№2 Том3 2015

Фармакоэкономика
теория и практика

Pharmacoeconomics
theory and practice

№2 Volume3 2015

- IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ» г.УФА, 16-17 МАРТА 2015 года
- ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ

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PHARMACOECONOMIC ANALYSIS OF THE USE OF GAZYVA (OBINUTUZUMAB) FOR THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA IN THE RUSSIAN FEDERATION

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Abstract: *In this study, a pharmacoeconomic analysis of chronic lymphocytic leukemia therapy in previously untreated patients was conducted, using treatment regimens obinutuzumab (Gazyva) + chlorambucil and rituximab + chlorambucil. The results of the study showed that though the costs of the first treatment course with obinutuzumab + chlorambucil are significantly higher, this regimen reduces the cumulative cost of subsequent therapy lines in patients with CLL (due to a longer progression-free survival). In the end of the third year of therapy, cumulative costs become relatively similar: with the use of the obinutuzumab + chlorambucil regimen, the cumulative cost per 1 patient/year will be 38,390 rubles higher compared to the rituximab + chlorambucil regimen. At the same time, the obinutuzumab regimen showed a lower cost-effectiveness ratio, i.e. it had an advantage over the alternative technology.*

Key words: *chronic lymphocytic leukemia, modeling, cost analysis, effectiveness analysis, budget impact analysis, sensitivity analysis.*

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults. The risk of developing CLL increases with age as in Europe the median age at diagnosis is 69 years [4]. In the Russian Federation, considering that life expectancy is shorter and a diagnosis level is lower, the median age may be lower (reliable statistical data are not available) [2]. However, according to the Hematological Scientific Center of the Russian Academy of Medical Sciences, out of 492 patients examined only 28% of patients were at the age of 65-74 years and 6% over 75 years [2]. By contrast, in the USA 44% of patients were at the age of 65-74 years, while over 23% of the total number of patients with CLL were over 75 years old [2].

At present, CLL is an incurable disease. A wide range of medicines which can be used for the treatment of CLL is now available on the pharmaceutical market.

However, it should be noted that in most clinical studies the safety and effectiveness of such medicines were examined in rather young, apparently healthy patients [11]. In real practice, though, most patients are older and have one or more complications. Obviously, the designated differences between patient cohorts make it difficult to evaluate the medicines and also complicate the process of selecting the optimum therapy regimen for patients.

Gazyva (obinutuzumab) is a glycoengineered, humanized type II monoclonal antibody tested in the group of elderly patients with one or more comorbidities [9].

The objective of this study was to determine, from a pharmacoeconomic point of view, the preferred regimen for the treatment of chronic lymphocytic leukemia in previously untreated elderly patients, on the basis of comparison of the cost-effectiveness ratio and safety of the following treatment regimens:

- obinutuzumab (Gazyva) + chlorambucil;
- rituximab (Mabthera) + chlorambucil.

Selection of these treatment regimens was based on the modern approach to CLL therapy, according to which patients are recommended to receive a more effective treatment regimen in the first therapy line. In CLL11 study (the only large multicenter study of CLL therapy in elderly patients (median age 73 years) with comorbidities (creatinine clearance 62 mL/min and mean CIRS baseline score 8), monotherapy with chlorambucil demonstrated significantly lower effectiveness in terms of response to therapy, progression-free survival, and overall survival compared to obinutuzumab + chlorambucil and rituximab + chlorambucil [8].

Population

In this study, a patient cohort was represented by a hypothetic group of average elderly patients with CLL (age >70 years) with one or more comorbidities. The cohort size was 1,593 patients, which was consistent with the number of "other leukemia" cases (chronic lymphocytic leukemia, subacute lymphocytic leukemia, ICD-10 codes: C91.1-9) in the selected age category registered in the Russian Federation in 2012 [1]. Medication dosages were calculated using data obtained from the cohort that had participated in CLL11 study. The average surface area of patients was 1.8 m^2, and the average body weight was 72.03 kg.

Effectiveness analysis

The effectiveness analysis was performed using the Markov model with a period of 1 month (Fig. 1). The time frame of this study was 3 years, which was consistent with the duration of CLL11 clinical study.

