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BUDGET IMPACT ANALYSIS FOR PHARMACOLOGICAL THERAPY OF CHRONIC MYELOID LEUKEMIA (CML) WITH NILOTINIB AS THE SECOND-LINE TREATMENT

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Executive summary: *budget impact analysis and cost-effectiveness analysis for the therapy of chronic myeloid leukemia (CML) by tyrosine kinase inhibitors were performed by means of a developed analytical model of decision-making. This analysis defined potential budget impact of nilotinib as the second-line therapy in the frame of drug reimbursement program for subjects with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher's disease, tumors of the lymphoid, haemopoietic and related tissues, multiple sclerosis, as well as for patients subjects to organ (tissue) transplantation (hereafter reimbursement program for high-cost drugs). Budget impact analysis has shown that conversion from imatinib to nilotinib for all subjects with chronic myeloid leukemia (CML) in Russian Federation receiving second-line therapy, based on theoretic consumption, would lead to RUR 1.985 billion increase of the federal budget (compared to imatinib only). Taking into account the actual nilotinib consumption, budget of the Scenario 1 does not exceed the real cumulative amount for chronic myeloid leukemia (CML) treatment in the framework of the reimbursement program for high-cost drugs and regional subsidized drug lists. In addition, it was demonstrated that nilotinib compared to imatinib can be characterized as a strictly preferable drug from the cost-effectiveness analysis point of view, as it has a lower cost - effectiveness ratio.*

Key words: *pharmacoeconomics, chronic myeloid leukemia (CML), second-line therapy, nilotinib, imatinib, budget impact analysis, cost-effectiveness analysis, reimbursement program for high-cost drugs, high-cost diseases, analytical model of decision-making.*

Chronic myeloid leukemia (CML) is a malignant hematological disease characterized by a clonal myeloproliferative process as a result of malignant transformation in early haemopoietic stem cells [1]. Prevalence of CML is 1:100000 population. According to the CML treatment register of Russian Federation, in early 2015 total number of patients in Russian Federation was 7100, 93% of which were in the chronic phase (CP), and 7% were in advanced phases, including acceleration phase (AP) and blast crisis (BC) [1,2]. Currently, standard treatment for CML consists of tyrosine kinase inhibitors (TKI); these are so-called target drugs, and their development has permitted to significantly increase life expectancy in patients. For example, in case of disease duration of 8 years, survival of CML patients reaches 85%, while in the period before TKI development this disease was considered fatal [1]. The first tyrosine kinase inhibitor (TKI) used in clinical practice was imatinib. It should be noticed that CML sometimes is accompanied by primary or secondary resistance to imatinib. On the other hand, CML treatment requires continuous and prolonged effect on tumor cells clone, which may not be possible in patients with intolerance (grade 3 or 4 toxicity, persistent grade 2 toxicity) [1]. These features of the disease became the basis for further development of tyrosine kinase inhibitors (TKI) for chronic myeloid leukemia (CML) treatment. After the first generation drugs (imatinib), the second generation drugs (nilotinib, dasatinib) were developed.

Active implementation of tyrosine kinase inhibitors (TKI) into the chronic myeloid leukemia (CML) therapy practice in Russian Federation was associated with the start of the state reimbursement program for high-cost drugs in 2008; this program is for subjects with high-cost diseases which include chronic myeloid leukemia (CML). This reimbursement program for high-cost drugs plays an important role in the availability of modern therapy (tyrosine kinase inhibitors (TKI)) for the subjects with chronic myeloid leukemia (CML), because these drugs are innovative and thus expensive, and their availability is low if patients use their own funds. During the development of the reimbursement program for high-cost drugs a special list of budget-purchased drugs was prepared; this list contained one drug for chronic myeloid leukemia (CML) treatment approved at that time, i.e. imatinib. Currently patients with imatinib resistance or intolerance do not virtually have access to effective treatment which may consist of second generation tyrosine kinase inhibitors (TKI). In addition, continuation of imatinib therapy in subjects with chronic myeloid leukemia (CML) and imatinib resistance (up to 25% of all patients [2]) require imatinib dose increase [1]. This leads to an increase in general costs, as well as to a decrease in efficacy of the reimbursement program for high-cost drugs. This, the important issue is potential inclusion of second generation tyrosine kinase inhibitors (TKI), for example, nilotinib, into the list of drugs of the reimbursement program for high-cost drugs for subjects with chronic myeloid leukemia (CML) and imatinib resistance or intolerance.

