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PHARMACOECONOMIC ANALYSIS OF EPORATIO FOR TREATMENT OF ANEMIA IN CANCER PATIENTS

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Abstract:
This article deals with pharmacoeconomic study of erythropoietin use in patients with chemotherapy-induced anemia. Four treatments were evaluated, i.e. Epoetin alfa, Epoetin beta, Epoetin theta and Darbepoetin alfa. The results of pharmacoeconomic analysis show that use of Epoetin theta (Eporatio) is the most cost-effective regimen for anemia treatment in cancer patients. Cost-cutting upon patient's transition to Eporatio amounts up to 9,129 rubles (transition from Epoetin beta), up to 13,812 rubles (transition from Epoetin alfa) and 165,527 rubles (transition from Darbepoetin alfa). Budget impact analysis demonstrated a possibility of total cost-cutting in the amount of 197,075,449 rubles if purchase share of Eporatio increases to 30% via reducing purchase share of Epoetin alfa by 15%, Epoetin beta by 13% and Darbepoetin alfa by 2%.

Key words: *cost analysis, cost-minimization analysis, budget impact analysis, Epoetin alfa, Epoetin beta, Epoetin theta, Darbepoetin alfa, pharmacoeconomics, clinical economic analysis.*

Introduction

For the recent decades treatment of cancer diseases remains one of the most important healthcare tasks. Economic aspect of such therapy is of special significance, namely cost characteristics of expenditures in the healthcare budget. Moreover, efficient treatment of cancer diseases makes it possible to save patient's life and their working capacity.

Main methods of antitumor treatment include surgical treatment, radiotherapy and chemotherapy. Advances in chemotherapy for treating cancer diseases are worth making a special mention. Currently this term comprises drugs with various mechanisms of action and antitumor activity spectrum. Despite molecular, biological and genetic predictors of efficacy, chemotherapy is characterized by certain toxicity. In addition to general clinical manifestations, such as weakness, asthenia, depression, more serious complications may develop: hematologic, gastrointestinal, endocrine disorders, etc. All these factors may contribute to patient's refusal to continue the therapy, delay in subsequent cycle of chemotherapy or dose reduction of antitumor treatments. This results in lower treatment efficacy.

According to practical guidelines for anemia treatment in cancer patients, incidence of anemia associated with chemo- and/or radiotherapy comprises 54% (mild – 39%, moderate – 14% and severe – 1%). Anemia is most common in patients with lung cancer (71%) and tumors of the female reproductive system (65%). Anemia occurrence increases with the number of performed therapy cycles [1].

Anemia significantly worsens quality of life in cancer patients due to increased fatigue (reduction of physical and mental activity) that is the main complaint in the majority of cancer patients [40].

The trial evaluating economic burden associated with anemia in cancer patients in the USA has shown a 1.7-fold increase of total medical expenditures per one cancer patient, who developed anemia, compared to a non-anemic patient within 6 months. This difference is explained by greater (1.7-fold) average number of hospitalization days, increased frequency of drug prescriptions (from 18.6 to 25), greater number of outpatient visits (from 25.1 to 35.5). In addition, anemic patients visit emergency departments and intensive care units more often (by 86%) compared to non-anemic patients (1.3 visits vs. 0.7) (Table 1) [41].

Table 1. Results of analysis for anemia economic consequences per one cancer patient in the USA (time interval – 6 months). Lyman G.H. et al. 2005 [41].

	Mean expenditures per one anemic patient ($)	Mean expenditures per one non-anemic patient ($)	Difference
Hospitalization	30 639	13 152	233%
Intensive care	588	318	185%
Outpatient services	30 354	22 607	134%
Drug prescriptions	2 409	1324	182%
Total	62 499	36 871	170%
	Mean expenditures per one anemic patient ($)	**Mean expenditures per one non-anemic patient ($)**	**Difference**
Hospitalization (inpatient days in hospitals)	10,9	6,4	170%
Intensive care (number of visits)	1,3	0,7	186%
Outpatient services (visit days)	35,5	25,1	141%
Number of drug prescriptions	25,0	18,6	134%

High healthcare expenditures on treatment of cancer patients with anemia and social significance of this pathology determine the need in pharmacoeconomic analysis of the use of erythropoietins marketed in Russia in order to improve current treatment regimens and cut costs in the healthcare budget.

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Study purpose: to identify (based on budget impact and cost-minimization analyses) an optimal recombinant human erythropoietin used to treat chemotherapy-induced anemia, in terms of pharmacoeconomic analysis.

