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Results of darbepoetin alfa treatment of anaemia in chemotherapy-receiving breast cancer patients: a single-centre retrospective observational study

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ABSTRACT

A retrospective observational study of the outcomes of darbepoetin alfa treatment for chemotherapy-induced anaemia in breast cancer patients was conducted. A group of 152 patients treated during 13 months in one oncology centre was assessed. Ninety-eight patients (64.5%) received perioperative chemotherapy, and 54 patients (35.5%) received palliative chemotherapy. The results of treatment with darbepoetin alfa were analysed by age (< 65 vs. ≥ 65 years), the aim of chemotherapy (perioperative vs. palliative), and body mass index (< 25 vs. 25–29 vs. 30 and more). The effectiveness of the therapy was estimated at 80.9% (95% CI: 74.7–87.2%). Significantly higher effectiveness of ESA was found in patients treated perioperatively compared to patients treated for metastatic breast cancer (85.7% vs. 72.2%, $p = 0.043$). There were no differences in the effectiveness of ESA depending on age and BMI. No serious ESA-related adverse events were observed.

Key words: chemotherapy-induced anaemia, breast cancer, darbepoetin alfa, erythropoietin-stimulating agents

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Introduction

Erythropoietin-stimulating agents (ESA) are recombinant human erythropoietin preparations which stimulate bone marrow to produce red blood cells [1]. Apart from relieving anaemia symptoms, the application of ESA can prevent the necessity of the red blood cells transfusion in patients with chemotherapy-induced anaemia (CIA) [2] and thus avoid transfusion-related complications [3, 4]. During the COVID-19 pandemic no need for hospitalization in order transfusion of blood products is an additional value.

CIA is estimated to affect as many as 67% of patients undergoing chemotherapy [5]. Apart from the adverse influence on the patients' quality of life [6], CIA contributes to shortening the survival time of patients with solid tumours, lymphomas and myelomas [7].

Aim of study

The aim of the study is to assess the results of the application of darbepoetin alfa in the treatment of anaemia in patients undergoing chemotherapy for breast cancer.

Material and methods

A retrospective assessment was carried out of the results of darbepoetin alfa (Aranesp[®] manufactured by Amgen) treatment of 152 patients receiving chemotherapy for breast cancer in the Clinic of Breast Tumours and Reconstructive Surgery, National Institute of Oncology, Public Research Institute in Warsaw, in whom therapy was initiated in the period from 2 January 2019 to 16 February 2020. Darbepoetin alfa

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was administered to patients with both early and metastatic breast cancer. The drug was given to symptomatic anaemia patients, with a haemoglobin (Hb) level of 8–11 g/dL. In addition, it was also applied in chemotherapy-undergoing patients, with asymptomatic anaemia, with a haemoglobin concentration of < 8 g/dL. The indications were consistent with the position of Polish experts [8] as well as with the position of the ESMO [9].

In all the patients, Aranesp® therapy was initiated after prior and/or simultaneously with possible iron deficiency, B12 and folic acid supplementation as well as after exclusion of other, chemotherapy aside, causes of the occurrence of anaemia. All the patients received Aranesp® in the dose of 500 µg subcutaneously every 3 weeks. No other erythropoietin preparations were administered to the study group.

The results of darbepoetin alfa treatment were assessed retrospectively on the basis of changes in haemoglobin levels as well as the duration of the ESA therapy. The aim of the therapy was considered to have been reached when the Hb level increased by at least 1 g/dL within 4–6 weeks and when no indication for red blood cells (RBC) transfusion was seen in the course of ESA administration. The treatment was continued until a stable Hb level was reached, ensuring the security of further oncological treatment without the necessity of RBC transfusion or termination of chemotherapy.

The results of darbepoetin alfa treatment were analysed with reference to age (< 65 yrs. vs. ≥ 65 yrs.), aim of the chemotherapy applied (perioperative vs. palliative) as well as the body mass index (BMI), (< 25 vs. 25–29 vs. 30 and more).

What was also assessed, on the basis of patient documentation, were the side effects which could result from the application of ESA, with particular attention to thromboembolic complications, occurrence of pure red cell aplasia (PRCA) as well as anaphylaxis and allergic reactions of 3rd and 4th degree according to Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v.4.03) [10]. What was resigned from due to incomplete source documentation, was the assessment of the occurrence or exacerbation of venous hypertension as well as allergic reactions and injection site reactions. It should be emphasized that no patient was administered darbepoetin alfa after reaching an Hb level of ≥ 12 due to the possibility of a significant increase in the number of thromboembolic complications, in compliance with ESA application guidelines [8, 11].