In the Russian Federation Government Regulation N871 dated 28 Aug 2014 (About the approval of rules of development of drug lists for medical use and minimal range of drugs necessary for medical care) it is noticed, that inclusion of a drug into any state list, for example, high-cost drugs list, it is required to present clinical data characterizing efficacy and safety, as well as results of pharmacoeconomic analysis.

Therapeutic efficacy profile of second generation tyrosine kinase inhibitors (TKI) has been demonstrated in clinical trials. Kantarjian Hagop M., Giles Francis J., Bhalla Kapil N. et al. [5] performed an international, multicenter, open, non-randomized Phase II study, where nilotinib 400 mg BID in adults with Ph+ chronic myeloid leukemia (CML) in the chronic phase, who had imatinib resistance or intolerance, permitted to observe major cytogenetic response (MCR) in 59% subjects, complete cytogenetic response (CyCR) in 44% subjects, complete hematologic response (CHR) in 85% subjects after 24 months of follow-up. Overall survival (OS) was 87% after 2 years. Jorge E. Cortes, Carmino Antonio De Souza, Jose Luis Lopez et al. performed a Phase III study in 2013 [7], where complete cytogenetic response (CyCR) rate after 6 months was 49% in the nilotinib group and 42.1% in the imatinib group. At the same time, major molecular response (MMR) was reached in 55% subjects in the nilotinib group and only in 39% subjects in the imatinib group (only subjects with available blood samples were counted). A multicenter,

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open, randomized, Phase III clinical study ENESTnd demonstrated, that after 12 months of follow-up, general major molecular response (MMR) rate in subjects who received nilotinib as first-line therapy (44% in the group of nilotinib 300 mg BID, 43% in the group of nilotinib 400 mg BID) was almost two times higher than in the group of imatinib 400 mg QD (80%, 78% и 65%, respectively). Frequency of progression to acceleration phase (AP) and blast crisis (BC) was significantly lower in patients who received nilotinib, and after 12 months of follow-up this frequency was <1% (2 subjects), <1% (1 subject), and 4% (11 subjects) in the groups of nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib 400 mg QD, respectively. According to the 5-year follow-up data, frequency of progression, including clonal evolution, was 1,1% (3 subjects), 1,8% (5 subjects), and 6,0% (17 subjects) in the groups of nilotinib 300 mg BID, nilotinib 400 mg BID, and imatinib 400 mg QD, respectively [8-11].

According to the requirements of the Russian Federation Government Regulation N871 dated 28 Aug 2014, role of pharmacoeconomic analysis of drugs has become more important for its inclusion into state reimbursed drug lists. The pharmacoeconomic analysis has even greater significance, taking into account high cost of tyrosine kinase inhibitors (TKI), limited possibilities of the reimbursement program for high-cost drugs, and necessity of budget planning.

According to described issues, a pharmacoeconomic assessment of the treatment of patients with chronic myeloid leukemia (CML) and imatinib resistance or intolerance was performed for a second generation tyrosine kinase inhibitor (TKI), nilotinib, using cost-effectiveness and budget impact analyses.

Methods and materials

Pharmacoeconomic research was based on the developed analytical model of decision-making (AMDM) using combined scenarios of decision tree and Markov cycles. Time horizon of the model varies from one to five years for budget impact analysis and has duration of two years for cost-effectiveness analysis. Discounting index is 3%. Pharmacoeconomic analysis in the frame of analytical model of decision-making (AMDM) may be performed from the point of view of healthcare system in general, including direct costs of tyrosine kinase inhibitors (TKI) therapy, side effects correction, and costs of standard treatment of chronic myeloid leukemia (CML) [18], as well as from the point of view of the reimbursement program for high-cost drugs, where only costs of tyrosine kinase inhibitors (TKI) therapy are taken into account. This article presents results of modeling from the point of view of the reimbursement program for high-cost drugs. Investigational products included imatinib and nilotinib described in Table 1 [4].