The results of CLL11 3-arm comparative study (average data of two phases) showed that the median progression-free survival was 29.56 months in G-Clb group, and 15.86 months in R-Clb group.

Probabilities of each of the events required for pharmacoeconomic modeling were based on the results of CLL11 study.

Considering that G-Clb therapy shows a significantly longer period of progression-free survival, the third and the second treatment courses

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were also taken into account. At the same time, national and international guidelines recommend that, in case of disease progression within a period of less than two years after the first treatment course, other treatment regimens should be used. In case of the first treatment course with R-Clb regimen, the median progression-free survival is shorter, while in the therapy with G-Clb regimen the respective median is longer than the specified period. However, according to the instructions for use, obinutuzumab is recommended for use as the first line therapy only and, therefore, irrespective of the initial therapy line, all patients were administered bendamustine + rituximab regimen after disease progression (B-R). The median progression-free survival in this case was 15.2 months [7].

Cost analysis

The cost analysis included only direct costs associated with CLL therapy with the medicines being analyzed (Fig. 2). Rates of the Federal Compulsory Medical Insurance Fund (FCMIF), hospital care standards, healthcare facility pricelists, data of drugs wholesales (IMS), State Register of Selling Price Limits, pharmindex.ru) were used as cost data sources.

In this study, costs of the first treatment course with the regimens being analyzed and costs of the subsequent treatment courses (2nd and 3rd courses) with bendamustine + rituximab (B-R) were taken into account.

Costs associated with the correction of drug-related adverse events (Table 1) were also included.

Table 1. Costs associated with the correction of drug-related adverse events

Adverse drug reaction	Price	Source of data on medical services/ medicines/nutrition
Anemia	47,541 rubles	FCMIF rates as of 01.10.14
Neutropenia	122,422 rubles	Standard of care for acquired neutropenia [6]
Infection: pneumonia	33,322 rubles	FCMIF rates as of 01.10.14
Thrombocytopenia	46,357 rubles	FCMIF rates as of 01.10.14
Infusion reactions	95 rubles	Instructions for use of Gazyva on the manufacturer's website, date of access: 15.03.15

