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- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ
- МАТЕРИАЛЫ X НАЦИОНАЛЬНОГО КОНГРЕССА С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ» 4-5 апреля 2016 г., г. Нижний Новгород

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PHARMACOECONOMIC ANALYSIS OF THE USE OF GRANULOCYTE COLONY-STIMULATING FACTOR DRUGS IN PROPHYLAXIS OF FEBRILE NEUTROPENIA IN CANCER PATIENTS UNDER HEALTHCARE SETTINGS IN THE RUSSIAN FEDERATION

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Summary:
As part of this work a pharmacoeconomic study of prophylaxis for febrile neutropenia with granulocyte colony-stimulating factor drugs was carried out. Four prevention schemes of G-CSFs were compared: lipegfilgrastim, pegfilgrastim, filgrastim, lenograstim. As a result, it was found that prophylaxis with lipegfilgrastim is characterized by the lowest "cost-effectiveness" ratio (217,352 rubles) as compared to prophylaxis with pegfilgrastim (342,748 rub.), filgrastim (302,077 rub. for 11 days of prophylaxis), lenograstim (788,582 rub. for 11 days of prophylaxis) by the end of the 1st year of prophylaxis. In the context of budget impact analysis, the least costly scheme was prophylaxis with lipegfilgrastim (211,484 rubles) by the end of the 1st year when calculating per 1 patient. Costs in pegfilgrastim group resulted in 314,986 rubles, in filgrastim group (11 days of treatment) – 264,620 rubles, in lenograstim group (11 days of treatment) – 690,798 rubles. In the context of pharmacoeconomic analysis it is preferable to use lipegfilgrastim for prophylaxis of febrile neutropenia as compared to other G-CSFs (pegfilgrastim, filgrastim, lenograstim), as it allows to increase the number of patients who responded to prophylaxis of febrile neutropenia while reducing costs as compared to other granulocyte colony-stimulating factor drugs.

Keywords: *effectiveness analysis, cost analysis, cost-effectiveness analysis, budget impact analysis, febrile neutropenia, granulocyte colony-stimulating factors, lipegfilgrastim, pegfilgrastim, filgrastim, lenograstim, pharmacoeconomics, clinical and economic analysis.*

Introduction

Chemotherapy is an integral part of modern therapy in cancer patients. However, chemotherapy has a significant disadvantage in terms of serious side effects. One of the most life-threatening complications of cytostatic therapy is febrile neutropenia. According to the practical recommendations on the administration of colony-stimulating factors for prophylaxis of febrile neutropenia in the Russian Federation, the term febrile neutropenia indicates an increase in body temperature of more than 38.0°C for an hour or more as measured in the axillary area with absolute neutrophil blood count of less than $0.5x10^9$/L (less than 500 cells/mcL) [4].

Despite significant advances in prevention and treatment, febrile neutropenia (FN) remains one of the most life-threatening complications of chemotherapy for malignant tumors, limiting the planned intensity of anticancer chemotherapy and, as a rule, requires a delay in the next course of treatment or reducing the dose of cytostatics that affects the efficacy of anticancer treatment [3, 6]. On the background of neutropenia the risk of infections in patients is significantly increased. The maximum risk occurs in patients with Grade IV neutropenia in severity, especially in those patients who has ANC below 0.1×10^9/L. Patients with Grade III neutropenia are at high risk of infectious complications, as well as patients who have a rapid decrease in the number of neutrophils. The risk of infectious complications increases with the severity and duration of neutropenia. Febrile neutropenia associated with chemotherapy requires hospitalization of the patient, administration of antibiotics and is accompanied by a delay of the next course of chemotherapy or a reduction in the chemotherapy dose thus decreasing the effectiveness of treatment, patients' quality of life and may lead to death [5,8].

The main method of prophylaxis for febrile neutropenia or reduction of neutropenia duration after cytostatic therapy is prophylactic administration of granulocyte colony-stimulating factors (G-CSFs) - proteins that specifically stimulate hematopoietic progenitor cells of myeloid focus and accelerate production of normal neutrophils [1, 2, 7, 16, 17, 18, 21].

