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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 EVALUATION OF POMALIDOMIDE (IMNOVID) USE IN TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA WHO HAVE RECEIVED AT LEAST TWO LINES OF THERAPY COMPRISING LENALIDOMIDE AND BORTEZOMIB

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Abstract: *This paper represents the results of pharmacoeconomic study of the drug pomalidomide use in treatment of patients with relapsed or refractory multiple myeloma (MM) with more than 50% reduction in M protein, who have received at least two lines of therapy comprising lenalidomide and bortezomib. Lenalidomide and bortezomib were used as comparative treatment options in the study. The pharmacoeconomic study was carried out using the methods for analysis of efficiency, cost, cost-effectiveness, sensitivity and impact on the budget under frame of the medicinal assistance program for people suffering from hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher's disease, formation of malignant lymphoid haematogenic and related tissues, multiple sclerosis, as well as organ and/or tissue transplants (hereinafter referred to as the Seven Nosologies (VZN) Program). The time horizon of the «impact on the budget» analysis for the "Seven Nosologies" program was consisted of 4 years (2015–2018).*

The pharmacoeconomic analysis showed that pomalidomide can be recommended for inclusion in the "Seven Nosologies" federal program within the existing budget.

From the perspective of the cost-effectiveness analysis, pomalidomide is the dominant option, since the use of pomalidomide in the MM treatment has a significant advantage over lenalidomide and bortezomib therapy in terms of «cost of the average time to disease progression» and «value of survival time». In other words, pomalidomide therapy has the lowest cost of achieved efficiency unit.

Analysis of the impact on the budget in case of pomalidomide (Imnovid) inclusion into the pattern of government procurement as part of the "Seven Nosologies" program for the target period (2016–2018) showed that pomalidomide inclusion will not lead to increase the program budget.

Key words: *pharmacoeconomics, multiple myeloma (MM), pomalidomide, lenalidomide, bortezomib, efficiency analysis, cost analysis, cost-effectiveness analysis, analysis of impact on budget, "Seven Nosologies" program, generic products.*

Introduction

Multiple myeloma (MM) is an incurable, progressive oncological disease of the blood system. MM accounts for approximately 1% of all malignant tumors and 13% of the hematopoietic tumors [1].

In the Russian Federation, the incidence of MM is about 2.1 cases per 100,000 people. In 2013, 3041 people were newly diagnosed, and 2205 patients died in the same year [2].

MM is included in the list of life-threatening and chronic progressive rare (orphan) diseases that can shorten life expectancy of the Russian population and increase disability. [22]

Multiple myeloma is considered to be a disease of the second half of life. In the Russian Federation, about 63% of patients are older than 60 years. Another part of patients are people who develop MM and die at working age [2].

MM is characterized by an excess of abnormal plasma cells in bone marrow (BM) and overproduction of intact monoclonal immunoglobulins (Ig) (M protein) or Bence Jones protein (monoclonal kappa and lambda free light chains) [3].

The main symptoms of myeloma manifest due to the excessive accumulation of myeloma cells in the BM and this causes:

- Abnormal function of the BM that is caused by anemia and/or low white blood cells or platelet count.
- Decrease in immunity caused by a decrease in normal immunoglobulin, resulting in increased susceptibility to infectious diseases.
- Production and penetration of monoclonal (M protein) from myeloma cells into blood and/or urine.
- Perimyelis destruction and its penetration into the BM cavities [4].

The symptoms of MM include bone pain (usually in the lower back and ribs), which is observed in about 68% of cases, anemia (in 62%), renal failure (in 55%), hypercalcemia (in 30% of cases), respectively [3].

Bone pain and hypercalcemia are caused by osteolytic damage of the bone tissue. Anemia is caused by infiltration of BM with MM cells and subsequent suppression of normal hematopoiesis. Kidney failure and increased blood viscosity arise mainly due to high levels of M protein.

The level of M protein is recognized as a major diagnostic criterion for evaluation of the treatment results [4]. Abnormal protein, M protein, is produced by the myeloma cells and can be found in blood and urine [5].

