IJBC 2018; 10(1): 9-15

Iranian Journal of Blood & Cancer

Journal Home Page: www.ijbc.ir

ORIGINAL ARTICLE

Recombinant Human Erythropoietin in Children with Solid Tumors and Chemotherapy-induced Anemia

Amir Ataollah Hiradfar[1], Azim Rezamand[2], Matin Pourghasem[1], Sepideh Karkon Shayan[3], Behnaz Ghamari[4], Farid Karkon Shayan[5*]

[1]Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Pediatrics, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Students' Research Committee, Gonabad University of Medical Science, Gonabad, Iran
[4]Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Medical Philosophy and History Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Article History:
Received: 06.08.2017
Accepted: 11.11.2017

Keywords:
Human recombinant erythropoietin
Anemia
Chemotherapy-induced anemia
Solid tumor
Children
Blood transfusion

**Corresponding author:*
Farid Karkon Shayan, MD;
Medical Philosophy and History Research Center,
Tabriz University of Medical Sciences,
Tabriz, Iran
Tel: +98 914 1064017
Email: faridkarkonshayan@yahoo.com

ABSTRACT

Background: In patients undergoing chemotherapy for cancer, anemia is part of the progression of the disease. Considering the effects of anemia on quality of life of the patients, the prevention and treatment of chemotherapy-induced anemia is crucial. This study was aimed to evaluate the efficacy of recombinant human erythropoietin in reducing the need for blood transfusion in children with solid tumors receiving chemotherapy.

Methods: In a clinical trial, 57 children referred to the pediatric centre of Tabriz University of Medical Sciences with a diagnosis of solid tumor were randomly assigned into two groups. The intervention group (n=29) received recombinant human erythropoietin (rHuEPO) at a dose of 450 IU/kg subcutaneously once a week for 12 weeks, and the control group (n=28) received no intervention in this regard. Hemoglobin levels were analysed at the beginning and end of the study. The need for blood transfusion was also assessed in the patients.

Results: The mean Hb at the beginning of the study was 8.85±1.01 and 8.98±0.11 g in the intervention and control groups, respectively. The mean Hb at the end of the study was 9.78±0.32 g/dl in the intervention group and 7.79±0.24 g/dl in the control group. Hb level was significantly higher in the intervention group at the end of the 12 weeks of treatment with rHuEPO than in the control group (P=0.001).

Conclusion: Based on the results of this study, rHuEPO administration seems to be beneficial in the prevention and treatment of chemotherapy-induced anemia in children with solid tumors and reduces the amount of blood transfusion in these patients.

Please cite this article as: Ataollah Hiradfar A, Rezamand A, Pourghasem M, Karkon Shayan S, Ghamari B, Karkon Shayan F. Recombinant Human Erythropoietin in Children with Solid Tumors and Chemotherapy-induced Anemia. IJBC 2018; 10(1): 9-15.

Introduction

Chemotherapy-induced anemia is a common problem in children with cancer.[1, 2] It has been shown that chemotherapy directly targets hematopoiesis by affecting the precursor cells of the red blood cells in the marrow. Also, the nephrotoxic effects of cytotoxic agents can reduce the renal production of erythropoietin.[3, 4]

Blood transfusion is one of the most commonly used measures for cancer-related severe anemia. Although blood transfusions are the fastest way to reduce the symptoms of anemia, they are associated with short and long-term risks, such as infection, alloimmunization reactions and other blood transfusion reactions.[5] Thus, alternative strategies have been developed to overcome chemotherapy-induced anemia.[6] Human recombinant erythropoietin (rHuEPO), as the prototype of the

hematopoietic stimulants, was first developed in the 1980s and was among the first recombinant human proteins used in clinics for cancer treatment.[1] Decreased fatigue and improved quality of life were also reported at first with the treatment of anemia with rHuEPO in patients undergoing chemotherapy. However, the clinical significance of these symptoms has repeatedly been doubted.[1, 7]