The high cost of complex therapy of febrile neutropenia and social importance of cancerous diseases requires pharmacoeconomic analysis of the use of G-CSF drugs marketed in Russia in order to reduce healthcare budget costs and optimize the existing schemes of prophylaxis for febrile neutropenia.

The goal of the study - to determine the most preferable medication in the context of pharmacoeconomic analysis for the use as prophylaxis of febrile neutropenia, based on the budget impact analysis and comparison of cost and effectiveness ratio.

To achieve this goal the following tasks have been consistently completed:

1. Collection and analysis of data on clinical experience of the use of colony-stimulating factors (lipegfilgrastim, pegfilgrastim, filgrastim and lenograstim) in the prophylaxis of febrile neutropenia.
2. Selection of effectiveness criteria for the use of lipegfilgrastim, pegfilgrastim, filgrastim and lenograstim in the prophylaxis for febrile neutropenia.
3. Cost analysis using comparable schemes of prophylaxis of febrile neutropenia.
4. Implementation of the following methods as part of pharmacoeconomic study: cost-effectiveness analysis, budget impact analysis, sensitivity analysis.

The relevance of this work is in the fact that this study is the first comparative pharmacoeconomic analysis of side-by-side use of four granulocyte colony-stimulating factors (lipegfilgrastim, pegfilgrastim, filgrastim, lenograstim) in the prevention of febrile neutropenia. As a result of this pharmacoeconomic study an analytical model was developed in Microsoft Excel 2013 format, allowing computer simulations of clinical and economic consequences of the decisions taken regarding selection of drugs for prevention of febrile neutropenia with the help of modern methods of pharmacoeconomic analysis both at the federal and regional levels.

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Objects of the study:

1. lipegfilgrastim (Lonquex) – a long-acting G-CSF
2. pegfilgrastim (Neulastim®) – a long-acting G-CSF
3. filgrastim (Granogen®, Tevagrastim, Immugrast®, Zarzio, Leucostim®, Leucita, Mielastra, Neupogen®, Neitrostim, Filegrim®, Filgrastim, Filgrastim-Nanolek, Neupomax®) – a short-acting G-CSF
4. lenograstim (Granocyt® 34) – a short-acting G-CSF

Effectiveness analysis

The first phase of this study included information search using the data from the largest bibliographic databases: Medline, Medscape, PubMed, Cochrane Library, database "Russian Medicine" of the Central Scientific Medical Library at I.M. Sechenov First Moscow State Medical University, scientific electronic library "elibrary.ru", free search engines such as Yandex, Google. The search query included the following terms: «нейтропения», «нейтропения, вызванная химиотерапией», «фебрильная нейтропения», «абсолютное число нейтрофилов», «гранулоцитарный колониестимулирующий фактор», «липэгфилграстим», «пэгфилграстим», «филграстим», «леноrрастим» and the same terms in English ("neutropenia", "chemotherapy-induced neutropenia", "febrile neutropenia", "absolute neutrophil count", "granulocyte colony-stimulating factor", "lipegfilgrastim", "pegfilgrastim", "filgrastim", "lenograstim"). The meta-analysis was selected as the result of this research: «Meta-analysis and indirect treatment comparison of lipegfilgrastim for the reduction of chemotherapy-induced neutropenia» authored by T.C. Bond, U. Mueller, G. Barnes, R. Gennero, B. Tang, L. Schwartzberg [44]. It should be noted that this work is the only published meta-analysis which has statistical justification and a high degree of reliability for the results comparing the effectiveness of prophylaxis with long-acting G-CSFs (lipegfilgrastim, pegfilgrastim) and short-acting G-CSFs (filgrastim with 11 days of prophylaxis). During this meta-analysis the advanced information search was performed within MEDLINE and EMBASE databases. 24 studies were selected in relation to efficacy and safety of G-CSFs, where the incidence of febrile neutropenia served as an indicator of efficacy in the population of patients undergoing chemotherapy (Table 1).