Modern concept of multiple myeloma treatment

For the treatment of patients with multiple myeloma for whom BM transplantation is not indicated, combination of melphalan and prednisolone (MP) or high-dose dexamethasone (HDD) have been used for many years as a standard therapy. A large number of studies show that MP or HDD therapy is characterized by a low response and median survival of 2–3 years. [6, 7, 8]. Nowadays, traditional chemotherapy (TC) has not completely lost its role, but its range of use significantly narrowed. Despite the use of various chemotherapeutic regimens and attempts to enhance their effectiveness by increasing the doses of drugs comprising different combinations of cytostatic agents or change of one chemotherapy program to another, treatment of MM

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patients not always been successful [6, 9, 10]. Low efficacy of chemotherapy has led to the development of a new generation medicines — immunomodulators (thalidomide, lenalidomide) and proteasome inhibitors (bortezomib), that have completely different mechanisms of antitumor effect [11, 12, 13, 14, 15]. However, after some time of the use of immunomodulators, treatment with innovative drugs turned out to be ineffective in some patients. This, in turn, has led to the development of a new generation immunomodulator. Pomalidomide is a unique class IMiDs(R) immunomodulator with numerous cellular effects that inhibit the growth of myeloma cells [16]. Preclinical studies have demonstrated efficacy of pomalidomide in the treatment of resistant patients, since it is active in drug-resistant myeloma cells, including those resistant to lenalidomide and bortezomib [17, 18, 19].

The use of new drugs has radically changed therapeutic paradigm of MM and enabled to look more optimistically at the prognosis of this severe disease, as well as differently formulate the therapy goals. This necessitated introduction of new criteria for evaluating the treatment effectiveness [20, 21].

Materials and methods

Pharmacoeconomic analysis was performed using the model developed in Microsoft Excel. The time horizon of modeling for the cost analysis was 1 year. For the analysis of impact on the budget, in case of pomalidomide inclusion in the "Seven Nosologies" federal program, time horizon was 4 years. As part of the developed model, we conducted pharmacoeconomic assessment of pomalidomide (Imnovid) use for the treatment of patients with relapsed or refractory multiple myeloma, who have received at least two lines of therapy that included lenalidomide and bortezomib.

Efficiency analysis

At this stage of the study, to examine the effectiveness of pomalidomide, lenalidomide and bortezomib, information retrieval was carried out to search the papers investigating effects of the above drugs on patients found to be refractory to first- and second-line therapy drugs (lenalidomide and bortezomib). The criterion for determining refractoriness was the lack of response to the chemotherapy or disease progression within 60 days after the last treatment [24].

To find the relevant studies, Pubmed and Medline databases were used. The search was made by keywords: refractory multiple myeloma. Three studies on the topic were found. One of the RCT found (CC4047) was excluded from this study, as it used the old pomalidomide dose (2 mg OD), which is currently not in use, as the dose 4 mg/day in days 1–21 of the 28-day-long course was recommended as more effective for the treatment of MM patients [25, 27].

Thus, 2 studies were selected for the efficiency analysis; the data obtained from these studies were defined as comparable. The data on the efficiency of lenalidomide and bortezomib in the treatment of patients previously treated with this therapy and found to be refractory to it were taken from the study in which medical records of 213 patients drawn from several medical centers in the US, Europe and Asia were examined. According to the results obtained, median overall survival (OS) for patients receiving bortezomib was 9 months. Median OS for patients treated with lenalidomide and was also 9 months. Progression-free survival for both categories of patients was 5 months [24].

Of particular note is the unique nature of the study MM-003: this is the only phase 3 study which examined effectiveness in such hardly pretreated patients with MM who received up to 18 previous therapy lines (median 5) and had «double» refractorness (75% of them) — to bortezomib and lenalidomide. There are no other studies with similar design investigating drugs to treat myeloma. Therefore, the data of subanalysis MM-003 were used for comparison. MM-003 showed the results of treatment of the group of patients with >50% decrease in M protein. This was done to make the groups as much as possible comparable.

Comparison was made among patients with «single refractorness» receiving bortezomib or lenalidomide.

It was shown that the use of the scheme with pomalidomide in patients with MM in indirect comparison with lenalidomide or bortezomib therapy was associated with longer median time to progression (8.4 and 5 months) and improvement of median overall survival (19.9 and 9.0 months) [25, 26].

Cost analysis

At this stage of the cost analysis, the cost of medication treatment of MM with pomalidomide, lenalidomide and bortezomib was calculated. The course dose for the drug therapy was determined based on the dosing schedules specified in prescribing information for these drugs.