Results

Group characteristics

The results of darbepoetin alfa treatment were assessed in a group of 152 subsequent patients, in the

course of chemotherapy for breast cancer, in whom the administration of the preparation was initiated in the period from 2 January 2019 to 16 February 2020.

At the moment of the initiation of ESA administration, 33 patients (21.7%) were aged 65 or more (the oldest patient was 78 yrs.) while 119 (78.3%) were below 65 yrs. of age (the youngest patient was 28 yrs.)

Prior to the commencement of ESA treatment, 33 patients (21.7%) received intravenous iron supplementation. Ten patients (6.6%) in the course of ESA administration began intravenous iron supplementation simultaneously and 6 continued the intravenous iron supplementation started earlier. In total, 44 patients (28.9%) received iron preparations intravenously. Iron isomaltoside III in a dose of 1000 mg IV was administered in one or two doses during the observation period. No indication for vitamin B12 supplementation was found in any of the patients. It was not possible to determine exactly how many patients received folic acid-containing preparations. Oral iron preparations available on prescription were taken in the course of ESA therapy by 111 patients (73%). They included mainly *Ferri proteinatosuccinas* and iron sulphate II.

Red blood cells transfusion due to symptomatic anaemia and lack of response to ESA was necessary only in 17 patients (11.2%)

In the course of ESA treatment, perioperative chemotherapy was received by 98 patients (64.5%) and palliative chemotherapy by 54 patients (35.5%).

In the majority of patients (n = 108 patients, 71%), ESA treatment was initiated when a patient's Hb level was ≥ 10 g/dL while in 44 patients (28.9%), due to peripheral anaemia, when Hb level was above 10 but below 11 g/dL.

In the majority (90) of patients receiving perioperative chemotherapy the number of Aranesp® doses administered did not exceed 3, but 8 patients (5.3%) received 4 doses of the drug. Simultaneously, in the group receiving palliative treatment, as many as 20 patients received 4 or more doses of ESA, with 11 patients given 7 or more doses. It should be added that patients receiving more than 4 doses of ESA had them administered at time intervals longer than 3 weeks.

The group characteristics of the perioperatively treated patients, divided into two age groups, are described in Table 1 while that of the group of palliatively treated patients, also in two age groups, in Table 2. For the purpose of clarity, the patients were divided into four groups: 1 — early breast cancer (EBC) patients < 65 yrs. of age, 2 — early breast cancer (EBC) patients ≥ 65 yrs. of age, 3 — metastatic breast cancer (MBC) patients < 65 yrs. of age, 4 — metastatic breast cancer (MBC) patients ≥ 65 yrs. of age.

The Hb levels at the time of the first and the last ESA dose in individual groups are presented in Figure 1.

Table 1. Characteristics of early breast cancer (EBC) patients according to age group (Groups 1 and 2)

	Group 1 (EBC) < 65 yrs.	Group 2 (EBC) ≥ 65 yrs.	Total 1+2 (EBC)
Number of patients	80	18	98
Age: median (scope)	56 years (28–64)	69 years (65–76)	58 years (28–76)
Chemotherapy regimen:			
AC/PCL	28	6	34
AC/PCL+ carboplatin	9	0	9
TCH	25	7	32
TCH-P	6	2	8
Others	12	3	15
Hb level on the first dose of Aranesp®			
< 8 g/dL	1	0	1
8–10 g/dL	52	14	66
> 10 and ≤ 11 g/dL	27	4	31
Hb level on the final (or last during the observation period) Aranesp® dose			
< 8 g/dL	0	0	0
8–10 g/dL	9	2	11
> 10 g/dL	71	16	87
BMI 16–18.49 (underweight)			
	0	0	0
BMI 18.5–24.99 (normal value)			
	44	7	51
BMI 25–29.99 (overweight)			
	23	6	29
BMI 30–43 (obesity)			
	13	5	18
IV iron supplementation before and/or in the course of ESA application			
	25	4	29
Number of patients by the number of Aranesp® injections in the observation period			
1–3	72	18	90
4	8	0	8
5 and more	0	0	0

AC — doxorubicin with z cyclophosphamide; PCL — paclitaxel; TCH — docetaxel, carboplatin, trastuzumab; TCH-P — docetaxel, carboplatin, trastuzumab and pertuzumab; Hb — haemoglobin level; BMI — body mass index.