Figure 1. Markov model forming the basis for this study

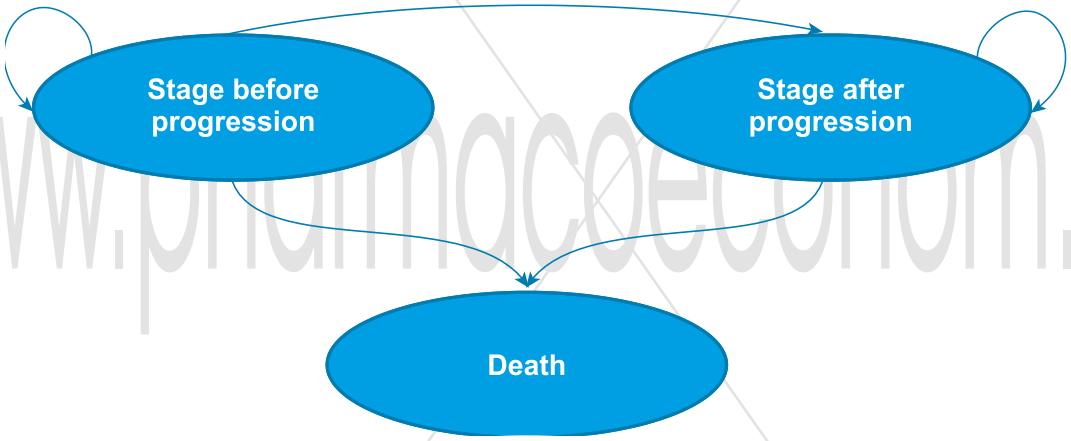


Figure 2. Structure of costs included in this study

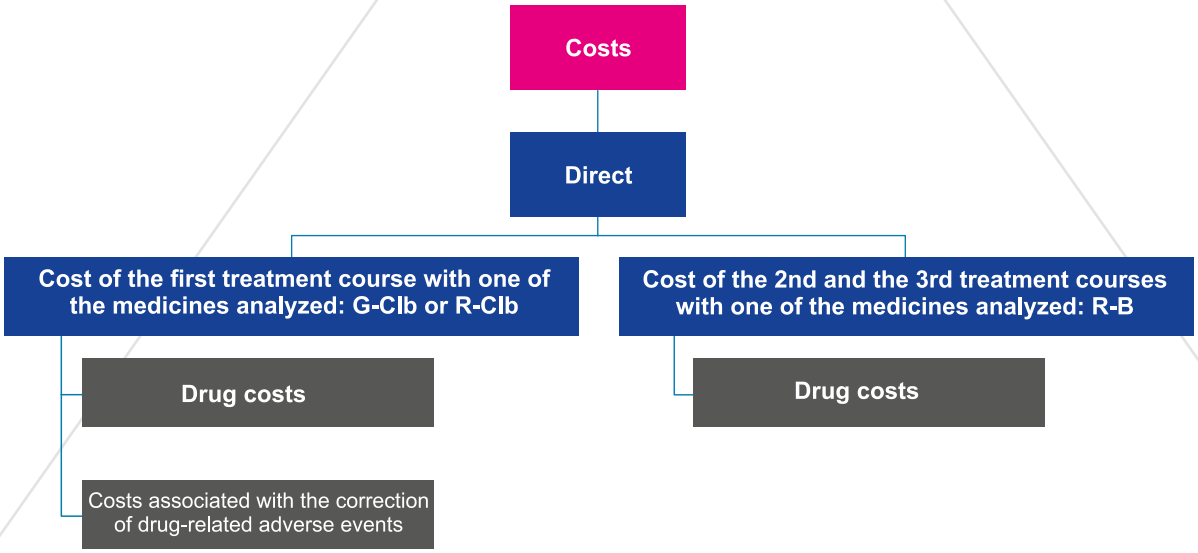


Table 2. Prices of the medicines analyzed

Drug	Dosage	Pack price	Source
Obinutuzumab (Gazyva)	1,000 mg No.1	250,290 rubles	Selling price limit to be registered by the manufacturer (including VAT)
Chlorambucil	2 mg No.25	2,633 rubles	State Register of Selling Price Limits (including VAT)
Rituximab	500 mg No.1	73,836 rubles	State Register of Selling Price Limits (including VAT)
Bendamustine	100 mg No.1	30,500 rubles	IMS data

The cost of a treatment course with rituximab was calculated taking into account that dosage is based on the patient's body surface area and, therefore, actual costs were used, i.e. those of the required number of vials instead of the required amount of the medication in milligrams. It should be noted that in the case of obinutuzumab the dose is fixed for all patients (drug dose for infusion corresponds to vial volume) and consequently there are no losses r

Results

As a result of modeling the survival of patients over a period of three years, it turned out that changes in the cohort size over time were similar to those of CLL11 clinical study (Fig. 3 and 4). The observed differences in the plots, namely, no intersection of curves in modeling can possibly be associated with the use of average data of event (death) probabilities per unit time.

According to the developed model, one average patient received one treatment course with G-Clb, while with R-Clb regimen the average patient received two treatment courses, which is explained by the difference in the duration of progression-free survival.

Along with that, the difference in life expectancy over the designated period of time in average representatives of the cohorts being analyzed, receiving G-Clb and R-Clb, was 0.13 months (1 month 18 days) (Fig. 5).

The cost analysis showed that the cumulative cost for the first treatment course was significantly higher in G-Clb group compared to R-Clb: the amount of 1,110,599 rubles was additionally required for the treatment (Table 3).

The cumulative cost per one patient over 3 years was also higher in the group of patients receiving G-Clb (Fig. 7). However, in the end of the third year, cumulative costs turned out to be relatively similar (Fig. 6). The budget impact analysis showed that CLL therapy with G-Clb required 38,390 rubles more per one patient/year compared with R-Clb (in the entire cohort analyzed over three years – 183,464,297 rubles).

