VIA MEDICA

REVIEW ARTICLE

Acta Haematologica Polonica 2021
Number 4, Volume 52, pages 397–401
DOI: 10.5603/AHP.2021.0074
ISSN 0001–5814
e-ISSN 2300–7117

Anemia in cancer patients

Lukasz Bolkun*, Janusz Kloczko

Department of Hematology, Medical University of Bialystok, Poland

Equal contribution by both authors

Abstract

Anemia is a common feature in c.40% of patients at the time of cancer diagnosis and in more than half of patients undergoing anticancer therapy. Cancer-related anemia does have an unfavourable impact on the functional capacity of the relevant tissue and organs. Its pathogenesis is complex and often difficult to identify. Symptoms related to cancer and chemotherapy-induced anemia may have a negative impact on the quality of life and may influence treatment efficacy, disease progression and even survival. Moreover, anemia causing tumor hypoxia leads to tumor progression through the increase of local tumor expansion and spreading of metastases. Tumor hypoxia directly or indirectly confers resistance to irradiation, some chemotherapeutic drugs, and photodynamic therapy. Therapeutic alternatives in cancer patients with anemia include the substitution of the lacking agents, red blood cell (RBC) transfusions, iron supplementation, and erythropoiesis-stimulating agents (ESAs). Using ESAs reduces the need for red blood cell transfusions, decreases the risk of post-transfusion adverse reactions, and improves the quality of life for cancer patients with chemotherapy-induced anemia. The immediate administration of RBC transfusions is justified in patients with hemoglobin (Hb) under 7–8 g/dL and/or severe anemia-related symptoms (even at higher Hb levels) and who require immediate Hb and symptom improvement.

Therefore, clinical evidence supports the need to closely monitor Hb level in cancer patients. Anemia should be corrected to improve chemo- and radiosensitivity and the quality of life.

Key words: anemia, cancer, cancer-related anemia, chemotherapy-induced anemia

Acta Haematologica Polonica 2021; 52, 4: 397–401

Introduction

Anemia is commonly encountered in cancer patients at various stages of disease progression, especially among those who receive active chemotherapy with or without radiotherapy [1]. In a group of patients with cancer, anemia can cause a wide range of signs and symptoms involving organs of the body. Their severity depends on the level of anemia, the speed of its onset, and existing co-morbidities and, above all, the type of cancer. The impact of anemia on survival is connected with a delay in onset of the therapy or failure to complete chemotherapy regimens on time. Furthermore, the cytotoxicity induced by chemotherapy drugs or/and radiotherapy requires adequate oxygen levels in tissue. Since tumor hypoxia boosts tumor resistance to radiation and chemotherapy, it can lead to the lack of tumor response [2, 3].

Multiple studies have suggested that, aside from its important role in QOL issues, anemia constitutes an independent factor of survival in patients with cancers, especially those who received chemotherapy and radiotherapy at the same time [4, 5].

*Address for correspondence: Lukasz Bolkun, Department of Hematology, Medical University of Bialystok, ul. Skłodowskiej-Curie 24A, 15–276 Białystok, Poland, phone +48 85 831 82 30, fax +48 85 831 84 84, e-mail: lukasz.bolkun@umb.edu.pl

Received: 30.04.2021 Accepted: 26.05.2021

Epidemiology of anemia and its definition

In a group of cancer patients, anemia occurs frequently, according to the data, even more than in 40% of cases [1]. In patients who received chemotherapy or/and radiotherapy the incidence of anemia may rise even to 90% of cases [2]. A higher percentage of anemia is observed in some myelo- and lymphoproliferative cancers, e.g. acute leukemias (100%), myelodysplastic syndrome (95%), multiple myeloma (85.3%), Hodgkin lymphoma (66%), and other non-Hodgkin lymphomas (77.9%) [6].