Effectiveness of darbepoetin alfa treatment

The estimated effectiveness of darbepoetin alfa therapy in the treatment of anaemia in patients receiving chemotherapy for breast cancer amounted to 80.9% (95% CI: 74.7–87.2%).

Both the univariate and the multivariate analysis revealed statistically higher significant effectiveness in early breast cancer patients as compared with patients treated for metastatic breast cancer (85.7% vs. 72.2%, $p = 0.043$). The estimated odds ratio, OR = 2.330 (95% CI: 1.015–5.351, $p = 0.046$).

No statistically significant differences in the ESA effectiveness were found depending on age or BMI. The estimated effectiveness in the < 65 vs. ≥ 65 years of age groups was 84.8% vs. 79.8%, respectively.

The estimated effectiveness values in the following BMI-dependent groups, namely: underweight + normal weight (the 2 groups were combined because there were

only two patients with underweight: BMI: 16–24.99), overweight (BMI 25–29.99) and obesity (BMI 30–43.1), were 86.3%, 76.6% and 72.0%, respectively.

Side effects of darbepoetin alfa

Two patients (1.3%) with metastatic breast cancer were diagnosed with vascular access port thrombosis in the course of ESA therapy. In the remaining 150 patients, no other thromboembolic disturbances were observed. Nevertheless, it should be pointed out that 9 patients (9.2%) from the early breast cancer group and 12 (22.2%) from the group treated for metastatic breast cancer were treated with low molecular weight heparin as an adjuvant treatment (overall, 13.8%).

No case of pure red cell aplasia (PRCA) was reported. No case of anaphylaxis or significantly exacerbated (3rd or 4th degree acc. to CTCAE v. 4.03) allergic reaction were reported.

Table 2. Characteristics of palliatively treated patients (MBC, metastatic breast cancer) according to age group (Groups C and D).

	Group 3 (MBC) < 65 years	Group 4 (MBC) ≥ 65 years	Total 3 + 4 (MBC)
Number of patients	39	15	54
Age: median (range)	58 years (35–64)	71 years (65–78)	61 years (35–78)
Chemotherapy regimen:			
NPLD + CTX	7	0	7
Paclitaxel q7	8	5	13
Doxorubicin q7	7	5	12
Carboplatin + gemcytabin	3	0	3
Capecytabin	2	2	4
Others	12	3	15
Hb level on the first Aranesp® dose:			
< 8 g/dL	5	1	6
8–10 g/dL	22	13	35
> 10 and ≤ 11 g/dL	12	1	13
Hb level on the final (or last during the observation period) Aranesp® dose			
< 8 g/dL	2	2	4
8–10 g/dL	15	2	17
> 10 g/dL	22	11	33
IV iron supplementation before and/or in the course of ESA application	11	4	15
BMI 16–18.49 (underweight)	2	0	2
BMI 18.5–24.99 (normal value)	17	10	27
BMI 25–29.99 (overweight)	16	4	20
BMI 30–43 (obesity)	4	1	5
Number of patients by the number of Aranesp® injections in the observation period			
1–3	26	8	34
4–6	8	1	9
7 and more	5	6	11

NPLD — non-pegylated liposomal doxorubicin; CTX — cyclophosphamide; q7 — every 7 days; Hb — haemoglobin level; BMI — body mass index.