Table 3. Cost analysis results

Parameter	G-Clb	R-Clb
Cost for one treatment course (theoretical)	2,099,517 rubles	835,961 rubles
Cost for one treatment course (actual)	2,099,517 rubles	957,790 rubles
Cumulative cost per 1 person over three years	3,217,189 rubles	3,102,020 rubles

Figure 3. Modeling results: Overall survival of patients with CLL over three years

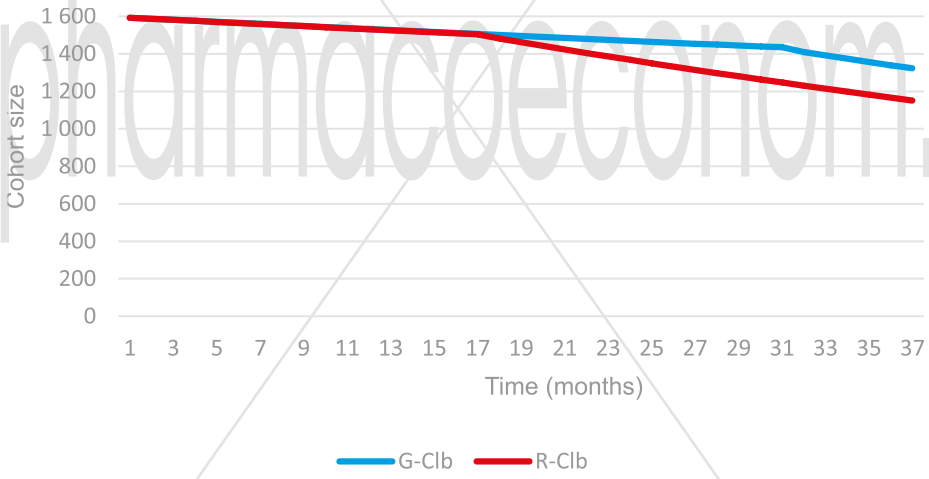


Figure 4. Results of CLL11 clinical study: Overall survival of patients with CLL over three years

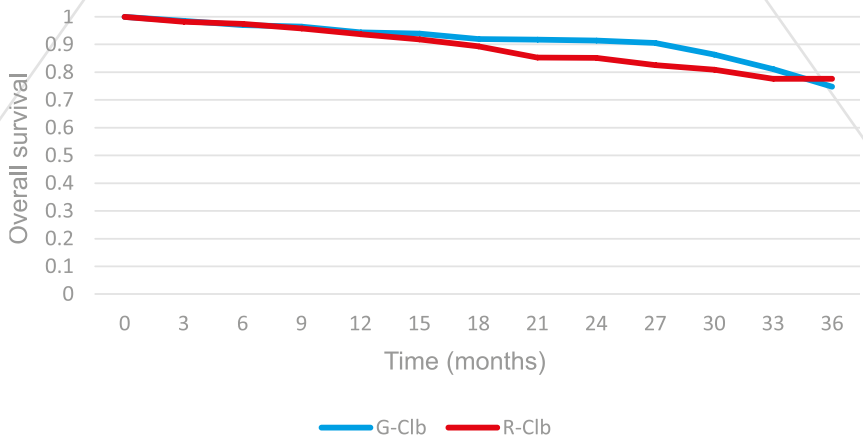


Figure 5. Number of years of life per one patient: model time frame – three years

