global health status on the prognosis of elderly patients with endometrial and ovarian cancer. Front Oncol. 2022; 12: 967421, doi: 10.3389/fonc.2022.967421.
69. Al-Refaie WB, Parsons HM, Markin A, et al. Blood transfusion and cancer surgery outcomes: a continued reason for concern. Surgery. 2012; 152(3): 344–354, doi: 10.1016/j.surg.2012.06.008, indexed in Pubmed: 22938895.
70. Busch OR, Hop WC, Hoynck van Papendrecht MA, et al. Blood transfusions and prognosis in colorectal cancer. N Engl J Med. 1993; 328(19): 1372–1376, doi: 10.1056/NEJM199305133281902, indexed in Pubmed: 8292113.
71. Squires MH, Kooby DA, Poultsides GA, et al. Effect of Perioperative Transfusion on Recurrence and Survival after Gastric Cancer Resection: A 7-Institution Analysis of 765 Patients from the US Gastric Cancer Collaborative. J Am Coll Surg. 2015; 221(3): 767–777, doi: 10.1016/j.jamcollsurg.2015.06.012, indexed in Pubmed: 26228017.
72. Kooby DA, Stockman J, Ben-Porat L, et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Ann Surg. 2003; 237(6): 860–9; discussion 869, doi: 10.1097/01.SLA.0000072371.95588.DA, indexed in Pubmed: 12796583.
73. Khorana AA, Francis CW, Blumberg N, et al. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med. 2008; 168(21): 2377–2381, doi: 10.1001/archinte.168.21.2377, indexed in Pubmed: 19029504.
74. Xenos ES, Vargas HD, Davenport DL. Association of blood transfusion and venous thromboembolism after colorectal cancer resection. Thromb Res. 2012; 129(5): 568–572, doi: 10.1016/j.thromres.2011.07.047, indexed in Pubmed: 21872295.
75. Vamvakas EC, Blajchman MA. Deleterious clinical effects of transfusion-associated immunomodulation: fact or fiction? Blood. 2001; 97(5): 1180–1195, doi: 10.1182/blood.v97.5.1180, indexed in Pubmed: 11222359.
76. Cata JP, Wang H, Gottumukkala V, et al. Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions. Br J Anaesth. 2013; 110(5): 690–701, doi: 10.1093/bja/aet068, indexed in Pubmed: 23599512.
77. Mispelbaum R, Hattenhauer ST, Brossart P, et al. Red blood cell transfusions impact response rates to immunotherapy in patients with solid malignant tumors. Front Immunol. 2022; 13: 976011, doi: 10.3389/fimmu.2022.976011, indexed in Pubmed: 36159812.
78. Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. Cochrane Database Syst Rev. 2021; 12(12): CD002042, doi: 10.1002/14651858.CD002042.pub5.
79. Watkins T, Surowiecka MK, McCullough J. Transfusion indications for patients with cancer. Cancer Control. 2015; 22(1): 38–46, doi: 10.1177/107327481502200106, indexed in Pubmed: 25504277.
80. Scott JM, Weir DG. Drug-induced megaloblastic change. Clin Haematol. 1980; 9(3): 587–606, indexed in Pubmed: 6450011.
81. Danaei G, Vander Hoorn S, Lopez AD, et al. Comparative Risk Assessment collaborating group (Cancers). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005; 366(9499): 1784–1793, doi: 10.1016/S0140-6736(05)67725-2, indexed in Pubmed: 16298215.

82. Dong B, Qi Y, Lin Lu, et al. Which Exercise Approaches Work for Relieving Cancer-Related Fatigue? A Network Meta-analysis. J Orthop Sports Phys Ther. 2023; 0(6): 1–10, doi: 10.2519/jospt.2023.11251, indexed in Pubmed: 36947532.
83. Brown JC, Ma C, Shi Q, et al. Association between physical activity and the time course of cancer recurrence in stage III colon cancer. Br J Sports Med. 2023; 57(15): 965–971, doi: 10.1136/bjsports-2022-106445, indexed in Pubmed: 36878665.
84. Rørth M, Madsen KR, Burmølle SH, et al. Effects of Darbepoetin Alfa with exercise in cancer patients undergoing chemotherapy: an explorative study. Scand J Med Sci Sports. 2011; 21(3): 369–377, doi: 10.1111/j.1600-0838.2009.01066.x, indexed in Pubmed: 20136754.
85. Drouin JS, Young TJ, Beeler J, et al. Random control clinical trial on the effects of aerobic exercise training on erythrocyte levels during radiation treatment for breast cancer. Cancer. 2006; 107(10): 2490–2495, doi: 10.1002/cncr.22267, indexed in Pubmed: 17031805.
86. Mohamady HM, Elsisi HF, Aneis YM. Impact of moderate intensity aerobic exercise on chemotherapy-induced anemia in elderly women with breast cancer: A randomized controlled clinical trial. J Adv Res. 2017; 8(1): 7–12, doi: 10.1016/j.jare.2016.10.005, indexed in Pubmed: 27872759.
87. Ashem HN, Hamada HA, Abbas RL. Effect of aerobic exercise on immunoglobulins and anemia after chemotherapy in breast cancer patients. J Bodyw Mov Ther. 2020; 24(3): 137–140, doi: 10.1016/j.jbmt.2020.01.001, indexed in Pubmed: 32825979.
88. Vadhan-Raj S, Abonour R, Goldman JW, et al. A first-in-human phase 1 study of a hepcidin monoclonal antibody, LY2787106, in cancer-associated anemia. J Hematol Oncol. 2017; 10(1): 73, doi: 10.1186/s13045-017-0427-x, indexed in Pubmed: 28327200.
89. Jeng SS, Chen YH. Association of Zinc with Anemia. Nutrients. 2022; 14(22), doi: 10.3390/nu14224918, indexed in Pubmed: 36432604.
90. Greffeuille V, Fortin S, Gibson R, et al. Associations between Zinc and Hemoglobin Concentrations in Preschool Children and Women of Reproductive Age: An Analysis of Representative Survey Data from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) Project. J Nutr. 2021; 151(5): 1277–1285, doi: 10.1093/jn/nxaa444, indexed in Pubmed: 33693923.