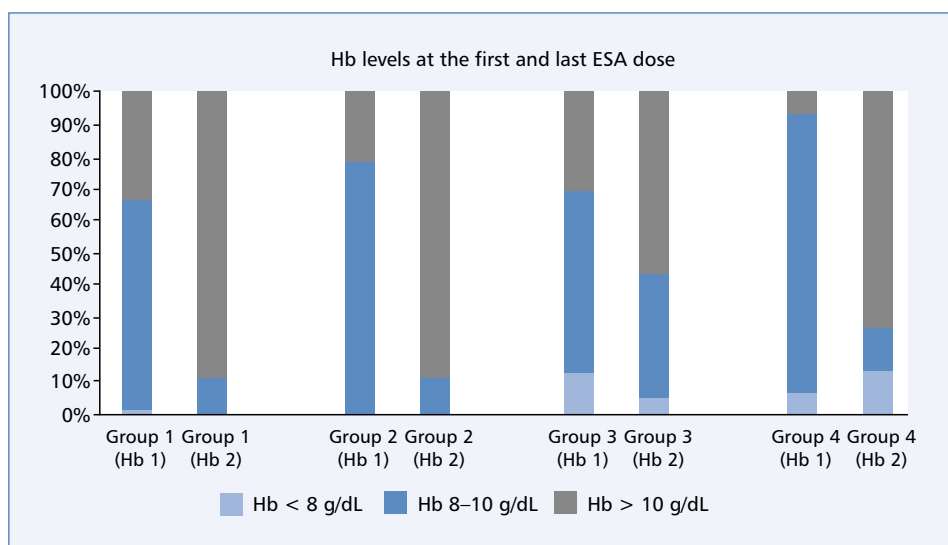


Figure 1. Hb level on the first (Hb 1) and last (Hb 2) Aranesp® dose in individual groups: 1 — perioperatively treated (EBC) patients < 65 years of age, 2 — perioperatively treated (EBC) patients ≥ 65 years of age, 3 — palliatively treated (MBC) patients < 65 years of age, 4 — palliatively treated (MBC) patients ≥ 65 years of age

Discussion

Chemotherapy-related anaemia constitutes one of the most common side effects in oncological patients [12, 13]. According to various authors, the incidence of anaemia in breast cancer patients is estimated at 6–97% [13, 14]. It has been most frequently reported in patients receiving docetaxel and carboplatin-based regimens [14, 15].

Red blood cells transfusions, iron preparations supplementation and erythropoiesis-stimulating drugs are recommended in CIA treatment depending on the severity of anaemia and the clinical situation [8, 9].

European guidelines suggest that ESA-group drugs should be applied primarily in patients with symptomatic anaemia who receive chemotherapy or a combination of chemotherapy and radiotherapy, with a haemoglobin concentration of 8–10 g/dL as well as in patients with asymptomatic anaemia who receive chemotherapy, with a haemoglobin concentration of < 8 g/dL. ESA administration can also be considered in patients with the Hb level of 10–11 g/dL, in the case of persisting symptomatic anaemia, after iron deficiency, B12 and folic acid supplementation and exclusion of other causes of anaemia [8]. Some authors advocate modification of ESMO guidelines and argue for more categorical recommendation of ESA, also in the last group of patients [16]. What is definitely not recommended is the application of ESA when the level of haemoglobin exceeds 12 g/dL [8, 9, 16].

In this study, the majority of patients (71%) had the ESA therapy initiated at the Hb level of ≥ 10 g/dL. Neither was Aranesp[®] administered in patients with an Hb level of above 12 g/dL.

Similar Hb values at the time of the initiation of ESA administration have been described in other observational studies. In the European observational CHOICE study, carried out in 11 European countries with the participation of 1900 patients with solid tumours, 57% of the included patients had a baseline Hb level of < 10 g/dL and 91% had < 11 g/dL [17].

The response rate to darbepoetin alfa in the study group was estimated at 80.9% (95% CI: 74.7–87.2%). This is consistent with the findings by other authors. In the clinical studies assessing the effectiveness of ESA in the treatment of CIA in different types of neoplasms, response rates ranged from 50 to 90% [18–22].

It is definitely worth emphasizing that our analysis confirmed statistically higher effectiveness of darbepoetin alfa in radically treated patients in comparison with patients treated in a palliative way (85.7% vs. 72.2%, $p = 0.043$). This is likely to be due to the complex aetiology of anaemia in patients with a generalized neoplastic disease and consequently worse response to ESA.

The perioperatively treated (EBC) patients received a significantly lower number of Aranesp[®] injections

than the palliation-oriented chemotherapy (MBC) patients. This is consistent with expectations, as the duration of perioperative chemotherapy is strictly defined and ESA administration is not recommended in patients who have completed chemotherapy.

Numerous publications emphasize the necessity of a concurrent iron supplementation which improves ESA effectiveness [8, 9, 16, 19, 23].

In the group of patients covered by this study, almost one third (28.9%) received intravenous iron supplementation, which might have affected the obtained results of response to ESA. In addition, as many as 73% of the patients took oral iron supplementation which should, in turn, have no influence on the effectiveness of darbepoetin alfa [8].