The cost of bortezomib was calculated based on the average auction prices within the procurement for the "Seven Nosologies" program. In this regard, the data on 2 government drug procurements in 2015 were reviewed. To determine the price of the drug, the formula for weighted arithmetic average was used:

$$\bar{x} = \frac{\sum_{i=1}^{n} w_i \cdot x_i}{\sum_{i=1}^{n} w_i}, \text{ where:}$$

w_i, w_i – substance weight of procurement (0 to 1)

w_i, w_i – price for the unit of active substance in procurement

The cost of one vial of bortezomib (vial, 3.5 mg N1) was:

$$\frac{14\,884{,}5 \times 0{,}72 + 14\,696{,}05 \times 0{,}28}{1} \times 3{,}5 = \textbf{51 796 rub.}$$

Similarly, the cost of drug lenalidomide was determined. For the analysis of the weighted average cost of the drug, the data on 10 government procurement of lenalidomide within the "Seven Nosologies" program were analyzed. Thus, the cost of one pack of the drug lenalidomide (25 mg capsules N21) was 447,989 rub.

The data on the cost of pomalidomide were provided by the manufacturer. Pharmacoeconomic analysis was carried out on the basis of the cost of pomalidomide (4 mg capsules N21) of 723,000 rubles without VAT per pack.

The average cost of bortezomib treatment for 1 year per patient approaches to 2 mln rubles, according to the letter of the Russian Ministry of Health of the Russian Federation to the Government of the Russian Federation No. 25-1/10/1-1792 dated 09.21.12. On this basis, the estimated number of vials of bortezomib required to treat one patient for a year, will be 36 (2 mln rubles / 51.8 thous. rubles = 36), which corresponds to 9 cycles of therapy. Thus, the average cost for bortezomib treatment for 1 year per patient will amount to 1,864,664 rubles.

Similarly, the costs for treatment of multiple myeloma relapse with lenalidomide was calculated in accordance with the data of European clinical practice. According to international epidemiological research on multiple myeloma, conducted by an independent agency Kantar Health in 2010, the annual average duration of lenalidomide therapy was 4.5 months [23]. This is determined by several factors:

- not all the patients simultaneously begin the therapy with the beginning of the year;
- not all the patients continue their treatment for the whole calendar year. Sometimes, as during treatment with other medications, patients may stop the treatment earlier and/or can be switched to another therapy.

Thus, the average costs for medication therapy with lenalidomide for 1 year per patient amounts to 2,015,952 rubles. (447,989 rubles x 4.5 pkg. = 2,015,952 rubles).

The average cost of treatment with pomalidomide was determined based on the data of RCT (MM-003), in which one patient receives an average of 5 cycles of the drug, which is equivalent to 5 packs. Given these data, the average cost of the treatment with pomalidomide amounted to 3.615.000 rubles (723.000 rubles x 5 pkg. = 3,615,000 rubles).

Graphical representation of data obtained in the cost analysis of the basic medication therapy of MM is shown in Figure 1.

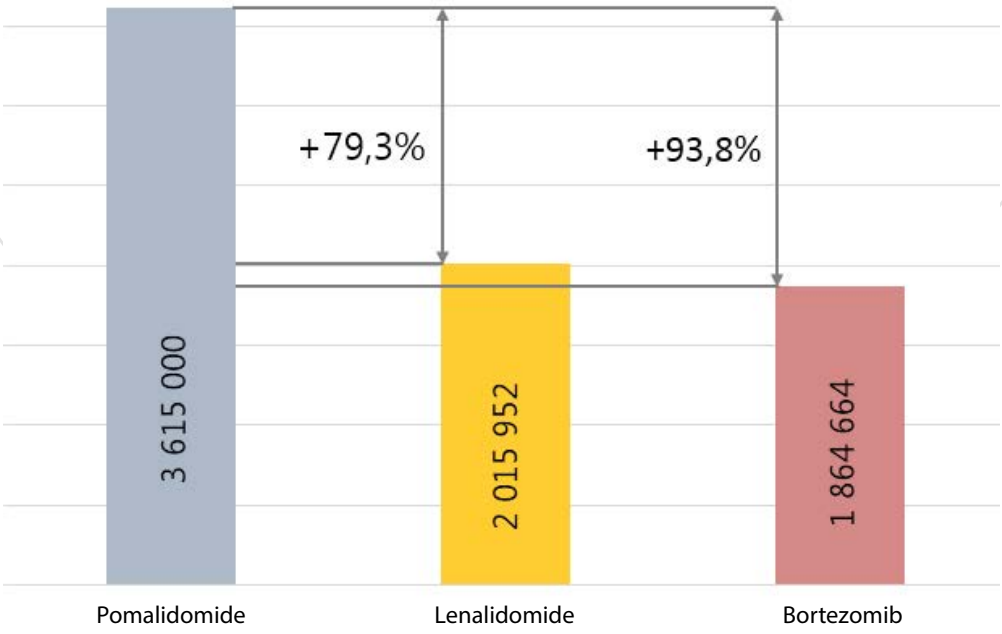

Figure 1. The costs for basic medication of MM therapy

As can be seen from the graph, the basic medication therapy with pomalidomide is by 79.3% and 93.8% more expensive than that with lenalidomide and bortezomib, respectively.