To achieve the purpose, several consecutive tasks have been handled:

1. to determine modern approaches towards anemia treatment in cancer patients;
2. to perform information search for results of randomized clinical trials on efficacy of contemporary approaches towards treatment of this nosology;
3. to perform information search for conducted pharmacoeconomic studies of medicines used to treat anemia in cancer patients;
4. to perform a pharmacoeconomic analysis of medicines by simulation using cost analysis, cost-minimization analysis and budget impact analysis, as well as by assessing sensitivity of the used model.

Studied medicines:

1) Epoetin alfa (Aeprin, Binocrit, Epocrin, Eprex, Eralfon)
2) Epoetin beta (Vero-Epoetin, Recormon, Epoetin beta, Epostim, Erythropoietin, Erythrostim)
3) Epoetin theta (Eporatio)
4) Darbepoetin alfa (Aranesp)

Information search

To perform a pharmacoeconomic study in accordance with the above-mentioned purpose, an information search was performed to detect appropriate publications; PubMed, Medlink, Cochrane databases were analyzed using key words "Epoetin alfa", "Epoetin beta", "Epoetin theta", "Darbepoetin alfa", "anemia in oncology patients". In addition, an information search was conducted in Russian language using "Russian medical science" database of Central Scientific Medical Library, I.M. Sechenov First Moscow State Medical University, scientific electronic library "elibrary.ru", as well as free search engines (e.g., Yandex, Google, etc.). The search was performed using the following key words "anemia in cancer patients", "Epoetin alfa", "Epoetin beta", "Epoetin theta", "Darbepoetin alfa".

A total of 1,457 articles and abstracts were reviewed.

In the course of information search a Cochrane review by Tonia et al. [12] and a systematic NICE review performed by PenTAG Scientific Group from Exeter University [13], were selected.

Cost analysis

During the study cost components of Eporatio use were determined in comparison with expenditures on other epoetins.

Total expenditures consisted of:

- expenditures on epoetin purchase;
- expenditures on epoetin administration in patients.

Expenditures on management of adverse events caused by erythropoietin administration were not evaluated separately due to their relatively low frequency and, therefore, negligible share in total expenditures.

Data from the State Registry of Maximum Sale Prices Set by Pharmaceutical Manufacturers for Medicines on the List of Vital and Essential Drugs (as of 08.02.2016) were used as a source of information for epoetin prices [39]. Calculations were made based on maximum allowed wholesale price excluding VAT. Price for Eporatio was specified according to the information provided by the manufacturer.

Erythropoietin treatment regimen and average weekly doses were taken from randomized controlled trials and a systematic review of the use of various erythropoietins, as well as from prescribing information for the drugs. In particular, we used data on average weekly dose of Epoetin theta and Epoetin beta from a randomized, double-blind trial conducted by Tjulandin et al. [35]. The trial included 223 patients and was performed at 54 study sites in 10 countries.

Erythropoietin treatment regimen used in this trial was as follows:

The starting dose in Epoetin theta group was 20,000 IU subcutaneously (s.c.) once weekly. This starting dose was increased to 40,000 IU/week in patients with insufficient increase of Hb concentration (less than 10 g/L) after 4 weeks of treatment, and again to 60,000 IU/week in case of insufficient response after a second 4-week period of treatment. If the patient's Hb level increased by more than 20 g/L in a 4-week period, the weekly dose was reduced by 50%. If the Hb level exceeded 130 g/L the dose was reduced to 50% of the recent dose or was temporarily withheld [35].

In this randomized clinical trial (RCT) patients, randomized to Epoetin beta group, received the drug as follows: the starting dose was 450 IU/kg per week, administered in 3 equal doses. The dose was doubled to 900 IU/kg per week in patients who did not have a partial Hb response after 4 weeks of treatment [35]. It should be noted that treatment regimens for Epoetin theta and Epoetin beta were selected in accordance with the corresponding product prescribing information.

The mean treatment duration in this RCT was comparable between all treatment groups (75 days for Epoetin theta vs. 71 days for Epoetin beta vs. 70.5 days for placebo). The average weekly EPO dose was 26,425 IU for Epoetin theta vs. 36,973 IU for Epoetin beta [35].

Data on average weekly dose of Epoetin alfa were taken from a randomized placebo-controlled trial conducted by Moebus et al. among 643 patients [31]. The mean treatment duration was 16.9 weeks.