Studies show that rHuEPO reduces the need for blood transfusion in patients and also improves their quality of life.[8, 9] However, some of the recent clinical trials conducted since 2003 have reported some complications associated with rHuEPO treatment including increased risk of tumor progression, vascular thrombotic events and death. Accordingly, there has been a limitation to minimize the potential damage following the use of rHuEPO.[1, 10, 11]

It is important to note that the main mechanism of anemia in cancer is the production of inflammatory cytokines which decrease both the production of erythropoietin and reduce hematopoiesis, and lead to a relative or absolute lack of iron. Therefore, the American Society for Clinical Oncology (ASCO) has updated its therapeutic guidelines and have proposed the use of Erythropoiesis-Stimulating Agents only in chemotherapy-induced anemia when the hemoglobin level is less than 10 g/dL.[2, 12]

Several studies have shown the usefulness of subcutaneous erythropoietin administration in divided doses every one or two days. Also, recent evidence shows that subcutaneous administration of rHuEPO in a single weekly dose has not been associated with significant adverse drug reaction and has been able to reduce the need for blood transfusion in children.[13, 14] Considering the importance of anemia in children undergoing chemotherapy and the relatively satisfactory results of rHuEPO, this study was aimed to evaluate the utility of this medication at a dose of 450 units/kg of body weight subcutaneously once a week in anemic children who are under chemotherapy for solid tumors.

Materials and Methods

This study was a randomised one-way blinded clinical trial (RCT) performed at Children Hospital of Tabriz University of Medical Sciences (TUOMS), between March 2015 and February 2016. We registered this study at Iranian clinical trial with code of IRCT2015061822805N1 and the regional ethics committee of TUOMS, Iran approved it under TBZMED.REC.1394.165 code.

60 children diagnosed with solid tumor admitted to the pediatric hospital of TUOMS were enrolled. None of the patients had bone marrow infiltration by the tumoral cells. Then, we randomly assigned the patients to two control and intervention groups using randomly permuted block method via an online software at http://www.stat.ubc.ca/~rollin/stats /ssize.

Inclusion criteria for this study were: 1. Age of less than fifteen years at the time of enrollment, 2. Hemoglobin level less than 10 gr/dl upon enrollment, 3. A pathological diagnosis of a solid tumor with chemotherapy-induced anaemia, 4. No bone marrow involvement, 5. Normal lung, liver and kidney function upon enrollemnt, 6. Normal blood parameters for reticulocyte count, serum ferritin, serum vitamin B12 level and arterial blood gas along with negative direct and indirect Coombs test, 7. No history of transfusion in recent months, and 8. No history of receiving erythropoietin.

We excluded every patient with severe bleeding or hemolysis, or those with evidence of impaired renal, liver, and lung function during the study. The patients who experienced severe complications due to erythropoietin, including thrombosis, polycythemia and elevated systemic blood pressure were also excluded from the study. We also excluded the patients who declined to participate in the study.

We included 60 children with solid tumours admitted to the Children Hospital of TUOMS for chemotherapy and randomly divided them into intervention and control groups (n=30 each group). One patient was excluded from the intervention group due to hypertension and two children; one due to hemolysis and one due to renal failure were excluded from the control group. Finally, 29 patients in the intervention group and 28 in the control group entered the study (Figure 1).

Both groups received the scheduled protocol along with granulocytic growth factor (G-CSF). In the intervention group, patients received rHuEPO at a dose of 450 IU/kg subcutaneously once a week for 12 weeks. The control group received only the chemotherapy protocol without rHuEPO. In the present study, the minimum acceptable haemoglobin level in both groups was considered as 7 gr/dl and for the values less than that, blood transfusion was administered.

Ethical Considerations

This study was in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. We explained the aim of the study, the potential benefits and complications of rHuEPO (according to previous studies, side effects were not likely to occur) to the parents of the patients and patients themselves and stated that all information would be kept confidential and their personal information would not be mentioned anywhere. We also obtained the written informed consent from the parents.

There was no additional intervention except the administration of rHuEPO in the intervention group. The cost of drugs in the study was provided by the project implementer and supported by the vice chancellor of TUOMS.