The incidence of anaemia increases with age and some studies point to a significant growth in the incidence of anaemia in patients over 70 years of age [22]. Anaemia in the elderly leads to an increased number of falls as well as depression [23]. Although CIA is a common complication observed during chemotherapy of elderly patients, there is no information on a systematic clinical response to ESA in the elderly [23]. That is why this study strived to assess the effectiveness of the treatment with darbepoetin alfa in two age groups: below 65 years of age and 65 and more years of age. No statistically significant age-related differences were found in the effectiveness of ESA administration. Similar conclusions have been presented by other authors [13, 23].

In spite of the lack of relevant data in the literature, an attempt was made to assess the effectiveness of darbepoetin alfa depending on the BMI with the purpose of excluding the adverse influence of overweight and obesity on response to ESA. No statistically significant BMI-dependent differences in the effectiveness of Aranesp[®] were observed.

Numerous studies dealing with anaemia treatment discuss the question of the safety of ESA and RBC transfusion application [13, 24]. Both of these forms of treating anaemia involve the risk of thromboembolic complications. In addition, RBC transfusions have been reported to generate numerous immunological and non-immunological complications [25–27]. In this analysis, RBC transfusions concerned only 11.2% of patients in whom darbepoetin alfa treatment proved ineffective. This finding is worth emphasizing, particularly at the time of the COVID-19 pandemic when unnecessary hospitalization of chemotherapy-undergoing patients should be avoided.

Side effects of darbepoetin alfa in the study group were very rare. In 1.3% of the patients, thrombosis related to the earlier implanted venous access port was observed. No other thromboembolic complications were observed, which is inconsistent with relevant findings from the literature which describe these complications in about 20–30% of ESA-treated patients in the course

of chemotherapy for breast cancer [24, 28–30]. This very low percentage of thromboembolic complications can at least partly be attributed to the fact that 13.8% of the patients received concurrent adjuvant treatment with low molecular heparin.

This study is an observational study, performed retrospectively, and is thus of limited scientific value, but the presented findings are unique due to the collection of ESA-treatment data for a relatively large group of patients treated for breast cancer in one centre during nearly 13 months.

Conclusions

Darbepoetin alfa proved effective in the treatment of anaemia in chemotherapy-treated patients with breast cancer. The response to the treatment in the assessed group of patients was 80.9% (95% CI: 74.7–87.2%). Better response to darbepoetin alfa was found in early breast cancer (EBC) patients than in patients treated for metastatic breast cancer (MBC) (85.7% vs. 72.2%, $p = 0.043$). There were no statistically significant age- and BMI-related differences in ESA effectiveness. No significant side effects of darbepoetin alfa therapy were observed in either the EBC or the MBC group of patients.

Conflict of interest

The authors report no conflicts of interest.