Epoetin alfa was given as follows:

The patients received Epoetin alfa 150 IU/kg subcutaneously three times a week. Therapy goal was to achieve optimal Hb level (125-130 g/L). Epoetin alfa treatment was withheld if Hb level exceeded 140 g/L; the therapy was resumed at Hb level of 130 g/L. The dose was doubled to 300 IU/kg if Hb concentration was lower than 10 g/L after four weeks of treatment. In this study average weekly dose of Epoetin alfa was 441 IU/kg three times a week, i.e. 30,429 IU/week per a patient with weight of 69 kg [31].

Data on average weekly dose of Darbepoetin alfa were taken from a systematic review by Forbes et al. [11], including 4 RCTs of this drug. The mean treatment duration comprised 16.9 weeks. Mean weight in patients included into the trial was 70 kg. Three trials which were analyzed in the review used the following regimen: 500 μg every 3 weeks, and in one trial the drug was administered in the dose 2.25 μg/kg/week. Darbepoetin alfa was used in full accordance with the corresponding product prescribing information.

In summary, the average weekly dose of Darbepoetin alfa used in this trial was 136.5 μg, i.e. patients received, on average, 546 μg every 3 weeks. Results of expenditure analysis on erythropoietin purchase are given in Table 3.

Table 3. Expenditures on erythropoietin purchase

Drug	Average price per 1,000 IU epoetins and 1 μg Darbepoetin (rubles)	Average weekly dose during therapy (IU, μg for Darbepoetin)	Weeks of treatment	Expenditures on 12-week therapy (rubles)
Epoetin theta	391,59	26425	12	124 173
Epoetin alfa	375,35	30429		137 060
Epoetin beta	300,45	36973		133 302
Darbepoetin alfa	132,79	546		290 009

Average price per 1,000 IU of Epoetin alfa, Epoetin beta and Epoetin theta and per 1 μg of Darbepoetin alfa (rubles) was calculated based on information about maximum price for a drug package in rubles excluding VAT, number of ampules and syringes in the commercial packaging and number of IU in one ampule or syringe [39]. As a result, mean values were obtained for INN: Epoe-

Table 2. Description of trials on anemia treatments in cancer patients included into Cochrane review by Tonia et al. [12] and a systematic NICE review [13]

Author, year	Number of patients	Drug	Comparator	Type of malignancy	Type of chemotherapy	Clinical outcome
Abels 1993 [14]	413	Epoetin alfa	Placebo	Mixed	Combined	Hem. response, Hb, HCT, RCT, QoL, AE
Aravantinos 2003 [15]	47	Epoetin alfa	Standard therapy	Solid	Platinum-based	Hb, HCT, RCT
Boogaerts 2003 [16]	262	Epoetin beta	Standard therapy	Solid, lymphoid	No data	Hem. response, Hb, RCT, QoL
Dammacco 2001 [17]	145	Epoetin alfa	Placebo	Multiple myeloma	Combined	Hem. response, Hb, RCT, QoL, AE
Del Mastro 1997 [18]	62	r-HuEPO	Standard therapy	Solid (breast)	Nonplatinum-based	Hb, RCT, QoL, AE
Dunphy 1999 [19]	30	r-HuEPO	Standard therapy	Solid (head, neck, lungs)	Combined	Hb, RCT
Hedenus 2002 [20]	33	Darbepoetin alfa	Placebo	Lymphoproliferative pathology	No data	Hem. response, Hb, RCT, AE
Hedenus 2003 [21]	349	Darbepoetin alfa	Placebo	Lymphoproliferative pathology	No data	Hem. response, Hb, RCT, AE, QoL
Kotasek 2003 [22]	249	Darbepoetin alfa	Placebo	Solid	No data	Hem. response, Hb, RCT, QoL
Kurz 1997 [23]	35	Epoetin alfa	Placebo	Solid (uterus, ovary)	Combined	Hem. response, Hb, RCT, QoL, AE
Littlewood 2001 [24]	375	Epoetin alfa	Placebo	Mixed	Nonplatinum-based	Hem. response, Hb, RCT, QoL, AE
Österborg 2002 [25]	349	Epoetin beta	Placebo	Lymphoproliferative pathology	Nonplatinum-based	Hem. response, Hb, RCT, QoL, AE
Silvestris 1995 [26]	54	Epoetin alfa	Standard therapy	Multiple myeloma	No data	Hem. response, Hb, AE
Ten Bokkel Huinink 1998 [27]	122	Epoetin beta	Standard therapy	Solid (ovary)	Platinum-based	Hb, RCT, AE
Thatcher 1999 [28]	130	Epoetin alfa	Standard therapy	Solid (small-cell lung cancer)	Combined	Hb, RCT, QoL, AE
Vansteenkiste 2002 [29]	314	Darbepoetin alfa	Placebo	Solid (lung cancer)	Platinum-based	Hem. response, Hb, RCT, QoL, AE, disease progression, survival
Grote 2005 [30]	224	Epoetin alfa	Placebo	Solid (small-cell lung cancer)	Combined	Hb, RCT, TR, survival, AE
Moebus 2013 [31]	643	Epoetin alfa	Standard therapy	Solid (breast)	Nonplatinum-based	Hb, RCT, QoL, survival, AE
Ray-Coquard 2009 [32]	218	Epoetin alfa	Standard therapy	Mixed	No data	RCT, OS, QoL, AE
Österborg 2005 [33]	349	Epoetin beta	Placebo	Lymphoproliferative pathology	Nonplatinum-based	Hem. response, Hb, RCT, QoL, AE
Strauss 2008 [34]	74	Epoetin beta	Standard therapy	Solid (uterus)	Chemotherapy + radiotherapy	Hb, RCT, TR, survival, AE
Tjulandin 2010 [35]	223	Epoetin theta, Epoetin beta	Placebo	Solid	Platinum-based	Hem. response, RCT, QoL, AE
Tjulandin 2011 [36]	186	Epoetin theta	Placebo	Mixed	Nonplatinum-based	Hem. response, RCT, QoL, AE
Untch 2011 [37]	733	Darbepoetin alfa	Standard therapy	Solid (breast)	Nonplatinum-based	Hb, pathological response, disease progression, survival, AE