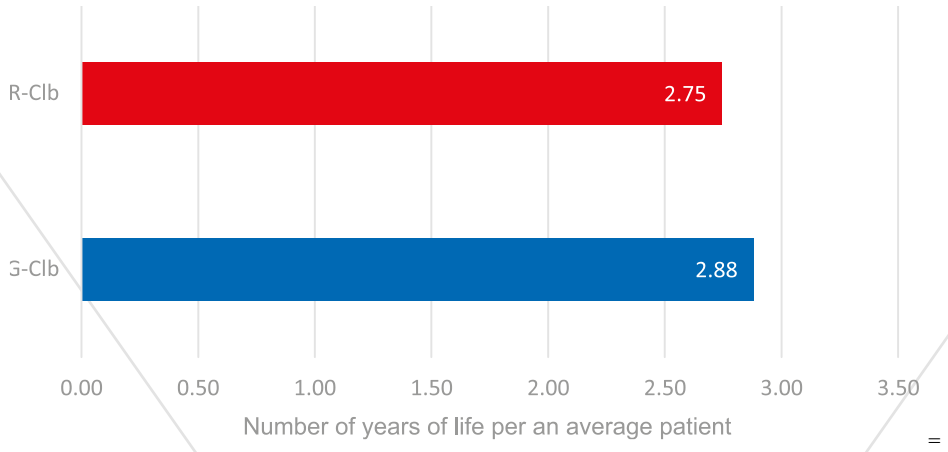


Figure 6. Cumulative cost over three years: amount of costs for survivors over the respective period of time

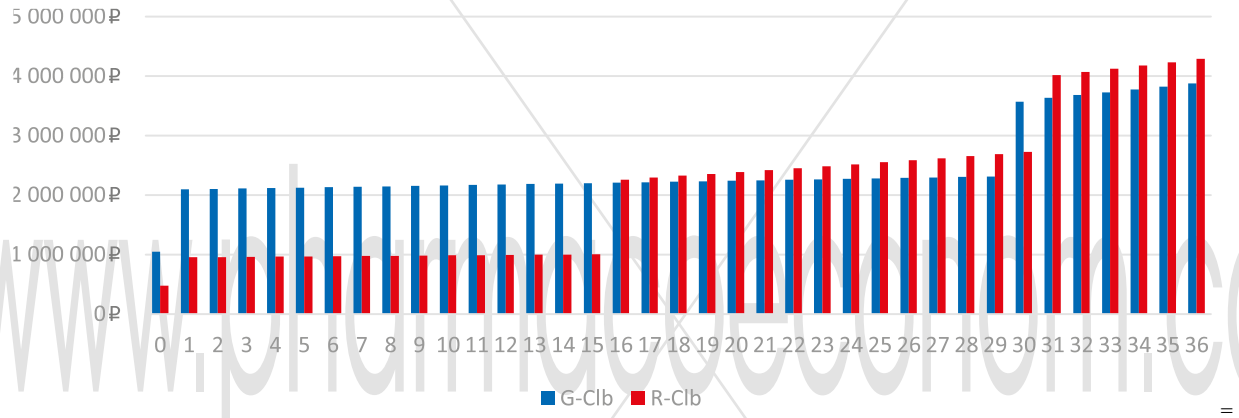
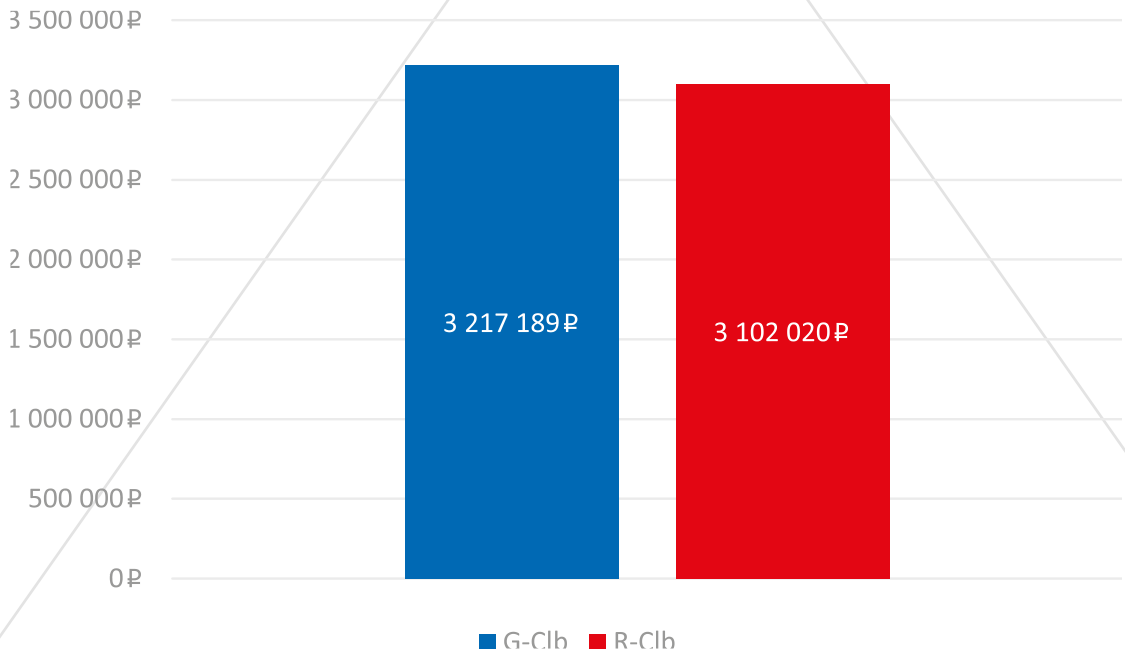