The severity of anemia is defined by the level of hemoglobin (Hb) in the blood <14 g/dL for male population and <12 g/dL for women. It is additionally subdivided into a few types: mild - when the level of Hb is below lower normal range but more than 10 g/dL, moderate - when the level of Hb is between 8–10 g/dL, severe — with Hb level 6.5–8 g/dL and life-threatening — when Hb is below 6.5 g/dL types.

Pathophysiology

Despite the well-established knowledge about the pathophysiology of cancer-induced anemia (CIA), its multifactorial background often makes it difficult to clearly identify the cause of the decrease in hemoglobin concentration in the population of cancer patients [7]. Attempts are being made to systematize the causes of anemia, emphasizing the role of chronic blood loss and the associated iron deficiency, as well as the chronic inflammatory process that implies a reduction in hematopoiesis [8]. In the development of anemia, importance is also attached to excessive destruction of red blood cells, which is caused by the appearance of auto-reactive antibodies [8].

Cancer patients very frequently develop iron deficiency, either absolute or functional. Absolute iron deficiency is caused mainly by bleeding, whereas other underlying factors such as insufficient intestinal iron resorption are usually of minor importance. Moreover, iron homeostasis seems to be associated with coexisting inflammation, and hepcidin, which is a cytokine-induced protein, is of particular importance [9]. Hepcidin, being a key regulator of iron uptake and release, reduces its absorption in the gastrointestinal tract and regulates its metabolism in the bone marrow microenvironment. As a consequence, iron is not used effectively during erythropoiesis, resulting in its impairment.

It should not be forgotten that the neoplastic process itself is often associated with bone marrow infiltration, thus exerting a suppressive effect on hematopoiesis [10]. Moreover, neoplastic cells, demonstrating the ability to secrete cytokines, stimulate macrophage-dependent iron sequestration [10].

Another important cause of anemia, especially in the field of hematooncology, is the development of autoimmune hemolytic anemia (AIHA), most often in the course of chronic lymphocytic leukemia, lymphomas or adenocarcinoma [11]. Moreover, in the course of neoplasms, there are cases of non-immune haemolysis caused by thrombotic microangiopathy (TMA) [11]. It manifests as microangiopathic haemolytic anemia (MAHA), characterized by the absence of increased reticulocytosis (normal reticulocytes <2%) [11].

Finally, selected chemotherapeutic agents, depending on the dose and mechanism of action, induce anemia by impairing myeloid hematopoiesis [12]. No less important in the context of anemia development is the nephrotoxic potential of selected substances, such as platinum salts, which is associated with reduced erythropoietin (EPO) production by renal Epo-producing cells (REPs) [13]. Moreover, commonly used chemotherapy regimens involving cytostatics from various groups are associated with a synergistic effect. Considering that an advanced stage of cancer usually requires more and more intensive chemotherapy, the incidence of anemia increases with each new cycle.

Treatment options

It is necessary that efforts be made to identify the etiology of anemia and that its treatment be directed at the underlying cause. The main purpose of its treatment should aim at improving or resolving the symptoms of anemia, such as fatigue and dyspnea, enabling anticancer therapy and increasing quality of life, especially taking into account a cancer patient's life expectancy. It must be borne in mind that this goal should be achieved with the possible safest methods and least intensive one. What should be treated first are the diagnosed deficiencies (like iron, folic acid or vitamin B_{12}). If their correction does not lead to an increase of hemoglobin, the options of treatment of anemia in cancer patients include iron treatment, a transfusion of packed red blood cells (RBC), and an application of the erythropoiesis-stimulating agents (ESAs). The treatment of cancer anemia or chemotherapy-induced anemia depends on the level of hemoglobin and the severity of its symptoms. Transfusion of red blood cells is the main option for patients who due to the symptoms, which lead to deterioration of comorbidities, need immediate correction of their anemia. In cancer patients who do not need a quick improvement of Hb level, the alternatives include a transfusion, an ESA therapy, and sometimes an iron therapy.