AE – adverse event, Hb – hemoglobin level, HCT – hematocrit, hem. response – hematologic response, OS – overall survival, QoL – quality of life, RCT – red cell transfusions, r-HuEPO – recombinant human erythropoietin, TR – tumor response

tin alfa (Aeprin, Binocrit, Epocrin, Eprex, Eralfon), Epoetin beta (Vero-Epoetin, Recormon, Epoetin beta, Epostim, Erythropoietin, Erythrostim), Darbepoetin alfa (Aranesp) from the State Registry of Maximum Sale Prices Set by Pharmaceutical Manufacturers for Medicines. Suggested maximum sale price for Epoetin theta was provided by the manufacturer.

Hence, for 12-week treatment of one patient 124,173 rubles will be spent to purchase Epoetin theta, 137,060 rubles – Epoetin alfa, 133,302 rubles – Epoetin beta, 290,009 rubles – Darbepoetin alfa.

Expenditures on drug administration were estimated on the basis of the rates established by the Federal Compulsory Medical Insurance Fund (FOMS) for parameter "Intramuscular subcutaneous injection" (38.54 rubles) considering frequency of drug administration [43]. In this pharmacoeconomic study administration frequency for Epoetin theta was once weekly (462 rubles per 12-week treatment), for Epoetin alfa – 3 times a week (1,387 rubles per 12-week treatment), for Epoetin beta – once weekly (462 rubles per 12-week treatment), for Darbepoetin alfa – once in 3 weeks (154 rubles per 12-week treatment) [40].

Cost analysis results for expenditures on anemia treatment per one cancer patient per year are given in Table 4.

Table 4. Expenditures on anemia treatment per one cancer patient per year (during 12 weeks)

Per 1 patient	Epoetin theta	Epoetin alfa	Epoetin beta	Darbepoetin alfa
Expenditures on erythropoietin purchase (rubles)	124 173	137 060	133 302	290 009
Expenditures on erythropoietin administration (rubles)	462	1 387	462	154
Total expenditures (rubles)	124 635	138 447	133 765	290 163

Cost-minimization analysis

Selection of method for cost minimization was determined by the fact that the information search revealed no randomized controlled trials comparing efficacy and safety of all four epoetins. Moreover, attention was given to practical guidelines for treating anemia in cancer patients [1], according to which there was no significant difference in efficacy and safety among various epoetins.

Cost-minimization analysis demonstrated that use of Eporatio is the most cost-effective regimen for anemia treatment in cancer patients in the Russian Federation. Cost-cutting upon patient's transition to Eporatio comprises 9,129 rubles (transition from Epoetin beta), 13,812 rubles (transition from Epoetin alfa), 165,527 rubles (transition from Darbepoetin alfa).

Budget impact analysis

Due to lack of accurate data on the number of cancer patients with anemia receiving erythropoietins in the Russian Federation, authors assumed a total number of 30,000 patients. Number of patients in each region was conventionally distributed in accordance with overall incidence of cancer diseases in each constituent unit of the Russian Federation [38].