Figure 7. Cumulative cost per one patient over three years



As a result of the cost-effectiveness analysis it was found that G-Clb regimen is associated with lower cost per 1 life year (Table 3, Fig. 8), i.e. is dominant compared to the alternative regimen.

Table 4. Cost-effectiveness analysis results

Drug	Life years	Cumulative cost per 1 patient	CER
G-Clb	2.88	3,217,189 rubles	1,116,724
R-Clb	2.75	3,102,020 rubles	1,129,204

To check the stability of the obtained results, the cost-effectiveness ratio was analyzed for sensitivity to changes in prices of the medicines being studied. According to the results of this analysis, G-Clb regimen shows lower cost per effectiveness unit if the price of obinutuzumab increases by +1% or the price of rituximab decreases by -2%.

Table 5. Results of the analysis of cost-effectiveness ratio sensitivity to drug price changes

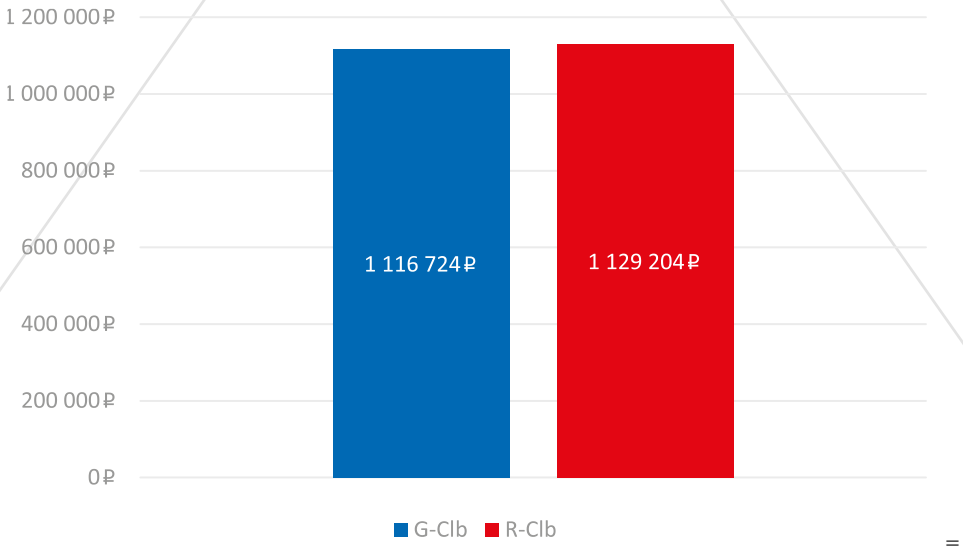
	Change (%)		
	-2%	0	+1%
G-Clb: Obinutuzumab price change	1,095,982 rubles	1,116,724 rubles	1,123,638 rubles
G-Clb: Chlorambucil price change	1,116,488 rubles	1,116,724 rubles	1,112,854 rubles
R-Clb: Rituximab price change	1,119,580 rubles	1,129,204 rubles	1,132,412 rubles
R-Clb: Chlorambucil price change	1,128,957 rubles	1,129,204 rubles	1,129,286 rubles

Conclusions

The treatment regimen with obinutuzumab and chlorambucil was accompanied by higher costs of the first treatment course. However, with a longer progression-free survival, this regimen reduced costs of the subsequent therapy lines in patients with CLL. In the end of the third year of therapy, cumulative costs become relatively similar: with the use of the obinutuzumab + chlorambucil regimen, the cumulative cost per 1 patient/year will be 38,390 rubles higher compared to the rituximab + chlorambucil regimen.