The authors used the following criteria for inclusion of studies into the meta-analysis:

Prospective study design

A randomized study

A double-blind study or a study blinded for evaluators of the clinical outcome

A sufficient sample size

Sufficient details in the description of patient populations

Concomitant therapy was comparable between all the groups

Follow up in at least 80% of patients

Studies with the use of G-CSFs for mobilization of peripheral blood stem cells, mobilization of bone marrow stem cells, as well as studies in pediatric population were excluded.

Table 1. Data on the studies included into the meta-analysis.

Study	Comparison groups	Age	Type of tumor	Females (%)	Grade / Stage	Chemotherapy regimen	Number of cycles	Prior chemotherapy (%)
Lipegfilgrastim and Pegfilgrastim								
Buchner 2014 [19]	LIP and PEG	18 +	Breast	99%	High risk II - IV	DD	4	0%
Bondarenko 2013 [20]	LIP and PEG	18 +	Breast	100%	II - IV	DD	4	0%
Lipegfilgrastim and placebo/no treatment								
XM22-04 [51]	LIP and PCB/NT	18+	NSCLC	86%	IIIb-IV	PE	4	0%
Pegfilgrastim and Filgrastim								
Green 2003 [24]	PEG and FIL	30-75	Breast	99%	High risk II-IV	DD	4	28%
Grigg 2003 [26]	PEG and FIL and PCB	60-82	NHL	47%	I-IV	CHOP	6	15%, 43%, 22%
Holmes II 2002 [25]	PEG and FIL	18+	Breast	100%	High risk II-IV	DD	4	80%, 91%
Holmes III 2002 [47]	PEG and FIL	>18	Breast	99%	High risk II-IV	DD	4	12%,9%
Park 2013 [23]	PEG and FIL	18+	Breast	100%	High risk II-III	TAC	6	md
Shi 2013 [39]	PEG and FIL	18-70	Solid, NHL	61%	I-IV	PC, AC, PA, CHOP	1	0%
Vose 2003 [22]	PEG and FIL	18+	NHL, HL	40%	I-IV	ESHAP	2	100%, 100%
Balducci 2007 [45]	PEG (primary) and PEG (secondary)	65+	Solid, NHL	Solid: 66% NHL: 53%	All	CHOP, CNOP, EPOCH	6	md
Hecht 2010 [28]	PEG and PCB	18-87	Colorectal	33%	Metastases identified	FOLFOX4, FOLFIRI, FOIL	4	md
Kosaka 2015 [30]	PEG and PCB	26-69	Breast	100%	I-III	TC	4-6	0%
Vogel 2005 [31]	PEG and PCB	>18	Breast	99%	md	Docetaxel	4	64%, 67%
Filgrastim and placebo/no treatment								
Crawford 1991/2005 [43,48]	FIL and PCB	31-80	SCLC	35%	Recently identified	CDE	6(1)	0%
del Giglio 2008 [29]	FIL and FIL (XM02) and PCB	18+	Breast	99%	High risk II-IV	DD	4	0%
Doorduijn 2003 [32]	FIL and PCB	65-90	NHL	45%	Recently identified, aggressive II-IV	CHOP	6/8	0%
Fossa 1998 [33]	FIL and PCB	16-65	Sex cells	md	Poor prognosis	BEP/EP, BOP/VIP-B	6	0%
Muhonen 1996 [34]	FIL and PCB/NT	18-70	Breast	100%	Metastases identified	MMM	6	md
Osby 2003 [35]	FIL and PCB/NT	60-86	NHL	47%	High risk II-IV	CHOP, CNOP	8	0%
Pettengell 1992 [36]	FIL and PCB/NT	16-71	NHL	34%	High risk II-IV	VAPEC-B	11	0%
Romieu 2007 [37]	FIL and PCB/NT	65-77	Breast	100%	High risk II-III	FEC-100	4-6	0%
Trillet-Lenior 1993 [38]	FIL and PCB/NT	md	SCLC	31%	Limited or extensive	CDE	6	0%
Zinzani 1997 [40]	FIL and PCB/NT	60-82	NHL	57%	High risk II-IV	VNCOP-B	2-4	0%