References

- Macdougall IC. Novel erythropoiesis-stimulating agents: a new era in anemia management. *Clin J Am Soc Nephrol*. 2008; 3(1): 200–207, doi: [10.2215/CJN.03840907](https://doi.org/10.2215/CJN.03840907), indexed in Pubmed: [18077782](https://pubmed.ncbi.nlm.nih.gov/18077782/).
- Aapro MS. Editorial: anemia management with erythropoiesis-stimulating agents: a risk-benefit update. *Oncologist*. 2008; 13 Suppl 3: 1–3, doi: [10.1634/theoncologist.13-S3-1](https://doi.org/10.1634/theoncologist.13-S3-1), indexed in Pubmed: [18458117](https://pubmed.ncbi.nlm.nih.gov/18458117/).
- Stramer SL. Current risks of transfusion-transmitted agents: a review. *Arch Pathol Lab Med*. 2007; 131(5): 702–707, doi: [10.1043/1543-2165\(2007\)131\[702:CROTA\]2.0.CO;2](https://doi.org/10.1043/1543-2165(2007)131[702:CROTA]2.0.CO;2), indexed in Pubmed: [17488155](https://pubmed.ncbi.nlm.nih.gov/17488155/).
- Bernard AC, Davenport DL, Chang PK, et al. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. *J Am Coll Surg*. 2009; 208: 931–937.
- 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](https://doi.org/10.1016/j.ejca.2004.06.019), indexed in Pubmed: [15454256](https://pubmed.ncbi.nlm.nih.gov/15454256/).
- 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](https://doi.org/10.1093/annonc/mdh235), indexed in Pubmed: [15151958](https://pubmed.ncbi.nlm.nih.gov/15151958/).
- Caro JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*. 2001; 91(12): 2214–2221, indexed in Pubmed: [11413508](https://pubmed.ncbi.nlm.nih.gov/11413508/).
- 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](https://doi.org/10.5603/OCP.2017.0023).
- Aapro M, Beguin Y, Bokemeyer C, et al. ESMO Guidelines Committee, ESMO Guidelines Committee. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. *Ann Oncol*. 2018; 29(Suppl 4): iv96–iv110, doi: [10.1093/annonc/mdx758](https://doi.org/10.1093/annonc/mdx758), indexed in Pubmed: [29471514](https://pubmed.ncbi.nlm.nih.gov/29471514/).
- https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06_14_QuickReference_5x7.pdf.
- https://www.ema.europa.eu/en/documents/product-information/aranesp-epar-product-information_pl.pdf.
- Moebus V, Jackisch C, Schneeweiss A, et al. AGO Breast Study Group. Adding epoetin alfa to intense dose-dense adjuvant chemotherapy for breast cancer: randomized clinical trial. *J Natl Cancer Inst*. 2013; 105(14): 1018–1026, doi: [10.1093/jnci/djt145](https://doi.org/10.1093/jnci/djt145), indexed in Pubmed: [23860204](https://pubmed.ncbi.nlm.nih.gov/23860204/).
- Sabir S, Khan YH, Khatoon M, et al. Effect of Erythropoiesis Stimulating Agents on Clinical Outcomes in Breast Cancer Patients: A Systematic Review of Randomised Controlled Trials. *J Coll Physicians Surg Pak*. 2020; 30(3): 292–298, doi: [10.29271/jcpsp.2020.03.292](https://doi.org/10.29271/jcpsp.2020.03.292), indexed in Pubmed: [32169139](https://pubmed.ncbi.nlm.nih.gov/32169139/).
- 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](https://doi.org/10.1093/jnci/91.19.1616), indexed in Pubmed: [10511589](https://pubmed.ncbi.nlm.nih.gov/10511589/).
- Valero V, Holmes FA, Walters RS, et al. Phase II trial of docetaxel: a new, highly effective antineoplastic agent in the management of patients with anthracycline-resistant metastatic breast cancer. *J Clin Oncol*. 1995; 13(12): 2886–2894, doi: [10.1200/JCO.1995.13.12.2886](https://doi.org/10.1200/JCO.1995.13.12.2886), indexed in Pubmed: [8523051](https://pubmed.ncbi.nlm.nih.gov/8523051/).
- Link H. Hematopoietic Growth Factors in the Management of Anemia and Febrile Neutropenia. *Breast Care (Basel)*. 2019; 14(2): 93–98, doi: [10.1159/000497408](https://doi.org/10.1159/000497408), indexed in Pubmed: [31798380](https://pubmed.ncbi.nlm.nih.gov/31798380/).
- Van Belle S, Karanikiotis C, Labourey JL, et al. Current practice of darbepoetin alfa in the management of haemoglobin levels in cancer patients undergoing chemotherapy - data from the CHOICE study. *Curr Med Res Opin*. 2011; 27(5): 987–994, doi: [10.1185/03007995.2011.562493](https://doi.org/10.1185/03007995.2011.562493), indexed in Pubmed: [21385113](https://pubmed.ncbi.nlm.nih.gov/21385113/).
- Vansteenkiste J, Pirker R, Massuti B, et al. Aranesp 980297 Study Group. Double-blind, placebo-controlled, randomized phase III trial of darbepoetin alfa in lung cancer patients receiving chemotherapy. *J Natl Cancer Inst*. 2002; 94(16): 1211–1220, doi: [10.1093/jnci/94.16.1211](https://doi.org/10.1093/jnci/94.16.1211), indexed in Pubmed: [12189224](https://pubmed.ncbi.nlm.nih.gov/12189224/).
- 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](https://doi.org/10.1038/sj.leu.2404562), indexed in Pubmed: [17252006](https://pubmed.ncbi.nlm.nih.gov/17252006/).
- Glaspy J, Bukowski R, Steinberg D, et al. Impact of therapy with epoetin alfa on clinical outcomes in patients with nonmyeloid malignancies during cancer chemotherapy in community oncology practice. Procrit Study Group. *J Clin Oncol*. 1997; 15(3): 1218–1234, doi: [10.1200/JCO.1997.15.3.1218](https://doi.org/10.1200/JCO.1997.15.3.1218), indexed in Pubmed: [9060566](https://pubmed.ncbi.nlm.nih.gov/9060566/).
- Pedrazzoli P, Farris A, Del Prete S, et al. Randomized trial of intravenous iron supplementation in patients with chemotherapy-related anemia without iron deficiency treated with darbepoetin alfa. *J Clin Oncol*. 2008; 26(10): 1619–1625, doi: [10.1200/JCO.2007.12.2051](https://doi.org/10.1200/JCO.2007.12.2051), indexed in Pubmed: [18375891](https://pubmed.ncbi.nlm.nih.gov/18375891/).
- Massa E, Madeddu C, Lusso MR, et al. Evaluation of the effectiveness of treatment with erythropoietin on anemia, cognitive functioning and functions studied by comprehensive geriatric assessment in elderly cancer patients with anemia related to cancer chemotherapy. *Crit Rev Oncol Hematol*. 2006; 57(2): 175–182, doi: [10.1016/j.critrevonc.2005.06.001](https://doi.org/10.1016/j.critrevonc.2005.06.001), indexed in Pubmed: [16213740](https://pubmed.ncbi.nlm.nih.gov/16213740/).
- Kurtz JE, Soubeyran P, Michallet M, et al. Biosimilar epoetin for the management of chemotherapy-induced anemia in elderly patients. *Onco Targets Ther*. 2016; 9: 6689–6693, doi: [10.2147/OTT.S104743](https://doi.org/10.2147/OTT.S104743), indexed in Pubmed: [27822071](https://pubmed.ncbi.nlm.nih.gov/27822071/).
- Berbec NM, Stanculeanu DL, Badelita NS, et al. APPLY: A prospective observational study of clinical practice patterns of darbepoetin alfa use in patients with chemotherapy-induced anemia in Romania. *Memo*. 2018; 11(2): 144–151, doi: [10.1007/s12254-018-0390-4](https://doi.org/10.1007/s12254-018-0390-4), indexed in Pubmed: [29983830](https://pubmed.ncbi.nlm.nih.gov/29983830/).
- <https://www.mp.pl/interna/chapter/B16.IV.24.21>.
- Welsh L, Panek R, Riddell A, et al. Blood transfusion during radical chemo-radiotherapy does not reduce tumour hypoxia in squamous cell cancer of the head and neck. *Br J Cancer*. 2017; 116(1): 28–35, doi: [10.1038/bjc.2016.386](https://doi.org/10.1038/bjc.2016.386), indexed in Pubmed: [27884018](https://pubmed.ncbi.nlm.nih.gov/27884018/).
- Meybohm P, Herrmann E, Steinbicker AU, et al. Patient blood management is associated with a substantial reduction of red blood cell