The obtained data were expressed as the mean±standard deviation (SD), frequency and percentage. We applied linear regression method to determine the relationship between data and Kolmogorov-Smirnov test to check the normal distribution of data. Finally, for comparing the qualitative variables, the chi-square test was used, and the independent t-test was used to compare the quantitative variables. $P<0.05$ was considered to be statistically significant in all comparisons.

Results

The mean±SD ages of the children in the control and

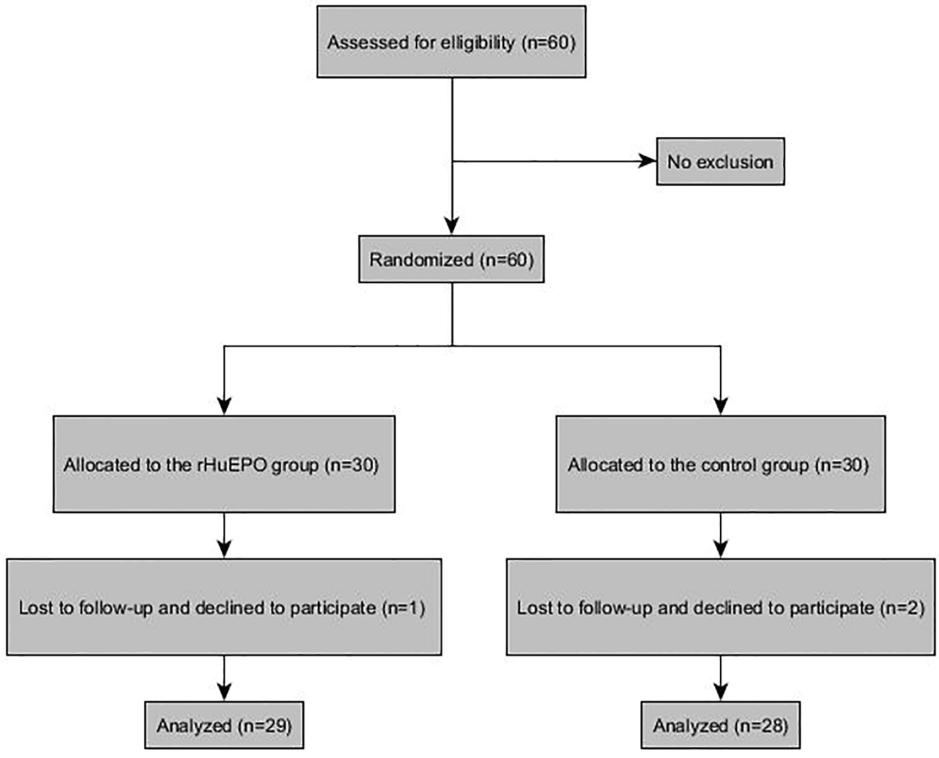

Figure 1: CONSORT statement diagram of the study.

intervention groups were 6.11±0.83 and 6.43±0.83 years, respectively with no significant statistical difference. In the control group, 13 patients (46.4%) were men and in the intervention group, 17 (58.6%) patients were men. There was no significant difference in the gender of the patients in the two groups (P=0.360). The mean hospitalization days in the intervention and control group were 22.6±4.23 and 20.7±4.56, respectively (P=0.080).

Table 1 represents the frequency of the patients based on the type of the malignancy in the two groups. We showed that there was no difference between the two groups regarding their malignancy (P=0.990).

Mean haemoglobin levels in the intervention and control group at the beginning of the study were 8.85±1.01 g/dl, and 8.98±0.11 g/dl, respectively. There was no significant difference in the haemoglobin levels at the beginning of the study between the two groups (P=0.390). In the intervention group, 11 (37.9%) patients received cisplatin-based regimen and in the control group, 14 (50.0%) children received such a regimen. There was no significant difference regarding receiving a cisplatin-based regimen between the two groups (P=0.360). During the study, in the 24 (82.8%) patients in the intervention group and 22 (78.6%) patients in the control group received G-CSF. There was no significant difference between the two groups regarding receiving G-CSF (P=0.690).