Epidemiological data for this study were obtained in an observational clinical study CSTI571ARU06 – Russian register of chronic myeloid leukemia (CML) treatment in routine clinical practice [2]. Efficacy data was retrieved from published clinical studies. Dosage information for imatinib and nilotinib was retrieved from Summary Product Characteristics (SmPC) and national recommendations for chronic myeloid leukemia (CML) treatment [1,4]. Dose of imatinib is 400 mg QD for patients in chronic phase (CP), and 800 mg QD for patients in acceleration phase (AP) or blast crisis (BC).

In case of low efficacy, according to the current clinical recommendations, imatinib dose is escalating from 400 mg to 600-800 mg QD in CP. [1]. Nilotinib as a second-line therapy is administered as 800 mg daily in CP and AP. Pharmacoeconomic research was performed taking into account direct costs calculated on the basis of upper limit of manufacturers' prices, as well as auction prices [4,17]. It should be noticed that imatinib is presented by pharmaceutical forms with dosage of 50 mg, 100 mg, and 400 mg, and nilotinib – 150 mg, and 200 mg. For this reason, it was assumed that if nilotinib is administered as 800 mg daily, the 200 mg dosage form is used. To calculate costs of imatinib therapy (400 mg or 600 mg QD), dosage forms of 50 and 100 mg were used, as well as 200 mg dosage form for 400 mg QD; to calculate cost of a treatment cycle for the 800 mg dose, another dosage form was added (400 mg). It also should be noticed that during the analysis of the costs of chronic myeloid leukemia (CML) therapy with imatinib, percentage of different brand names in a purchase was used along with percentage of different dosage forms for each brand name. Costs of treatment cycle with tyrosine kinase inhibitors (TKI) were calculated on the base of the cost of necessary number of pills or capsules (see Equation 1).

Table 1. Investigational products

INN	Trade name	Manufacturer
Imatinib	Glivec	Owner: Novartis Pharma AG, Switzerland. Manufacturer: Novartis Pharma Stein AG, Switzerland.
	Imatinib	ZAO Biokad, Russian Federation. Manufacturer: Shijiazhuang Yiling Pharmaceutical, Co.Ltd, China. Primary package, secondary package, release - ZAO Biokad, Russian Federation
	Imatinib - TL	OOO Technologia lekarstv, Russian Federation.
	Imagliv	Sandoz D.D, Slovenia. Manufacturing, primary package, secondary package, release: Novartis Pharma Stein AG, Switzerland.
	Imatib	ZAO Pharm-Synthesis, Russian Federation. Manufacturing, primary package, secondary package: ZAO Pharmproyekt, Russian Federation. Release: ZAO Pharm-Synthesis, Russian Federation.
	Gystamel	OAO VEROPHARM, Russian Federation
	Philachromin FS	ZAO F-Synthesis, Russian Federation.
	Imatinib-Teva	Teva Pharmaceutical Industries, Ltd., Israel. Manufacturing, primary package, secondary package, release: Pliva Hrvatska d.o.o., Croatian Republic
	Neopax	OOO KRKA-RUS, Russian Federation Manufacturing, primary package, secondary package: ZAO Vector-Medica, Russian Federation. Release: OOO KRKA-RUS, Russian Federation.
	Genfatinib	Laboratorio TUTEUR S.A.S.I.F.I.A., Argentina Manufacturing, primary package: Laboratorio VARIFARMA S.A., Argentina. Secondary package, release: Laboratorio TUTEUR S.A.S.I.F.I.A., Argentina
Nilotinib	Tasigna	Owner: Novartis Pharma AG, Switzerland. Manufacturer: Novartis Pharma Stein AG, Switzerland. Secondary package: OAO Pharmstandard, Ufa, Russian Federation.

$$Cost(Th) = \sum_{M}^{1}\left(\left(\sum_{k}^{1}\left(Price_{Pill} * N * D_D\right)\right) * D_F\right), \text{ where} \quad (1)$$