The amount of direct medical and direct non-medical costs for MM treatment of, basic medication therapy, adjunctive medication therapy and medical services is shown in Table 1.

Data on the necessary medical services and adjunctive medication therapy was obtained from the standard of health care in refractory and recurrent course of MM, approved by the order of the Russian Ministry of Health No. 1458n dated 24.12.12. The source of data on the cost of medical services was a rate agreement on payments for health care provided within the territorial program of compulsory health insurance in Moscow for 2015. Cost for adjunctive medication therapy was calculated on the basis of the registry of maximum sale prices for the most important vital medicines as amended on 26.09.2015 [31, 32].

Table 1. Data on the average costs for the treatment of one patient with MM for 1 year

Drug	Description of costs	Cost value	Total costs
Pomalidomide	Basic medication therapy	3,615,000, rubles	4 853 916 rubles
	Adjunctive medication therapy	974,432 rubles	
	Medical services	264,484 rubles	
Lenalidomide	Basic medication therapy	2 015 952 rubles	3 130 976 rubles
	Adjunctive medication therapy	876 989 rubles	
	Medical services	238 035 rubles	
Bortezomib	Basic medication therapy	1 864 664 rubles	3 537 209 руб.
	Adjunctive medication therapy	1 315 483 rubles	
	Medical services	357 061 rubles	

According to the data shown in Table 1, total costs of the course of treatment with Pomalidomide, Lenalidomide and Bortezomib equaled to 4,853,916 rubles, 3,130,976 rubles, and 3,537,209 rubles, respectively.

Graphical presentation of the results obtained in the cost analysis is shown in Figures 2–4.

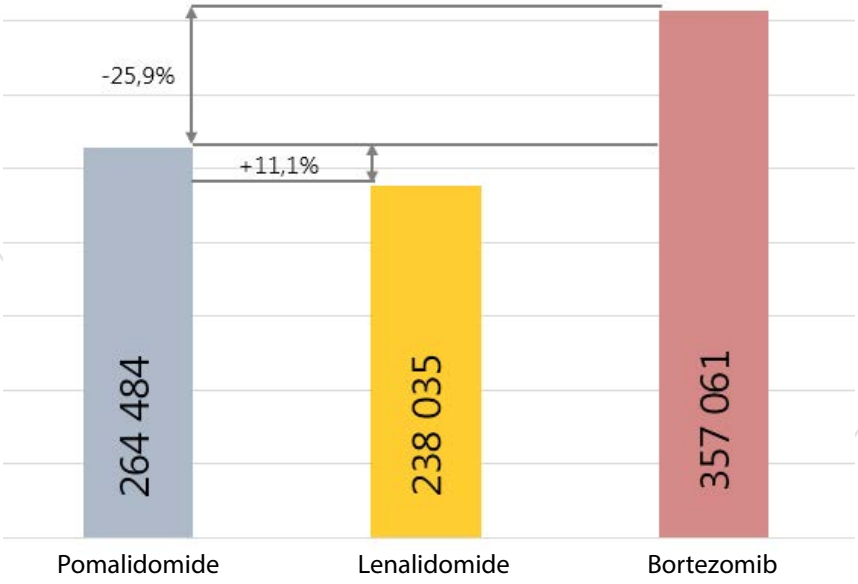

Figure 2. The costs for medical services in MM treatment (rubles)

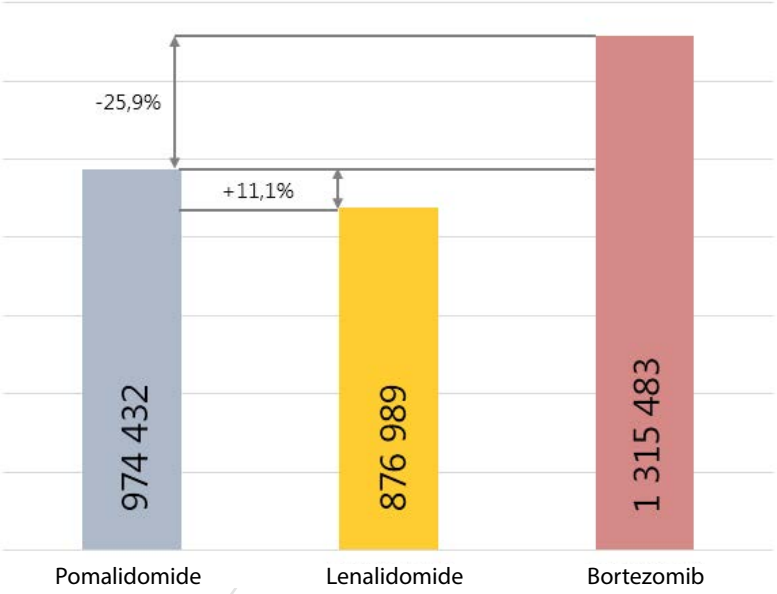

Figure 3. The costs for of adjunctive medication therapy in MM treatment (rubles)