The mean received blood volume in the intervention and control group was 2.52±1.11 and 8.43±1.67 cc/kg, respectively. Also, the number of blood recipients in the intervention group was 6 (20.7%), whereas in control group was 14 (50.0%). The two groups had a statistically significant difference in the volume of blood and the number of blood recipients (P=0.020). Mean number of blood transfusions in the intervention group and control groups were 6.60±0.08 and 6.60±0.06, respectively which the difference was not statistically significant (P=0.900). In general, the number of blood recipients and also the volume of the transfused blood was significantly lower in the intervention group than the control group (P=0.020).

The hemoglobin level of the patients at the end of the study (end of the 12th week) in the intervention and control groups was 9.38±0.38 and 7.79±0.24 g/dl, respectively.

Table 1: Frequency of the malignancies.

Malignancy	Total number	Intervention group	Control group	Malignancy	Total number	Intervention group	Control group
Non-Hodgkin's lymphoma	7 (12.2%)	4 (13.7%)	3 (10.7%)	Hodgkin's lymphoma	6 (10.5%)	3 (10.3%)	3 (10.7%)
Ependymoma	2 (3.5%)	1 (3.4%)	1 (3.5%)	Medulloblastoma	3 (5.2%)	1 (3.4%)	2 (7.1%)
Neuroblastoma	8 (14%)	4 (13.7%)	4 (14.2%)	Rhabdomyosarcoma	5 (8.7%)	2 (6.8%)	3 (10.7%)
Ewing's sarcoma	4 (7%)	2 (6.7%)	2 (7.1%)	Osteosarcoma	3 (5.2%)	1 (3.4%)	2 (7.1%)
Synovial sarcoma	0 (0%)	0 (0%)	0 (0%)	Fibrosarcoma	2 (3.5%)	1 (3.4%)	1 (3.5%)
Yok sac tumor	4 (7%)	2 (6.7%)	2 (7.1%)	Germinoma	1 (1.7%)	1 (3.4%)	0 (0%)
Hepatoblastoma	3 (5.2%)	2 (3.8%)	1 (3.5%)	Wilm's tumor	7 (10.5%)	4 (13.7%)	3 (10.7%)
Glioblastoma	1 (1.7%)	0 (0%)	1 (3.5%)	Nasopharyngeal carcinoma	1 (1.7%)	1 (3.4%)	0 (0%)

The hemoglobin levels in the intervention group were significantly higher than those in the control group at the end of the study (P=0.001).

The mean hemoglobin changes during the study period were +0.92±0.33 g/dl in the intervention and -1.19±0.26 g/dl in the control group. In the intervention group, the mean hemoglobin level increased during the study and in the control group, the mean hemoglobin level decreased during the study and this difference was statistically significant (P=0.001). Table 2 and Figures 2 and 3 show the comparison of changes in the hemoglobin among the patients.

In the intervention group, 11 patients (37.9%) and among all patients, 25 (43.8%) patients received cisplatin-based chemotherapy regimen which had haemoglobin changes based on the following tables (Tables 3 and 4). According to Tables 3 and 4, hemoglobin levels in patients receiving cisplatin-containing regimen at the end of the study were lower than those who did not receive cisplatin, but this difference was not statistically significant.

Side effects observed in the intervention group due to rHuEPO were as follows (Table 5). One patient developed

Table 2: The comparison of the changes in the hemoglobin values in the studied groups.