Cost(Th) – cost of a tyrosine kinase inhibitor (TKI) treatment course, RUR;
M – number of trade names of a drug included into analysis;
K - number of dosage forms for each trade name of one drug included into analysis;
PricePill – price of 1 pill or capsule of this dosage form, RUR;
N – number of pills or capsules for one tyrosine kinase inhibitor (TKI) treatment course;
DD – percentage of a dosage form of a trade name of a drug in a purchase, %;
DF – percentage of a trade name of a drug in a purchase, %.

$$N = (DD/Q) * 365, \text{ where:} \quad (2)$$

N – number of pills or capsules for one tyrosine kinase inhibitor (TKI) treatment course;
DD – daily dose of a tyrosine kinase inhibitor (TKI), mg;
Q – dosage form of a tyrosine kinase inhibitor (TKI), mg;
365 – number of days in one year.

$$PricePill = PricePackage/NPill, \text{ where:} \quad (3)$$

PricePill – price of 1 pill or capsule of this dosage form, RUR;
PricePackage – price of 1 package of a tyrosine kinase inhibitor (TKI), RUR;
NPill – number of pills or capsules in a package.

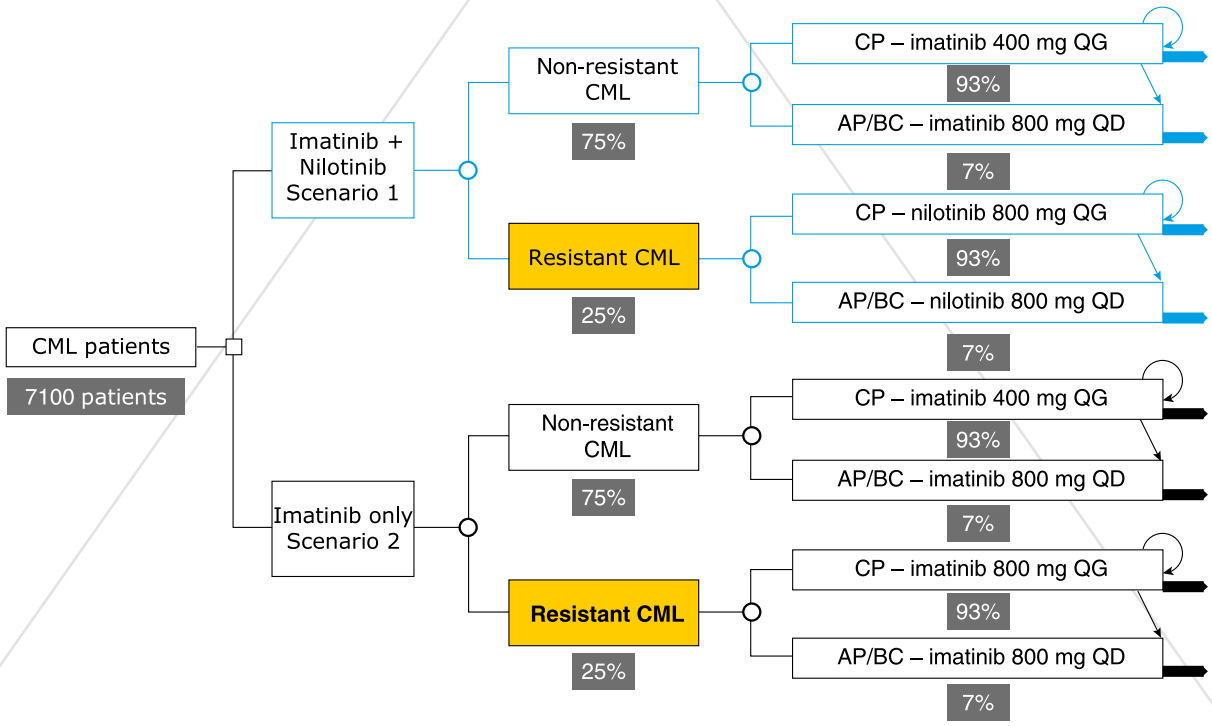
The objective of cost-effectiveness analysis was to find an optimal drug for the treatment of patients with chronic myeloid leukemia (CML) and imatinib resistance, from the point of view of efficacy unit reach cost. Cost-effectiveness ratio was calculated according to the Equation 4, taking into account average costs of the CML treatment (in chronic phase and advanced phases) in patients with resistant CML [16].

$$CER = ((CostХФ + CostФА/БК)/2)/Ef, \text{ where:} \quad (4)$$

CER – cost- effectiveness ratio;
CostCP – cost of the therapy of resistant CML in chronic phase, RUR;
CostAP/BC – cost of the therapy of resistant CML in acute phase or blast crisis, RUR;
Ef – effectiveness of the tyrosine kinase inhibitor (TKI) therapy.