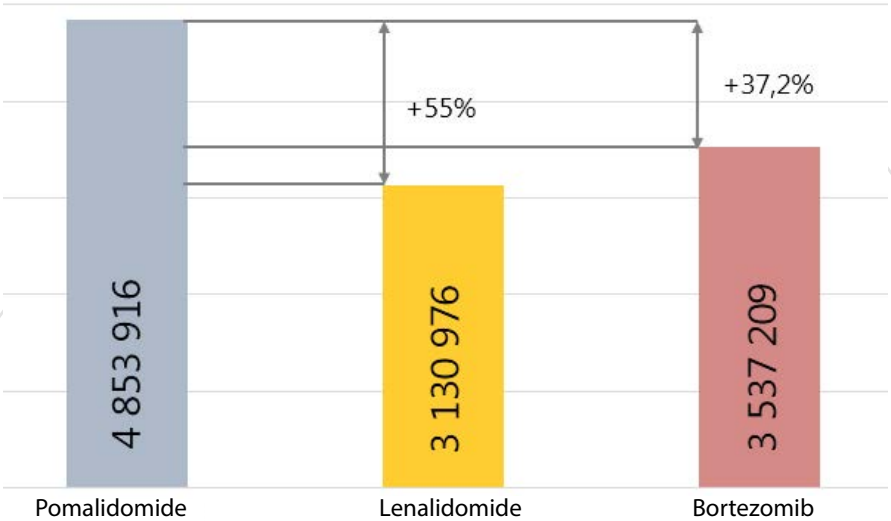

Figure 4. The total costs for MM treatment (rubles)

These results indicate that the basic medication therapy with pomalidomide involves the cost increase by 79.3% and 93.8% compared with bortezomib and lenalidomide, respectively. The total costs for pomalidomide treatment (including adjunctive medication therapy and medical services) compared to lenalidomide and bortezomib requires an overall costs increase by 55% and 37.2% respectively.

Cost-effectiveness analysis

The cost-effectiveness analysis aims to a comprehensive assessment of medical technology to determine the most efficient utilization of the limited health care resources. Median progression-free survival (PFS) and median overall survival (OS) were used as effectiveness measures. The cost-effectiveness ratio was defined by the formula:

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

The cost-effectiveness ratio by PFS

Pomalidomide CER (median PFS) = 4,853,916 rubles/8.4 months = 577,847 rubles/month.

Lenalidomide CER (median PFS) = 3,130,976 rubles/5 months = 626,195 rubles/month.

Bortezomib CER (median PFS) = 3,537,209 rubles/5 months = 707,442 rubles/month.

Cost-effectiveness ratio by PFS in the MM treatment with pomalidomide as a basic therapy amounted to 577,847 rubles per one month of MM progression-free survival. In case of prescription of lenalidomide and bortezomib the ratio was 626,195 rubles and 707,442 rubles, respectively. According to the cost-effectiveness ratios obtained by median PFS, the cost-effectiveness ratio for pomalidomide is lower than that for lenalidomide and bortezomib. Based on these data we can conclude that pomalidomide therapy carries the lowest cost to achieve the unit of efficiency and is the predominating option.

Subsequently, the cost-effectiveness analysis by the median OS was carried out, that is, the cost of achieving the unit of efficiency, i.e. 1 month of life, with each of the drugs was found.

The cost-effectiveness ratio by median survival in months (OS) was:

Pomalidomide CER (median OS) = 4,853,916 rubles/19.9 months = 243,915 rubles.

Lenalidomide CER (median OS) = 3,130,976 rubles/9 months = 347,886 rubles.

Bortezomib CER (median OS) = 3,537,209 rubles/9 months = 393,023 rubles.

Cost-effectiveness ratio by median overall survival in months in the treatment of MM with pomalidomide as a basic therapy amounted to 243,915 rubles per 1 month of survival. In case of prescription of lenalidomide and bortezomib the ratio was 347,886 rubles and 393,023 rubles, respectively. It should be noted that this ratio is also lower for pomalidomide than that for the compared options.