Time period / Group	Beginning of the study	End of the study	P value
Intervention	8.85±1.01	9.78±0.32	P=0.009
Control	8.98±0.11	7.79±0.24	P=0.001

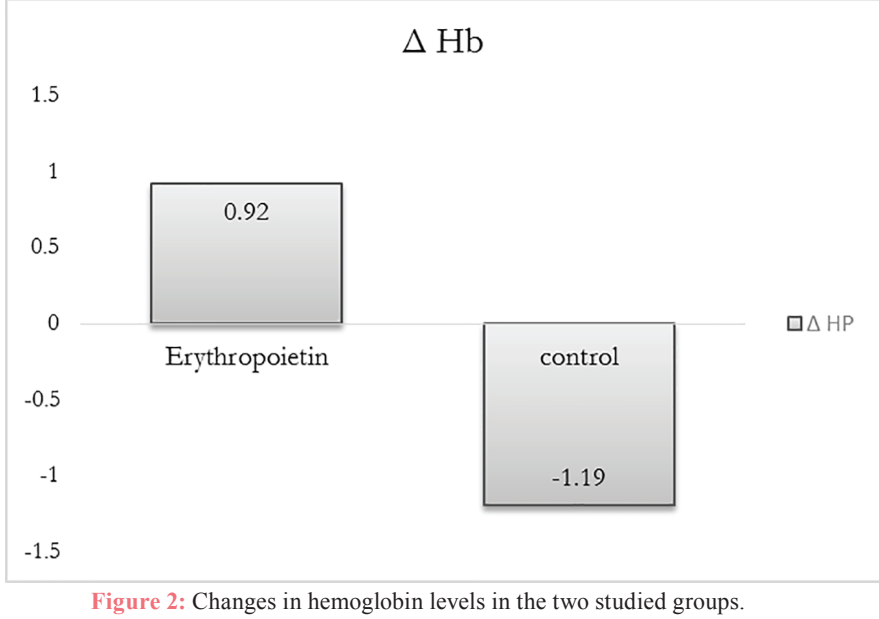

Figure 2: Changes in hemoglobin levels in the two studied groups.

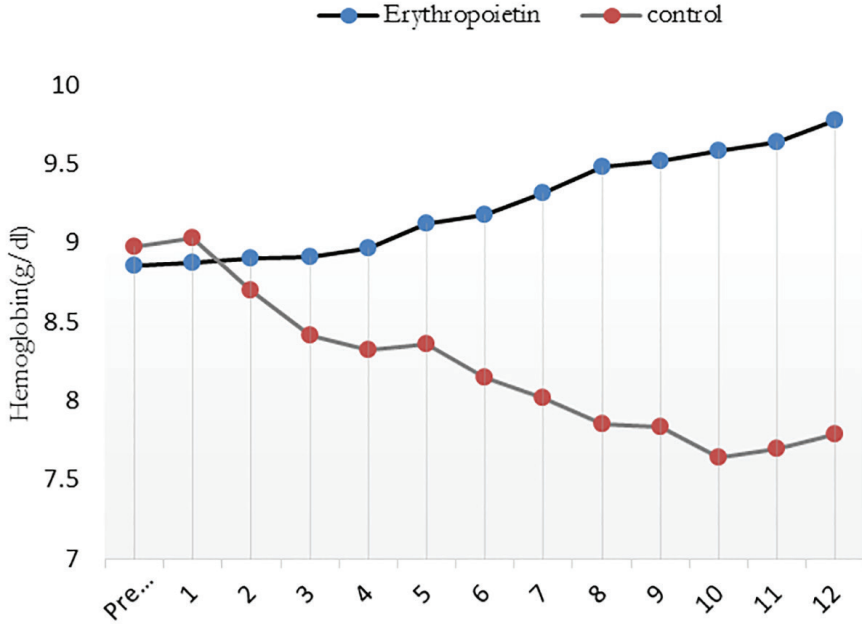

Figure 3: Hemoglobin changes during the study.

Table 3: Comparison of the level of hemoglobin in the intervention group in terms of receiving cisplatin containing regimen.

Regimen / Time	Regimen without cisplatin (hemoglobin level)	Cisplatin-based regimen (hemoglobin level)	P value
Beginning of the study	8.83±0.11	8.89±0.21	P=0.950
End of the study	10.03±0.38	9.36±0.56	P=0.160
Hemoglobin changes	+0.47±0.63	+1.20±0.36	P=0.240

Table 4: Comparison of the level of hemoglobin in the control group in terms of receiving cisplatin containing regimen.