Budget impact analysis was performed as a part of this pharmacoeconomic research and has permitted to predict changes in the budget of chronic myeloid leukemia (CML) treatment in case of introduction of nilotinib to the market [13]. In relation to aforementioned, this pharmacoeconomic research offers two possible scenarios: current (Scenario 2, Figure 1), when patients receive imatinib only, and predicted (Scenario 1, Figure 1), when patients may be offered nilotinib. Taking into account that healthcare system budget is established for the total CML patient population, the budget impact analysis included costs for subjects with and without imatinib resistance. It was assumed that nilotinib was not administered to the subjects without imatinib resistance, which is 75% of all CML patients. At the moment of study entry, percentage of subjects with chronic phase of chronic myeloid leukemia (CML) was 93%, and percentage of subjects with advanced phases was 7%. It also should be noticed that budget impact analysis, on one hand, took into account change of patients number in time; annual increase in patients number is 650 [2]. On the other hand, progression to advanced phases was taken into account. Data of chronic myeloid leukemia (CML) patients progression from chronic phase to advanced phases were retrieved from a work published by Deininger et al. Blood 2009; 114. [6]; according to these data, during the first year of therapy 1.5% patients converted from chronic phase to acceleration phase or blast crisis; percentage for the second year was 2.8%, for the third year – 1.8%, for the fourth year – 0.9%. Similar data of probable transition to advanced stages during nilotinib treatment were not available, but a study by FJ Giles et al. 2013 [15] was found, according to which, during 4 years of nilotinib therapy 3% patients converted to advances phases of chronic myeloid leukemia (CML). According to the publication by FJ Giles et al. 2013 [15], our pharmacoeconomic research model assumed that conversion to advanced stages of this 3% patients was homogeneously distributed for studied period of time. During the budget impact analysis also two possible situations of nilotinib consumption were studied. In theory, for the nilotinib dose of 800 mg daily, a calendar year (on the base of which the budget is formed) required 12.1 packages of a drug with the dosage form of 200 mg, 120 tablets. Nevertheless, analysis of actual nilotinib consumption revealed that in real practice in average 9 packages per patient per year were purchased (800 mg daily, 200 mg, 120 tablets) [17]. The difference between theoretic and actual nilotinib consumption may be explained by the fact that prescription and start of treatment do not take place at the same time for all subjects: different patients receive prescription at different moments of year and, thus, consume unequal amounts of the drug during a calendar year. The difference between theoretic and actual nilotinib consumption may also in part be explained by Grades 3 and 4 adverse events (AEs), which, according to national recommendations [1], require dose modification or therapy interruption. During the budget impact analysis, main directions of budget optimization were defined: change of the level of penetration by nilotinib, and redistribution of budget resources in the reimbursement program for high-cost drugs by purchase of less expensive imatinib forms. Budget impact analysis scenarios are presented in Figure 1.

Figure 1. Budget impact analysis scenarios



Results of cost-effectiveness analysis

Analysis of the effectiveness in the frame of cost-effectiveness analysis was retrospective [14]. Taking into account the chosen model of patients, the effectiveness criterion should have reflected effects of compared drugs on disease course in patients with confirmed imatinib resistance. Thus, for this objective the best criterion was percentage of subjects with molecular response at 24 months who did not have major molecular response at baseline. Data related to this effectiveness criterion were retrieved from the open, multicenter, randomized Phase III study ENESTcmr [12], where kinetics of non-detectable BCR-ABL concentration was compared between nilotinib and imatinib treated subjects with Ph+ chronic myeloid leukemia (CML) in chronic phase. Inclusion criteria were the following: therapy with imatinib (400 or 600 mg QD) during at least 2 years; complete cytogenetic response confirmed by standard cytogenetic methods or BCR-ABL IS<1% in peripheral blood; persistent disease on the base of two positive results of BCR-ABL transcripts by means of quantitative real time polymerase chain reaction (QRT-PCR) before the start of the study. Total of 207 subjects were included in this study, including 52 subjects without major molecular response at baseline. Study subjects were randomized in two groups: nilotinib 400 mg BID, and continuation of imatinib in the same dose. As was demonstrated in this study, molecular response at 24 months was reached in 29.6% subjects who did not have major molecular response at baseline in the nilotinib group, and in 3.6% subjects in the imatinib group.