Thus, from the perspective of the cost-effectiveness analysis, the use of pomalidomide in the MM treatment has an advantage over lenalidomide and bortezomib therapy in terms of median PFS and median OS, i.e. it is the predominating option.

Sensitivity analysis

To determine the degree of stability of the rates achieved in cost-effectiveness analysis, one-way sensitivity analysis was performed. The price change was an impact factor. To determine the stability of the results obtained, the price for pomalidomide was hypothetically changed up and down by 10% of its original value, and the rate of change of relevant pharmacoeconomic parameters was analyzed (Table 2).

Table 2. One-way sensitivity analysis of pharmacoeconomic parameters depending on changes in the cost of pomalidomide

Parameters	Cost of pomalidomide, % (abs.)		
	- 10% (650 700 rubles)	Исходное значение (**723 000** rubles)	+10% (795 300 rubles)
CER by median PFS	534 811	577 847	620 883
CER by median OS	225 750	243 915	262 081

With the increase in the price for pomalidomide by 10%, the cost-effectiveness ratio by PFS was 620,883 rubles; in turn, the ratio by OS was 262,081 rubles. These figures, even after the increase in the price, are lower than that of lenalidomide and bortezomib.

The sensitivity analysis shows that the treatment using pomalidomide remains effective from the standpoint of the cost-effectiveness analysis after the change in its price in the range of -10% to + 10%.

Analysis of the impact on the budget within the "Seven Nosologies" program

This stage of the study involved analysis of the economic impact of pomalidomide inclusion in the pattern of government procurement for the period of 2016–2018 within the "Seven Nosologies" (VZN) program started in 2008, for the treatment of patients who have diseases classified as high-cost nosologies, including, among others, multiple myeloma.

The time horizon of modeling was 4 years (2015–2018), as in 2018 according to the Federal Law «On Amendments to Article 101 of the Federal Law «On the basis of health care in the Russian Federation», it is planned to transfer the functions of drug provision for the treatment of high-cost diseases included in the "Seven Nosologies" program, from the federal to the state level [28]. At the same time, the analysis itself was performed in 2 stages (Figure 5): 1) Prediction of future budget costs in 2015–2018; 2) Analysis of the impact on the budget of pomalidomide introduction in the pattern of government procurement within the "Seven Nosologies" program.

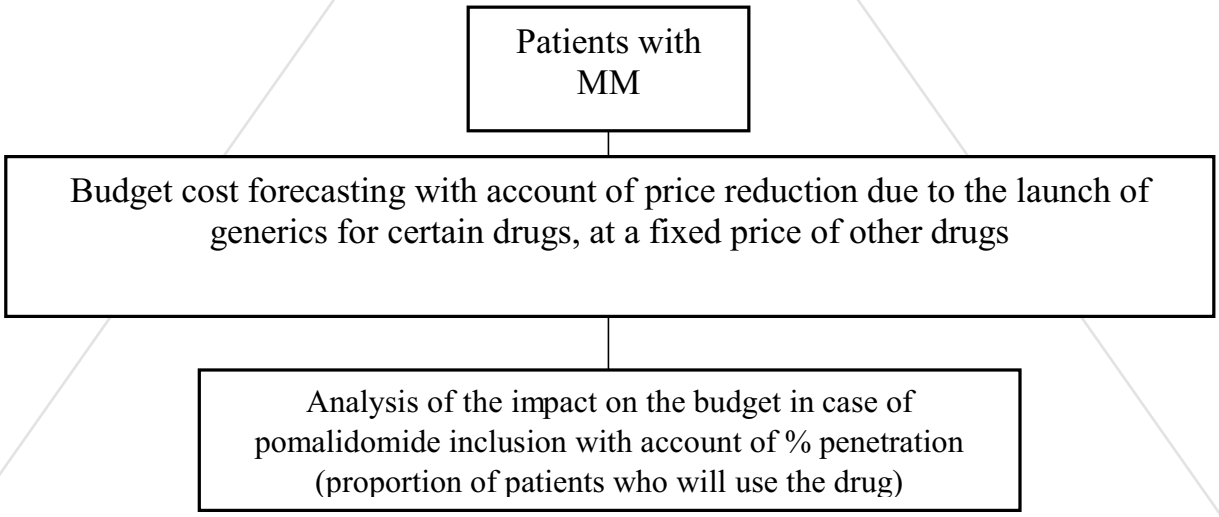

Figure 5. Analysis outline of impact on the budget within the "Seven Nosologies" program

The first step is prediction of the budget costs with account of reduction in prices due to the launch of generics for the drugs listed below (Table 3) within the planning period [29].