Red blood cell concentrations transfusion

Guidance on the use of red blood cell concentrations in patients with cancers has been recently published as an expert group recommendation [14]. However, RBC transfusions ought not to be used as a universal method to correct anemia in patients with diagnosed cancer They should be restricted to those conditions, in which they constitute the

only effective way to increase the Hb concentration or in which there are indications for quick removal or relief from symptoms related to anemia.

The RBC transfusions, according to the latest recommendation should be given for patients whose hemoglobin level falls under 7–8 g/dL, or in situations when a quick correction of serious, symptomatic anemia is needed [European Society for Medical Oncology (ESMO)]. The choice to use a blood transfusion should never be based solely on the Hb concentration. In patients with symptoms of severe anemia or existing co-morbidities (e.g. ischemic heart disease) and an ongoing or planned chemotherapy or radiotherapy, a red blood cell transfusion should be given even at a higher level of Hb than 8 g/dL. Moreover, available data showed that restrictive transfusion policies for patients with cancer who present anemia, appear to decrease blood utilisation without increasing side effects including morbidity or mortality [15].

Although transfusions offer obvious advantages, they are not risk-free, These risks include some transfusion-related reactions, congestive heart failure, an increased incidence of thromboembolism and bacterial and viral infections, and iron overload [16, 17]. Indeed, iron overload is one of the most common side effects in patients with myelodysplastic syndrome (MDS) who need transfusions over a long period. On the other hand, these problems are rarely seen in a group of patients with solid tumors for whom the transfusion period lasts less than a year [18].

The immune-modulatory effect of blood transfusions in patients with diagnosed cancer is also well described. Large population-based studies and available data from a meta-analysis implied a presence of a link between RBC transfusions and an increased risk of recurrence of malignancy [19, 20].

Because several post-transfusion adverse reactions can occur, including some fatal ones and in most of them the reason is the presence of leukocytes in the blood components, and to limit an adverse reaction, one ought to choose the appropriate red cell concentrate (RCC) for each individual: leukocyte-depleted, irradiated, irradiated leukocyte-depleted, or washed RCC.

Iron treatment

Iron supplementation

The criteria for starting iron supplementation include:

- concentration of hemoglobin between (8 <Hb <10 g/dL);
- absolute iron deficiency (ferritin <100 ng/mL and transferrin saturation <20%);
- relative iron deficiency (ferritin >100 ng/mL and transferrin saturation <20%).

Iron administration should be started before or at the same time as the ESA is started [1]. Iron supplementation is available in both oral and intravenous (i.v.) forms. The clinical studies have shown a significantly faster and higher increase in hemoglobin concentrations in the group of patients receiving ESA who received intravenous iron supplementation than patients receiving iron orally or no iron supplementation at all [21, 22]. On the other hand, i.v. iron boasts the superiority of bypassing the intestinal hepcidin-ferroportin pathway that regulates iron absorption. Additionally, i.v. iron leads to a faster rise of Hb concentration and ensures better and more effective replenishment of iron storage in the body. A randomized investigation demonstrated no negative influence of i.v. iron treatment when given to patients with diagnosed lymphoid malignancies or patients after autologous hematopoietic stem cell transplantations [23]. However, intravenous iron is not recommended to be given to patients who present an active infection. It is recommended that injection of iron is not administered simultaneously with cardiotoxic chemotherapy (anthracyclines, alkylating drugs and vinca alkaloids) [14].