At the same time, the obinutuzumab regimen showed a lower cost-effectiveness ratio, i.e. it had advantage over the alternative technology.

Figure 8. Results of the cost-effectiveness analysis: effectiveness criterion – life years saved



References

1. Malignant neoplasms in Russia in 2012 (Incidence and mortality) / ed. by A. D. Kaprina, V. V. Starinsky, G. V. Petrova. - M.: Fgbu mnioi. P. A. Herzen» Of Rmph, 2014. - 250C.
2. Nikitin E. A. Differential therapy of chronic lymphocytic leukemia: dissertation for doctor of sciences. / Nikitin Evgeniy Alexandrovich. - M., 2014. 202 p.
3. Nikitin E. A., Sudarikov A. B. Chronic lymphocytic leukemia high-risk: history, definition, diagnosis and treatment. Clinical Oncohematology, 2013; Volume 6, No. 1, Pp. 59-67.
4. Russian clinical recommendations on diagnostics and treatment lymphoproliferative diseases. Additions and updates 2014 this year, Under the guidance of Professor I. V. Poddubnaya, Professor V. G. Savchenko. S. 274.
5. The condition of cancer the slop of the population of Russia in 2013 / / under edited by A. D. Kaprina, V. V. Starinsky, G. V. Petrova. - M.: fgbu Moscow Oncology research Institute after P. A. Herzen» of rmph, 2014; 235 p.
6. The standard of care in acquired neutropenia. http://static-2.rosminzdrav.ru/system/attachments/attaches/000/020/935/ original/%D0%91%D0%9E%D0%9B%D0%AC%D0%9D%D0%AB%D0%9 C_%D0%9F%D0%A0%D0%98_%D0%9F%D0%A0%D0%98%D0%9E%D 0%91%D0%A0%D0%95%D0%A2%D0%95%D0%9D%D0%9D%D0%9E %D0%99_%D0%9D%D0%95%D0%99%D0%A2%D0%A0%D0%9E%D0%9F%D0%95%D0%9D%D0%98%D0%98_30.docx?1404301757. Date of access: 15.03.15.
7. Fischer, K. et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. Journal of Clinical Oncology, 2011; № 29, p. 3559-3566.
8. Goede V. et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014; №370, p.1101-1110. DOI: 10.1056/NEJMoa1313984.
9. Hoy S.M. Obinutuzumab: a review of its use in patients with chronic lymphocytic leukaemia. Springer International Publishing Switzerland, 2015. DOI: 10.1007/s40265-014-0340-3.
10. Iannitto E. et al. Bendamustine with or without rituximab in the treatment of relapsed chronic lymphocytic leukaemia: an Italian retrospective study. British Journal of Haematology, 2011; №153, p. 351-357. DOI: 10.1111/j.1365- 2141.2011.08597.x.
11. Smolej L. Hpw I treat elderly or comorbid patients with chronic lymphocytic leukemia. ACTA MEDICA (Hradec Kralove) 2010; Vol. 53, №4, p. 213-220.
12. Veliz M., Pinilla-Ibarz J. Treatment of relapsed or refractory chronic lymphocytic leukemia. Cancer Control, 2012; Vol. 19, № 1, p. 37-53.
13. Weide R. et al. Retreatment with bendamustine-containing regimens in patients with relapsed/refractory chronic lymphocytic leukemia and indolent B-cell lymphomas achieves high response rates and some long lasting remissions. Leukemia & Lymphoma, August 2013; Vol. 54, №8, p. 16401646. DOI: 10.3109/10428194.2012.747679.