Abbreviations: HL - Hodgkin lymphoma, LIP – lipegfilgrastim, SCLC – small cell lung cancer, md – missing data, NSCLC – non-small cell lung cancer, NHL - non-Hodgkin lymphoma, NT – no treatment, PCB – placebo, PEG – pegfilgrastim, FIL - filgrastim

Based on data from studies by Bönig H. et al. 2001, Hüttmann A. et al. 2005, Ria R. et al. 2010, Lefrère F. et al. 1999, according to which efficacy of lenograstim and filgrastim is comparable, it was assumed to consider the efficacy of filgrastim and lenograstim being identical [41,42,49,50]. In addition, during the effectiveness analysis it was assumed that the effectiveness of the drugs of each International Non-proprietary Name (INN) was identical.

The use of filgrastim and lenograstim at a scheme of 11-day prophylaxis in the present pharmacoeconomic study was justified by the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) under which it is recommended to introduce a daily G-CSF 24-72 hours after chemotherapy to restore the absolute neutrophil count which typically takes 10-11 days [46].

Based on the information search an efficacy criterion was defined allowing pharmacoeconomic assessment of the use of healthcare technologies being compared in the prevention of febrile neutropenia. In this study this criterion is the percentage of patients who successfully responded to prophylaxis of febrile neutropenia. Figure 1 displays the ratio of these parameters for various schemes of prophylaxis with regard to study time horizon equal to 1 year, based on the treatment of one patient [44]. Horizon 1 of the study within the 1st year is selected for the reason that it is the most acceptable in terms of healthcare budget formation.

of G-CSF drugs. Tender price calculation was based on the results of auctions held in 76 regions of the Russian Federation. Furthermore, for drugs included in the EDL list additional calculations were performed taking into account the given maximum selling manufacturer's price. The number of administrations and the number of bottles per administration for the duration of the study were calculated in accordance with Prescribing Information for the drugs.

Table 2. Costs for G-CSF drugs

INN	Average cost per pack under contract, rubles	Average cost per 1 million IU, rubles	Administration cost, rubles	Total cost, rubles
Lipegfilgrastim	49,129	-	132	49,261
Pegfilgrastim	67,439	-	132	67,571
Filgrastim (11 days)	26,027	115	1454	45,662
Lenograstim (11 days)	53,041	316	1454	157,041