- utilization and safe for patient's outcome: a prospective, multicenter cohort study with a noninferiority design. *Ann Surg.* 2016; 264: 203–211.
28. 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](https://doi.org/10.1093/annonc/mdu579), indexed in Pubmed: [25542926](https://pubmed.ncbi.nlm.nih.gov/25542926/).
29. Chavez-MacGregor M, Zhao H, Fang S, et al. Complications associated with erythropoietin-stimulating agents in patients with metastatic breast cancer: a Surveillance, Epidemiology, and End Results-Medicare study. *Cancer.* 2011; 117(16): 3641–3649, doi: [10.1002/ncr.25972](https://doi.org/10.1002/ncr.25972), indexed in Pubmed: [21656514](https://pubmed.ncbi.nlm.nih.gov/21656514/).
30. Leyland-Jones B, Bondarenko I, Nemsadze G, et al. A Randomized, Open-Label, Multicenter, Phase III Study of Epoetin Alfa Versus Best Standard of Care in Anemic Patients With Metastatic Breast Cancer Receiving Standard Chemotherapy. *J Clin Oncol.* 2016; 34(11): 1197–1207, doi: [10.1200/JCO.2015.63.5649](https://doi.org/10.1200/JCO.2015.63.5649), indexed in Pubmed: [26858335](https://pubmed.ncbi.nlm.nih.gov/26858335/).