Erythropoietin-stimulating agents treatment

Erythropoietin-stimulating agents (ESA) are biological analogues of human erythropoietin (EPO). Currently on the market, erythopoietin with a short (alpha, beta, theta, zeta) and long (darbepoetin) duration of action is available. Epoetin has the same acid sequence as EPO. Darbepoetin has an additional oligosaccharide, which results in a longer half-life [24]. The use of ESA aims to reduce the number of blood units transfused and thus reduces the possible risk of side effect reaction, improves fatigue-related symptoms and QOL with chemotherapy-induced anemia. ESA therapy might be considered as an option in the case of asymptomatic patients who can deteriorate to more severe anemia [25, 26]. Several clinical data and meta-analyses have reported that ESAs treatment results in a meaningfully significant betterment of the quality of life (QoL) and fatigue-related symptoms [27]. It is worth mentioning that ESA, differently from RBC concentrates, has a beneficial impact on the immune system. It was also found that ESA reduces the expression of numerous pro-inflammatory cytokine genes [interleukin (IL)-1B, IL-6, IL-10, tumor necrosis factor-alpha], contributes to lowering the concentration of IL-1α and IL-6, and by influencing the immune system, it causes a decrease in the number of suppressive cells like (CD8+CD152+) [28–30].

ESA is recommended to use for a patient with non-myeloid malignancies including lymphomas and multiple myelomas with chemotherapy-induced anemia (CIA). Moreover, in compliance with the ESMO, the use of ESAs are recommended in the case of patients with the diagnosed myelodysplastic syndrome but only those with the lower-risk myelodysplastic syndromes, whose serum erythropoietin

level is below 500 U/L and who have a normal level of blastic cells [31]. In patients who progress to acute myeloid leukiemia (AML), ESAs should not be used. Iron replacement (i.v.) can be applied with a view to improving Hb response and reducing RBC transfusions for patients receiving ESA with or without iron deficiency. The inclusion of ESA in treatment is considered in patients with anemia during or after chemotherapy when the Hb level is <10 g/dL, and the target value is 12 g/dL. The effectiveness of ESA is demonstrated by the increase in Hb concentration by 1–2 g/dL after 4 weeks of using the drug. Treatment with ESA should not be extended beyond 6–8 weeks when there is no desired Hb increase.

It is necessary that clinicians weigh the possible complications and advantages of ESA treatment and always inform about the possible side effects of applied therapy to the patient [25, 26]. ESA in patients with a history of hypersensitivity to the drug and hypertension that is not under control, is not approved. In recent years, however, there have been many concerns about the use of ESA and its likely impact on mortality, thrombotic complications and possible impact on tumor progression. Indeed, despite the significant benefits of ESAs for CIA, few randomized clinical investigations and meta-analyses have shown the risk of thromboembolic complications to be comparatively lower in patients treated with ESAs compared to the placebo groups [27, 32]. Various meta-analyses that have assessed deadliness and thromboembolic complications may have been prejudiced because they included clinical reports where ESAs were used even when the level of hemoglobin was above 12 g/dL [24, 33, 34]. Furthermore, according to the available reports, no significant data is confirming, that the use of ESA, significantly further increase the risk of thromboembolic complications in a group of patients who are treated with thalidomide or lenalidomide [35, 36].

Conclusion

Over the past decade, understanding has expanded of many aspects of the pathophysiology of anemia in cancers. Nevertheless, a lot remains to be elucidated including the role of iron supplementation, some possible complications after the use of ESA, as well as, transfusion-related side effects.

Authors' contributions

JK wrote the first version of the manuscript, LB corrected the manuscript, linguistic correction

Conflict of interest

None.