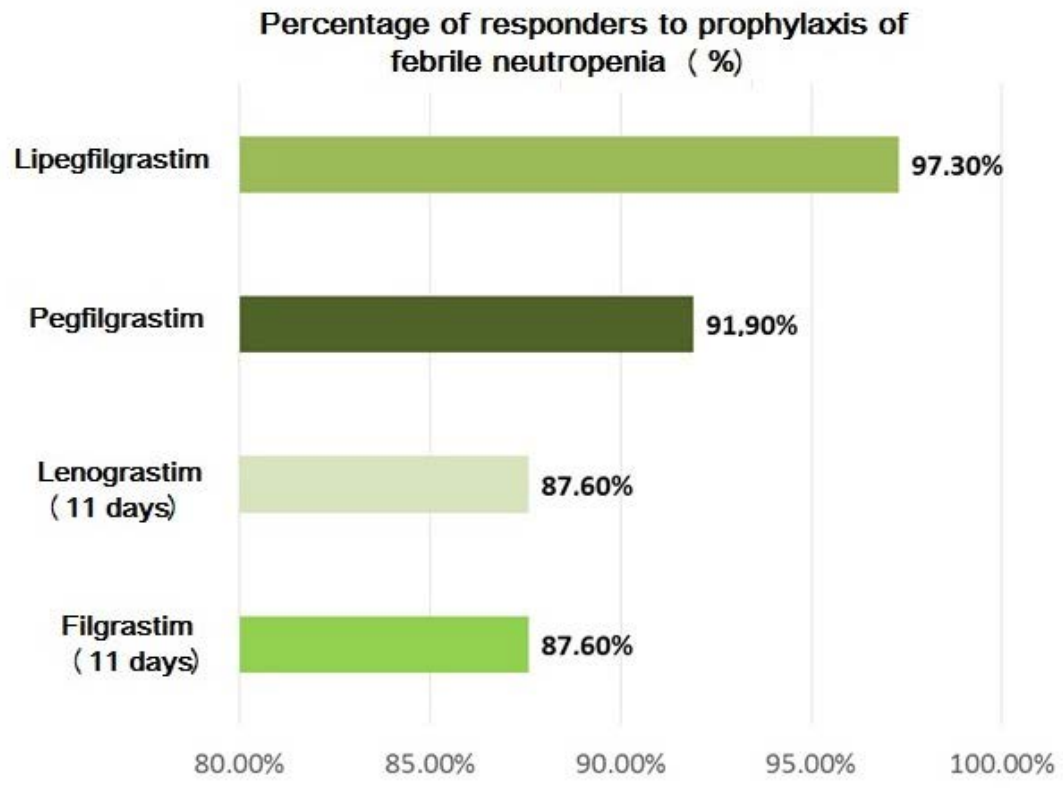

Figure 1. The result of effectiveness analysis

Cost analysis

In the course of this study the values of cost analysis components for lipegfilgrastim were determined in comparison with other G-CSFs.

In this study direct costs were taken into account including:

- Costs for the treatment course with granulocyte colony-stimulating factor drugs (together with expenses for administration of the drugs)
- Costs for the treatment of a febrile neutropenia event
- Expenses for management of adverse events associated with administration of granulocyte colony-stimulating factor drugs

The average tender price for the study drugs were used as the source of data on prices for G-CSFs for the period from 1 January 2012 to 14 December 2015 (database "Monitoring of tender purchases" within information-analytical system «Headway Company»). The selection of the average tender prices is the most appropriate, because it shows the real-world practice of state purchases

The cost of course of treatment with filgrastim and lenograstim was calculated for 11 days of duration respectively requiring 11 injections (1 injection per day) of the above drugs at a dose of 0.5 Mill. IU per kg of patient's body weight for filgrastim, and 0.64 Mill. IU per kg of patient's body weight for lenograstim. Costs for administration of the drugs were calculated according to the tariffs of Federal Compulsory Medical Insurance Fund per columns "Intramuscular subcutaneous injection" (36 rubles) and "Injection of medicines" (96 rubles) taking into account the frequency of dosing.

It was assumed that the average body weight in this patients population was 70 kg. The number of chemotherapy cycles per year in the meta-analysis was 4 cycles, therefore, the frequency of G-CSF drugs administration in the study was also 4 courses per year [44].

Decree №1273 of the Government of the Russian Federation dated November 28, 2014 "On the Program of state guarantees for provision of free medical care to citizens for the year 2015 and the planning period of 2016 and 2017" was used as the source of data on costs for treatment of febrile neutropenia [10] . This document includes the following category of patients - agranulocytosis with blood neutrophils of $0.5x10^9$/L or lower. According to this document the standard of financial costs per volume of health care in this group of patients was 119,808 rubles [10]. The calculations of this type of costs considered the frequency of FN and its prophylaxis using various G-CSFs. For lipegfilgrastim the frequency was 2.7%, for pegfilgrastim - 8.1%, for filgrastim (11 days) and lenograstim (11 days) - 12.4% [44]. Also, a different duration of hospitalization was taken into account in the treatment of FN with G-CSF drugs. For lipegfilgrastim it was 6.35 days, for pegfilgrastim - 8.10 days, for filgrastim and lenograstim - 8.23 days [44].