Table 3. Generics in the "Seven Nosologies" program for the planning period

International nonproprietary name	Trade name	Marketing authorization holder	Registration date
Bortezomib	Boramilan® FS	F-SINTEZ CJSC (Russian Federation)	09.04.2014
	Bortezomib	Biocad CJSC (Russian Federation)	12.01.2015
	Bartizar	Pharmaceutical company "Sotex" CJSC (Russian Federation)	01.04.2015
Rituximab	Acelbiya	Biocad CJSC (Russian Federation)	04.04.2014
	Rituximab	Biocad CJSC (Russian Federation)	04.04.2014
Generics for glatiramer acetate have not been registered in the Russian Federation yet [34].			

To determine the financial capacity of the "Seven Nosologies" program in the planning period we used the data on the size of the budget specified in the Federal Law dated 01.12.2014 No. 384-FZ «On the Federal Budget for 2015 and the planning period of 2016 and 2017» [29].

Data on the annual use of the budget and the average price for the drug pack within the "Seven Nosologies" program were based on the results of public procurement, published on the website: http://zakupki.gov.ru[30].

Registration data of generics was obtained from the official website of the state register of medicines http://grls.rosminzdrav.ru/ [36].

To predict the future changes in the prices of drugs for which generics are planned to be launched, we used the data of publication taken from electronic resource http://imshealth.com/, which demonstrates dynamics in the drug price change after release of generics [33].

Patients refractory to prior lines of therapy can receive both bortezomib and lenalidomide, according to the prescription of the attending physician. During modeling it was assumed that patients switched to pomalidomide will not receive bortezomib and lenalidomide in a ratio of 1:1, that is, before switching to pomalidomide, one half of the patients received therapy with bortezomib, and the other one — with lenalidomide.

The forecast on the future budget costs showed annual cost decrease within the planned (see Table 4).

Table 4. The forecast on use of the "Seven Nosologies" program funds

Year	2015	2016	2017	2018
Planned budget, bln rubles	44	44	44	44
Actual budget (all the program), bln rubles	42	38,8	37,9	37,1
Savings (all the program), bln rubles	2	5,2	6,1	6,9
Costs for в oncohematology, bln rubles	18,6	15,8	15,1	14,4

The forecast data within 4 years show an increase in budget savings in comparison with 2015 by 246%. At the same time, the savings by the end of the planning period will be at the level of 6.9 bln rubles. It is expected that by 2018 the costs for drugs used by the "Seven Nosologies" program in the treatment of hematological diseases will be reduced by 4.2 bln rubles or 22%.

The analysis showed the possibility of introducing pomalidomide in the pattern of public procurement of the "Seven Nosologies" program without additional funding, with only partial use of savings. Furthermore, additional savings were provided by the fact that patients receiving pomalidomide during the planning period will not receive bortezomib and lenalidomide within the program (Table 5).

Table 5. Analysis results of impact on the budget within the "Seven Nosologies" program

Year	2015	2016	2017	2018
Number of patients treated	6 588	6 670	6 663	6 656
Proportion of penetration with pomalidomide (proportion of patients who will use the drug), %	1	2	5	10
Planned number of patients receiving pomalidomide, people	66	133	333	666
Costs accounted for pomalidomide, bln rubles	0,38	0,77	1,93	3,85
Savings (the whole program), bln rubles	2	5,23	6,11	6,93
Savings accounted for bortezomib, bln rubles	0,06	0,11	0,26	0,48
Savings accounted for lenalidomide, bln rubles	0,06	0,14	0,34	0,67
Actual savings of the budget (including bortezomib and lenalidomide), bln rubles	2,12	5,48	6,71	8,08

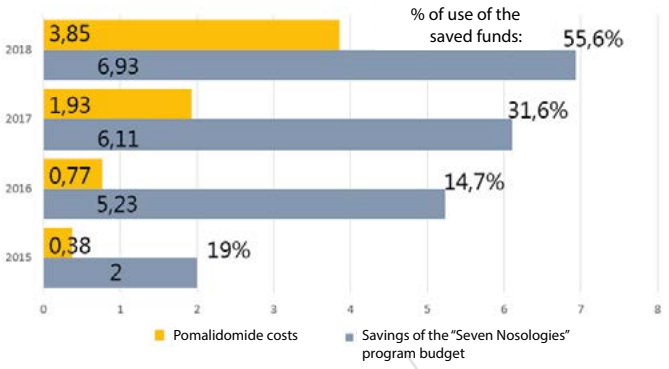

Figure 6. Comparison of the costs for pomalidomide with savings in the "Seven Nosologies" program, bln rubles

Comparison of the costs for pomalidomide and planned savings in the "Seven Nosologies" program is shown in Figure 6.