Financial support

None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

References

1. Abdel-Razeq H, Hashem H. Recent update in the pathogenesis and treatment of chemotherapy and cancer induced anemia. Crit Rev Oncol Hematol. 2020; 145: 102837, doi: 10.1016/j.critrevonc.2019.102837, indexed in Pubmed: 31830663.
2. Wu HM, Jiang ZF, Ding PS, et al. Hypoxia-induced autophagy mediates cisplatin resistance in lung cancer cells. Sci Rep. 2015; 5: 12291, doi: 10.1038/srep12291, indexed in Pubmed: 26201611.
3. Harrison L, Blackwell K. Hypoxia and anemia: factors in decreased sensitivity to radiation therapy and chemotherapy? Oncologist. 2004; 9 Suppl 5: 31–40, doi: 10.1634/theoncologist.9-90005-31, indexed in Pubmed: 15591420.
4. Shrivastava S, Mahantshetty U, Engineer R, et al. Gynecologic Disease Management Group. Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: a randomized clinical trial. JAMA Oncol. 2018; 4(4): 506–513, doi: 10.1001/jamaoncol.2017.5179, indexed in Pubmed: 29423520.
5. Dubray B, Mosseri V, Brunin F, et al. Anemia is associated with lower local-regional control and survival after radiation therapy for head and neck cancer: a prospective study. Radiology. 1996; 201(2): 553–558, doi: 10.1148/radiology.201.2.8888257, indexed in Pubmed: 8888257.
6. Yasmeen T, Ali J, Khan K, et al. Frequency and causes of anemia in Lymphoma patients. Pak J Med Sci. 2019; 35(1): 61–65, doi: 10.12669/pjms.35.1.91, indexed in Pubmed: 30881397.
7. Schwartz RN. Anemia in patients with cancer: incidence, causes, impact, management, and use of treatment guidelines and protocols. Am J Health Syst Pharm. 2007; 64(3 Suppl 2): S5–13; quiz S28, doi: 10.2146/ajhp060601, indexed in Pubmed: 17244886.
8. Adamson JW. The anemia of inflammation/malignancy: mechanisms and management. Hematology Am Soc Hematol Educ Program. 2008: 159–165, doi: 10.1182/asheducation-2008.1.159, indexed in Pubmed: 19074075.
9. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med. 2005; 352(10): 1011–1023, doi: 10.1056/NEJMra041809, indexed in Pubmed: 15758012.
10. Walkley CR. Erythropoiesis, anemia and the bone marrow microenvironment. Int J Hematol. 2011; 93(1): 10–13, doi: 10.1007/s12185-010-0759-6, indexed in Pubmed: 21222184.
11. Troppan KT, Melchardt T, Deutsch A, et al. The significance of pretreatment anemia in the era of R-IPI and NCCN-IPI prognostic risk assessment tools: a dual-center study in diffuse large B-cell lymphoma patients. Eur J Haematol. 2015; 95(6): 538–544, doi: 10.1111/ejh.12529, indexed in Pubmed: 25677782.
12. Wilson J, Yao GL, Raftery J, et al. A systematic review and economic evaluation of epoetin alpha, epoetin beta and darbepoetin alpha in anaemia associated with cancer, especially that attributable to cancer treatment. Health Technol Assess. 2007; 11(13): 1–202, iii, doi: 10.3310/hta11130, indexed in Pubmed: 17408534.

13. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst. 1999; 91(19): 1616–1634, doi: 10.1093/jnci/91.19.1616, indexed in Pubmed: 10511589.
14. Radziwon P, Krzakowski M, Kalinka-Warzocha E, et al. Anaemia in cancer patients — Expert Group recommendations. Oncol Clin Pract. 2017; 13(5): 202–10.
15. Prescott LS, Taylor JS, Lopez-Olivo MA, et al. How low should we go: a systematic review and meta-analysis of the impact of restrictive red blood cell transfusion strategies in oncology. Cancer Treat Rev. 2016; 46: 1–8.
16. Thomas P, Michelet P, Barlesi F, et al. Impact of blood transfusions on outcome after pneumonectomy for thoracic malignancies. Eur Respir J. 2007; 29(3): 565–570, doi: 10.1183/09031936.00059506, indexed in Pubmed: 17079259.
17. 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.
18. Jabbour E, Kantarjian HM, Koller C, et al. Red blood cell transfusions and iron overload in the treatment of patients with myelodysplastic syndromes. Cancer. 2008; 112(5): 1089–1095, doi: 10.1002/cncr.23280, indexed in Pubmed: 18186499.
19. 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.
20. Halabi WJ, Jafari MD, Nguyen VQ, et al. Blood transfusions in colorectal cancer surgery: incidence, outcomes, and predictive factors: an American College of Surgeons National Surgical Quality Improvement Program analysis. Am J Surg. 2013; 206(6): 1024–32; discussion 1032, doi: 10.1016/j.amjsurg.2013.10.001, indexed in Pubmed: 24296103.
21. Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist. 2007; 12(2): 231–242, doi: 10.1634/theoncologist.12-2-231, indexed in Pubmed: 17296819.
22. Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multicenter study. Leukemia. 2007; 21(4): 627–632, doi: 10.1038/sj.leu.2404562, indexed in Pubmed: 17252006.
23. Jaspers A, Baron F, Maertens J, et al. Long-term safety follow-up of a randomized trial of darbepoetin alpha and intravenous iron following autologous hematopoietic cell transplantation. Am J Hematol. 2015; 90(7): E133–E134, doi: 10.1002/ajh.24013, indexed in Pubmed: 25802012.
24. Bohlius J, Wilson J, Seidenfeld J, et al. Recombinant human erythropoietins and cancer patients: updated meta-analysis of 57 studies including 9353 patients. J Natl Cancer Inst. 2006; 98(10): 708–714, doi: 10.1093/jnci/djj189, indexed in Pubmed: 16705125.
25. Rodgers GM, Becker PS, Blinder M, et al. National Comprehensive Cancer Network. Cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw. 2008; 6(6): 536–564, doi: 10.6004/jnccn.2008.0042, indexed in Pubmed: 18597709.
26. Scrijvers D, Roila F. ESMO Guidelines Working Group. Erythropoiesis-stimulating agents in cancer patients: ESMO recommendations for use. Ann Oncol. 2009; 20 Suppl 4: 159–161, doi: 10.1093/annonc/mdp161, indexed in Pubmed: 19454443.
27. Tonia T, Mettler A, Robert N, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev. 2012; 12: CD003407, doi: 10.1002/14651858.CD003407.pub5, indexed in Pubmed: 23235597.
28. Zhang J, Zou YR, Zhong X, et al. Erythropoietin pretreatment ameliorates renal ischaemia-reperfusion injury by activating PI3K/Akt signalling. Nephrology (Carlton). 2015; 20(4): 266–272, doi: 10.1111/nep.12384, indexed in Pubmed: 25581532.
29. Rong R, Xijun X. Erythropoietin pretreatment suppresses inflammation by activating the PI3K/Akt signaling pathway in myocardial ischemia-reperfusion injury. Exp Ther Med. 2015; 10(2): 413–418, doi: 10.3892/etm.2015.2534, indexed in Pubmed: 26622330.
30. Li J, Xu J, Yan X, et al. Targeting Interleukin-6 (IL-6) Sensitizes Anti-PD-L1 Treatment in a Colorectal Cancer Preclinical Model. Med Sci Monit. 2018; 24: 5501–5508, doi: 10.12659/MSM.907439, indexed in Pubmed: 30087314.
31. Fenaux P, Haase D, Santini V, et al. ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021; 32(2): 142–156, doi: 10.1016/j.annonc.2020.11.002, indexed in Pubmed: 33221366.
32. 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.
33. 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.
34. Tonelli M, Hemmelgarn B, Reiman T, et al. Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. CMAJ. 2009; 180(11): E62–E71, doi: 10.1503/cmaj.090470, indexed in Pubmed: 19407261.
35. Galli M, Elice F, Crippa C, et al. Recombinant human erythropoietin and the risk of thrombosis in patients receiving thalidomide for multiple myeloma. Haematologica. 2004; 89(9): 1141–1142, indexed in Pubmed: 15377478.
36. Knight R, DeLap RJ, Zeldis JB. Lenalidomide and venous thrombosis in multiple myeloma. N Engl J Med. 2006; 354(19): 2079–2080, doi: 10.1056/NEJMc053530, indexed in Pubmed: 16687729.