Regimen / Time	Regimen without cisplatin (hemoglobin level)	Cisplatin-based regimen (hemoglobin level)	P value
Beginning of the study	0.09±8.89	0.12±8.97	P=0.950
End of the study	0.32±9.08	0.35±8.46	P=0.160
Hemoglobin changes	0.33±0.20 +	0.38±0.52 -	P=0.240

Table 5: Side effects of rHuEPO in the intervention group.

Time / Side effect	1st-4th weeks	5th-8th weeeks	9th-12th weeks	Total
Vomiting	5	3	6	14 (48.2%)
Fever	2	4	2	8 (48.2%)
Bone pain	1	3	2	6 (20.6%)
Flu-like syndrome	1	2	1	4 (13.7%)
Flushing	1	0	1	2 (6.8%)
Hypertension	1	0	0	1 (3.4%)
Total	11	12	12	35

hypertension due to rHuEPO who was excluded from the study.

Discussion

In cancer patients, anaemia is part of the progression of the disease. Cancer-induced anaemia is associated with the release of large amounts of cytokines, including interleukin 1, tumour necrosis factor, and interferons.[15] These immune modulatory peptides interfere with the function of the internal erythropoietin and prevent the production of erythroid cells in the bone marrow.[16] On the other hand, myelosuppressive chemotherapy can, in turn, aggravate the progression of anaemia in cancer patients.[17] Anemia causes fatigue, lethargy, dyspnea and cardiovascular symptoms such as reduced ability to perform physical activity in the patients.[18]

Patients with chemotherapy-induced anaemia may need to receive blood transfusion. Complications due to blood transfusion such as transmission of infections and immunologic responses are relatively rare, but if they occur result in serious comorbidities.[19] rHuEPO is used as an accessible and standard medication for the treatment of anaemia associated with renal failure. Studies have shown that rHuEPO can be used to control and treat the anemia associated with chronic diseases and also chemotherapy-induced anaemia, as a result it could reduce the need for blood transfusion in many patients.[20-23]

The results of this study showed that rHuEPO increases the level of hemoglobin and also reduces the need for blood transfusion in anemic patients with solid tumour who receive chemotherapy. Available data support that rHuEPO can be used in the treatment of chemotherapy-induced anemia in cancer patients independent of the type of the tumor and also prevents hemoglobin decline and reduces the need for blood transfusion.[1, 2, 24]

There was not a significant difference in the mean hemoglobin level between cisplatin recipients and non-recipients among intervention group and also when analysing all patients together. Contrary to the results of the present study, Oberhoff et al. stated that patients receiving cisplatin-based chemotherapy (75 mg/m^2/cycle) had a two-fold higher need for blood transfusion. Also, they found that the need for blood transfusion decreased in patients who received rHuEPO (15.3% vs 33.3%, P=0.019), and the patients had significantly lower frequency of anemia (16.6 % vs 45.8%, P=0.001). They concluded that rHuEPO with a dose of 10,000 units, three times a week reduced the need for blood transfusion and prevented significant anemia in patients with solid tumors.[18] In line with that study, the blood transfusion rate in rHuEPO recipients was significantly lower than the control group in our study.

Tzekova et al. assessed the safety and efficacy of subcutaneous injection of Epoetin zeta in 216 patients with solid tumors or non-myeloid leukemia at risk for transfusion. The results of this study showed a significant increase in the mean hemoglobin level (1.8 g/dl) after 12 weeks of treatment. Response to treatment (increased hemoglobin levels equal or higher than 1 g/dl or reticulocyte count of 40,000 cells per microliter) and improved quality of life were observed during the eight weeks of the study.[25]