As seen in Figure 6, the costs for pomalidomide in 2018 use only a part of the funds saved under the program.

Subsequently, comparative characterization of the planned costs for pomalidomide and estimated values of savings in oncohematology was carried out (Table 6).

Table 6. Analysis results of impact on the budget with respect to the savings in oncohematology

Year	2016	2017	2018
Number of patients treated	6 670	6 663	6 656
Proportion of penetration with pomalidomide (proportion of patients who will use the drug), %	5	5	10
Planned number of patients receiving pomalidomide, people	133	333	666
Costs accounted for pomalidomide, bln rubles	0,77	1,93	3,85
Savings made in oncohematology, bln rubles	2,78	3,49	4,14
Savings accounted for bortezomib, bln rubles	0,11	0,26	0,48
Savings accounted for lenalidomide, bln rubles	0,14	0,34	0,67
Actual savings of the budget (including bortezomib and lenalidomide), bln rubles	3,03	4,09	5,29

Comparison of pomalidomide costs and planned savings made in oncohematology is shown in Figure 7.

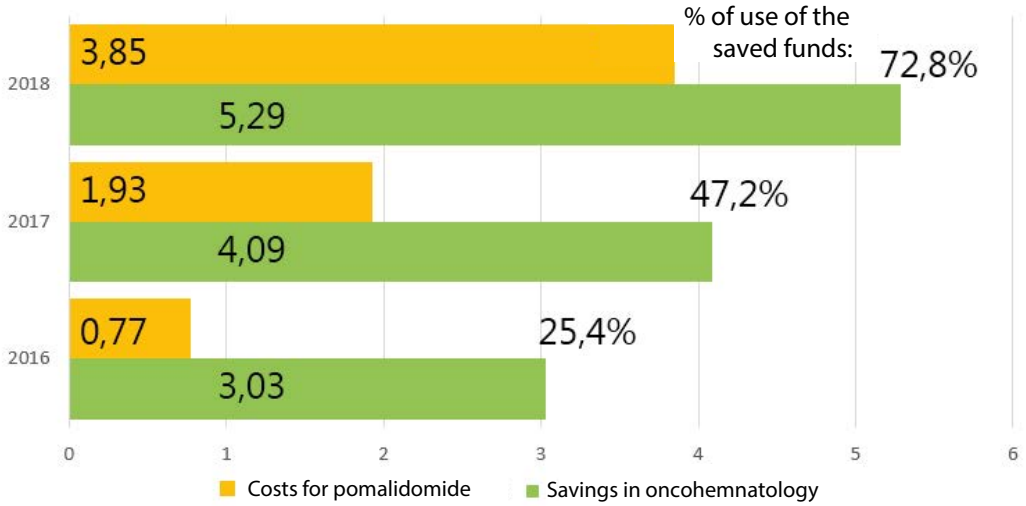

Figure 7. Comparison of pomalidomide costs and the savings made in oncohematology, bln rubles

According to the data obtained, it was concluded that introduction of the drug pomalidomide in the pattern of government procurement can be implemented at the expense of the savings made in oncohematology, without involvement of the funds saved in other nosologies.

Conclusions

As a result of pharmacoeconomic analysis carried out for patients with more than 50% reduction in M protein, it was found that:

– basic medication therapy with pomalidomide compared to lenalidomide and bortezomib requires the costs increase by 79.3% and 93.8%, respectively;

– total costs for the basic medication therapy, adjunctive medication therapy and medical services for the MM treatment, in case of pomalidomide prescription, is higher than total costs for lenalidomide and bortezomib by 55% and 37.2%, respectively;

– from the perspective of the cost-effectiveness analysis, pomalidomide use in the MM treatment has significant advantage over lenalidomide and bortezomib therapy in terms of median PFS and median OS, i.e., it is a predominant option;

– analysis of impact on the budget, in the case of pomalidomide inclusion in the "Seven Nosologies" federal program, showed that the total cost for the treatment of patients with hematological malignancies in 2016, 2017 and 2018 will amount to 15.8 bln rubles, 15.1 bln rubles and 14.4 bln rubles, respectively, that is 15%, 18.8% and 22.6% below the current costs of the program for oncohematology (18.6 bln rubles), respectively.

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