Expenses for management of adverse events were calculated according to the data on the incidence of adverse events from the Prescribing information documents for the above drugs, and also based on the Marketing Authorizations of the drugs in the database of the European Medicines Agency [11-14]. The expenses for management of adverse events were calculated utilizing data for the treatment of a single clinical event according to the tariffs of Federal Compulsory Medical Insurance Fund, as well as using prices for medicines from www.pharmindex.ru database. It should be noted that the study included only those adverse events that were reported as common or very common in the Prescribing information for the respective drugs. If the incidence of such events was not specified in the Prescribing information, the data on the incidence of adverse events from the dossier of the European Medicines Agency for the drug under consideration were used [15].

Table 3. Results of cost analysis for prevention and treatment of febrile neutropenia for 1 person per 1 year.

INN	Costs for G-CSFs, rubles	Costs of treatment of febrile neutropenia, rubles	Costs for management of adverse events, rubles	Total cost
Lipegfilgrastim	197,044	14,273	167	211,484
Pegfilgrastim	270,284	43,922	780	314,986
Filgrastim (11 days)	182,646	67,364	14 609	264,620
Lenograstim (11 days)	628,164	59,666	2 968	690,798

Based on the values obtained as part of cost analysis it was concluded that the use of lipegfilgrastim is the least costly scheme for prophylaxis of febrile neutropenia as compared to other G-CSF drugs, thus ensuring cost savings for 1 person per year to 103,502 rubles compared to pegfilgrastim, 53,136 rubles compared to filgrastim (11 days), 479,314 rubles compared to lenograstim (11 days).

Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is used to assess the cost of unit of effectiveness, represented by the healthcare technologies being compared. Thus, this type of pharmacoeconomic analysis allows for comparison of the studied technologies not only on the basis of the final results of cost analysis, but also by calculating "cost-effectiveness" ratio [9].

"Cost-effectiveness" ratio is calculated by the formula:

$$CER = \frac{Cost}{Ef}$$

where CER – is "cost-effectiveness" ratio; Cost – costs for the studied technology, rubles; Ef – is a measure of effectiveness of the studied technology. This type of pharmacoeconomic analysis allows to determine how the costs for a particular technology correlate to its effectiveness as well as to choose the most preferable alternative in terms of pharmacoeconomics on the basis of obtained results [9].

As noted above, the percentage of responders to prophylaxis of febrile neutropenia by the end of the 1st year was chosen as the effectiveness criterion. The results of the cost-effectiveness analysis are presented in Table 4.

Total costs for prophylaxis with pegfilgrastim by the end of the first year were lower by 53,136 rubles (20.1%) than that with filgrastim (11 days). At that the effectiveness of prophylaxis increased by 9.7%. CER for lipegfilgrastim at the end of the first year totaled 217,352 rubles per unit of effectiveness compared to filgrastim (11 days prophylaxis) – 302,077 rubles with calculation for 1 year. For pegfilgrastim CER is 342,748 rubles. For lenograstim (11 days) this parameter amounted to 788,582 rubles.

Table 4. The results of the cost-effectiveness analysis

INN	Costs, rubles	Effectiveness criterion, %	Cost-effectiveness ratio per 1 year of treatment, rubles
Lipegfilgrastim	211,099	97.30	**217,352**
Pegfilgrastim	314,601	91.90	**342,748**
Filgrastim (11 days)	264,620	87.60	**302,077**
Lenograstim (11 days)	690,798	87.60	**788,582**

Thus, prophylaxis with lipegfilgrastim is characterized by a reduced cost-effectiveness ratio in comparison with all G-CSF drugs, therefore, it is the dominant healthcare technology from perspective of the cost-effectiveness analysis.