Budget impact analysis was performed in the terms of healthcare expenditures on anemia treatment in cancer patients, using two scenarios, i.e. current situation (Scenario 1) and modeled situation (Scenario 2) [42]. These scenarios allow for regulation of patients' ratio in one or another treatment regimen, as well as make it possible to set the number of patients in the model. Time interval for budget impact analysis comprised 1 year (Table 5). IMS data for 2016 served as a source of information on the current distribution of market shares in Scenario 1. Calculations were made by market shares in packages of high-dose erythropoietins (10,000 IU and more), used to treat anemia in cancer patients.

Table 6. Budget impact analysis

Scenario	Treatment regimen	Market share (packages)	Expenditures, rubles
Current distribution	Epoetin theta	0%	4 269 454 500
	Epoetin alfa	49%	
	Epoetin beta	47%	
	Darbepoetin alfa	4%	
Modeled distribution	Epoetin theta	30%	4 072 379 052
	Epoetin alfa	34%	
	Epoetin beta	34%	
	Darbepoetin alfa	2%	
Cost-cutting			197 075 449

Budget impact analysis demonstrated a possibility of total cost-cutting in the amount of 197,075,449 rubles if purchase share of Eporatio increases to 30% for anemia treatment in cancer patients in the Russian Federation via reducing purchase share of Epoetin alfa by 15%, Epoetin beta by 13% and Darbepoetin alfa by 2% (see Table 6).

Lost opportunity analysis demonstrated that increase of Eporatio purchase share by 30% would result in additional financial resources for erythropoietin purchase to treat 1,581 cancer patients with anemia.

Sensitivity analysis

This pharmacoeconomic study included sensitivity analysis in order to determine robustness of the obtained results upon changing baseline parameters. The following parameters were set as variables: price per 1,000 IU of Epoetin theta (rubles), price per 1,000 IU of Epoetin alfa (rubles), price per 1,000 IU of Epoetin beta (rubles), price per 1 μg of Darbepoetin alfa (rubles).

One-way sensitivity analysis was conducted to evaluate changes in baseline parameters in the range from -100% to +100%. The column "Change (%)" includes maximum and minimum values of the parameter at which Epoetin theta still demonstrates superior results (see Table 7).

Table 5. Expenditures on anemia treatment per modeled population of cancer patients in the Russian Federation per year

Per general population	Epoetin theta	Epoetin alfa	Epoetin beta	Darbepoetin alfa
Expenditures on erythropoietin purchase (rubles)	3 725 185 100	4 111 796 391	3 999 069 316	8 700 259 058
Expenditures on erythropoietin administration (rubles)	13 874 400	41 623 200	13 874 400	4 624 800
Total expenditures (rubles)	3 739 059 500	4 153 419 591	4 012 943 716	8 704 883 858

Table 7. One-way sensitivity analysis for anemia treatment in cancer patients during 1 year.

Parameter	Baseline value (rubles)	Change (%)	Changed value (rubles)	Total expenditures per 1 patient (rubles)
Price for 1,000 IU of Epoetin theta (rubles)	391,59	+6%	419,00 ₽	132 086 ₽
Price for 1,000 IU of Epoetin alfa (rubles)	375,35	-4%	364,34 ₽	132 965 ₽
Price for 1,000 IU of Epoetin beta (rubles)	300,45	-1%	297,45 ₽	132 432 ₽
Price for 1 µg of Darbepoetin alfa (rubles)	132,79	-54%	61,08 ₽	133 558 ₽

Thus, sensitivity analysis demonstrated stability of data obtained in the course of the pharmacoeconomic analysis. Therapy with Epoetin theta gives superior results upon increase of price per 1,000 IU by 6% and reduction of price per 1,000 IU and 1 µg erythropoietins in the range from 1% to 54%.

Conclusions

Cost-minimization analysis demonstrated that use of Eporatio is the most cost-effective regimen for anemia treatment in cancer patients in the Russian Federation. Cost-cutting upon patient's transition to Eporatio comprises 9,129 rubles (transition from Epoetin beta), 13,812 rubles (transition from Epoetin alfa), 165,527 rubles (transition from Darbepoetin alfa).

Budget impact analysis demonstrated a possibility of total cost-cutting in the amount of 197,075,449 rubles if purchase share of Eporatio increases to 30% for anemia treatment in cancer patients in the Russian Federation via reducing purchase share of Epoetin alfa by 15%, Epoetin beta by 13% and Darbepoetin alfa by 2%.

Lost opportunity analysis demonstrated that increase of Eporatio purchase share by 30% would result in additional financial resources for erythropoietin purchase to treat 1,581 cancer patients with anemia.

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