Weigang-KöhlerK.a et al. evaluated the effects of treatment with Epoetin-α (HX575) at 150 IU/kg/dose, 3 times a week for 12 weeks or 300 IU/kg, three times a week if hemoglobin levels or reticulocyte counts

were not increased after 4 or 8 weeks of treatment in chemotherapy-induced patients with anemia. According to the results of this study, the mean hemoglobin level increased by 62% in 37 patients. They found that HX575 is effective in treating chemotherapy-induced anemia in patients with solid tumors.[26] In a study by Wauters et al. the authors showed that despite improvement in hemoglobin levels and reduction in frequency and amount of blood transfusion, the quality of life of patients with solid tumors under chemotherapy did not improve with Epoetin-α administration.[27]

Conclusion

We showed that rHuEPO increased hemoglobin level and reduced the need for blood transfusion in anemic children with solid tumors receiving chemotherapy. There were also no significant side effects with the use of rHuEPO. Therefore, rHuEPO can be suggested to effectively prevent and treat anemia caused by chemotherapy in children with solid tumors. On the one hand, the existence of some contradictory results on this subject signifies the need for further studies in this field for better decision making.

Acknowledgment

We are grateful to all our patinets for their patience and contribution to this study. This paper is based on Matin Pourghasem's specialty dissertation submitted to the Pediatric Health Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.

Conflict of Interest: None declared.

References

1. McKinney M, Arcasoy MO. Erythropoietin for oncology supportive care. Exp Cell Res. 2011;317(9):1246-54. doi: 10.1016/j.yexcr.2011.03.003. PubMed PMID: 21396935.
2. Spielmann M, Luporsi E, Ray-Coquard I, de Botton S, Azria D, Lasocki S, et al. Diagnosis and management of anaemia and iron deficiency in patients with haematological malignancies or solid tumours in France in 2009-2010: the AnemOnHe study. Eur J Cancer. 2012;48(1):101-7. doi: 10.1016/j.ejca.2011.09.011. PubMed PMID: 22044579.
3. Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock 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-iv. PubMed PMID: 17408534.
4. Rodgers GM, 3rd, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, et al. Cancer- and chemotherapy-induced anemia. J Natl Compr Canc Netw. 2012;10(5):628-53. PubMed PMID: 22570293.
5. Goodnough LT. Risks of blood transfusion. Crit Care Med. 2003;31(12 Suppl):S678-86. doi: 10.1097/01.ccm.0000100124.50579.d9. PubMed PMID: 14724466.
6. Spahn DR, Goodnough LT. Alternatives to blood transfusion. Lancet. 2013;381(9880):1855-65. doi: 10.1016/s0140-6736(13)60808-9. PubMed PMID: 23706802.
7. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. Semin Oncol. 1998;25(3 Suppl 7):43-6. PubMed PMID: 9671330.
8. Corwin HL. Anemia and blood transfusion in the critically ill patient: role of erythropoietin. Crit Care. 2004;8 Suppl 2:S42-4. doi: 10.1186/cc2411. PubMed PMID: 15196323; PubMed Central PMCID: PMCPMC3226146.
9. Rosti G, Petrini M, Bosi A, Galieni P, Bernardi D, Giglio G, et al. Management of anaemia in oncohaematological patients treated with biosimilar epoetin alfa: results of an Italian observational, retrospective study. Ther Adv Med Oncol. 2017;9(1):22-32. doi: 10.1177/1758834016670554. PubMed PMID: 28203295; PubMed Central PMCID: PMCPMC5298451.
10. Ribatti D. Erythropoietin and tumor angiogenesis. Stem Cells Dev. 2010;19(1):1-4. doi: 10.1089/scd.2009.0402. PubMed PMID: 19886790.
11. Wun T, Law L, Harvey D, Sieracki B, Scudder SA, Ryu JK. Increased incidence of symptomatic venous thrombosis in patients with cervical carcinoma treated with concurrent chemotherapy, radiation, and erythropoietin. Cancer. 2003;98(7):1514-20. doi: 10.1002/cncr.11700. PubMed PMID: 14508840.
12. Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63-74. PubMed PMID: 9095563.
13. Razzouk BI, Hord JD, Hockenberry M, Hinds PS, Feusner J, Williams D, et al. Double-blind, placebo-controlled study of quality of life, hematologic end points, and safety of weekly epoetin alfa in children with cancer receiving myelosuppressive chemotherapy. J Clin Oncol. 2006;24(22):3583-9. doi: 10.1200/jco.2005.03.4371. PubMed PMID: 16877725.
14. Abdelrazik N, Fouda M. Once weekly recombinant human erythropoietin treatment for cancer-induced anemia in children with acute lymphoblastic leukemia receiving maintenance chemotherapy: a randomized case-controlled study. Hematology. 2007;12(6):533-41. doi: 10.1080/10245330701521572. PubMed PMID: 17852440.
15. Nowrousian M. Pathophysiology of cancer-related anemia. Recombinant Human Erythropoietin (rhEPO) in Clinical Oncology: Springer; 2002. p. 39-62.
16. Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. Blood. 1992;79(8):1987-94. PubMed PMID: 1373333.
17. Von Hoff DD, Schilsky R, Reichert CM, Reddick RL, Rozencweig M, Young RC, et al. Toxic effects of cis-dichlorodiammineplatinum(II) in man. Cancer Treat Rep. 1979;63(9-10):1527-31. PubMed PMID: 387223.