Budget impact analysis

Budget impact analysis implies assessment of all costs associated with implementation of the new scheme of treatment with respect to all types of expenses for already existing scheme of treatment. Calculation of costs was performed using the formula:

$$BIA = Cost_1 - Cost_2 \text{, where}$$

$Cost_1$ - total costs for the first method of treatment (rubles);

$Cost_2$ - total costs for the second method of treatment (rubles);

BIA (Budget Impact Analysis) – the result of the budget impact analysis (rubles);

In the course of this study the values of budget impact analysis components for lipegfilgrastim were determined when used for prophylaxis of febrile neutropenia in comparison with other G-CSFs. The total value for each group was made up of the costs for G-CSF drugs, costs for the treatment of incurring cases of febrile neutropenia, costs for the management of side effects.

Budget impact analysis was conducted in two scenarios from perspective of the healthcare system for prophylaxis of febrile neutropenia - the current situation and the simulated situation for different schemes of treatment. The model allows to adjust the percentage of patients with a particular scheme of treatment and specify the number of patients. The time horizon of the budget impact analysis was one year (Tables 5, 6).

Table 5. The results of budget impact analysis for 1 patient per 1 year

Scenario	Scheme of treatment	Percentage of patients	Costs, rubles
Current distribution	Lipegfilgrastim	1%	304,963
	Pegfilgrastim	5%	
	Filgrastim (11 days)	85%	
	Lenograstim (11 days)	9%	
Simulated distribution	Lipegfilgrastim	47%	262,466
	Pegfilgrastim	3%	
	Filgrastim (11 days)	45%	
	Lenograstim (11 days)	5%	
Cost saving			42,497

Table 6. The results of budget impact analysis when transferring to lipegfilgrastim from another G-CSF drug, per 1 year

Lipegfilgrastim as compared to another G-CSF drug	The result
Pegfilgrastim	Saving of 103,502 rubles
Filgrastim (11 days)	Saving of 53,136 rubles
Lenograstim (11 days)	Saving of 479,314 rubles

Thus, according to budget impact analysis it was found that the use of lipegfilgrastim for the prevention of febrile neutropenia saves budget costs when compared to all other G-CSF drugs.

Sensitivity analysis

As part of this pharmacoeconomic study a sensitivity analysis was conducted to determine the extent of sustainability of the obtained results when changing the baseline settings. As a variable the following parameters were selected: costs for drug therapy with lipegfilgrastim, costs for drug therapy with filgrastim (11 days), basic standard costs for the treatment of a single febrile neutropenia event.

Univariate sensitivity analysis was carried out by evaluating changes in baseline parameters of the price for study drugs, changing standard costs for treatment of 1 FN event when correcting parameters from -50% to 100%. In the column “Change (%)” the maximum and minimum values of the parameters are shown for which the cost-effectiveness ratio for lipegfilgrastim prevails over cost-effectiveness ratio for filgrastim (11 days).

Table 7. Univariate sensitivity analysis of CER in the prophylaxis of febrile neutropenia during 1 year

Parameter	Baseline value	Changed value	Change (%)	CER for lipeg-filgrastim	CER for filgrastim
Costs for drug therapy with lipegfilgrastim	49 165	58 995	20%	257 855	257 586
Costs for drug therapy with filgrastim (11 days)	24 906	33 085	-33%	217 352	217 542
Basic standard costs for the treatment of a single febrile neutropenia event	119 808	65 894	-38%	211 778	212 577

Thus, the sensitivity analysis showed stability of the data of the pharmacoeconomic analysis. Prophylaxis with lipegfilgrastim as compared to prophylaxis with filgrastim (during 11 days) is dominant with significant changes in baseline price parameters for the study drugs, change in the basic standard costs for the treatment of a single FN event.

Conclusions

In terms of pharmacoeconomic analysis it is preferable to use lipegfilgrastim for prophylaxis of febrile neutropenia as compared to other G-CSFs (pegfilgrastim, filgrastim, lenograstim), as it allows to increase the number of patients who responded to prophylaxis of febrile neutropenia while reducing costs as compared to other granulocyte colony-stimulating factor drugs.

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