18. Oberhoff C, Neri B, Amadori D, Petry KU, Gamucci T, Rebmann U, et al. Recombinant human erythropoietin in the treatment of chemotherapy-induced anemia and prevention of transfusion requirement associated with solid tumors: a randomized, controlled study. Ann Oncol. 1998;9(3):255-60. PubMed PMID: 9602258.
19. Padhi S, Kemmis-Betty S, Rajesh S, Hill J, Murphy MF. Blood transfusion: summary of NICE guidance. Bmj. 2015;351:h5832. doi: 10.1136/bmj.h5832. PubMed PMID: 26581483.
20. Ten Bokkel-Huinink W. Controlled multicenter study of the influence of two different dosages of subcutaneous rhEPO on the development of anemia and transfusion dependency in patients with ovarian carcinoma treated with platinum-based combination chemotherapy. rhErythropoietin in Cancer Supportive Treatment New York: Marcel Dekker, Inc. 1996:99-112.
21. Ludwig H, Fritz E, Leitgeb C, Krainer M, Kuhrer I, Sagaster P, et al. Erythropoietin treatment for chronic anemia of selected hematological malignancies and solid tumors. Ann Oncol. 1993;4(2):161-7. PubMed PMID: 8448084.
22. Cody JD, Hodson EM. Recombinant human erythropoietin versus placebo or no treatment for the anaemia of chronic kidney disease in people not requiring dialysis. Cochrane Database Syst Rev. 2016(1):Cd003266. doi: 10.1002/14651858.CD003266.pub3. PubMed PMID: 26790135.
23. Thomaidis T, Weinmann A, Sprinzl M, Kanzler S, Raedle J, Ebert M, et al. Erythropoietin treatment in chemotherapy-induced anemia in previously untreated advanced esophagogastric cancer patients. Int J Clin Oncol. 2014;19(2):288-96. doi: 10.1007/s10147-013-0544-7. PubMed PMID: 23532629.
24. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer. 2001;91(12):2214-21. PubMed PMID: 11413508.
25. Tzekova V, Mihaylov G, Elezovic I, Koytchev R. Therapeutic effects of epoetin zeta in the treatment of chemotherapy-induced anaemia. Curr Med Res Opin. 2009;25(7):1689-97. doi: 10.1185/03007990903050876. PubMed PMID: 19505200.
26. Weigang-Kohler K, Vetter A, Thyroff-Friesinger U. HX575, recombinant human epoetin alfa, for the treatment of chemotherapy-associated symptomatic anaemia in patients with solid tumours. Onkologie. 2009;32(4):168-74. doi: 10.1159/000200783. PubMed PMID: 19372711.
27. Wauters I, Vansteenkiste J. Darbepoetin alfa in the treatment of chemotherapy-induced anaemia. Expert Opin Biol Ther. 2009;9(2):221-30. doi: 10.1517/14712590802652280. PubMed PMID: 19236252.