Costs analysis results

Analysis of costs included direct costs of chronic myeloid leukemia (CML) therapy. Calculation of costs of tyrosine kinase inhibitors (TKI) therapy was based on dosage forms. Cost of 1 year of tyrosine kinase inhibitors (TKI) therapy was calculated according to Equation 1, as the price of 1 pill or capsule multiplied by number of pills or capsules per year. Analysis of costs was performed separately for auction prices and upper limit of approved prices.

Cost of 1-year tyrosine kinase inhibitor (TKI) therapy course on the base of approved prices

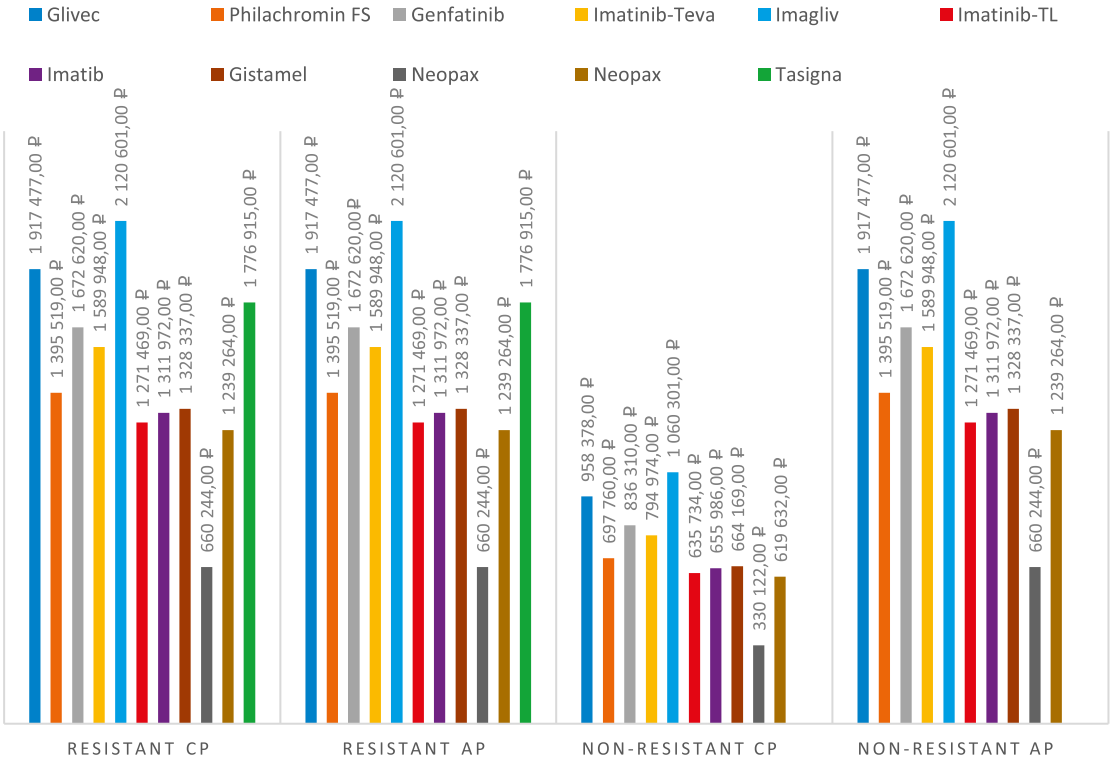
Cost of one year of imatinib therapy for a patient with non-resistant chronic myeloid leukemia (CML) in chronic phase, in case of daily dose of 400 mg, is 958738 RUR, 697760 RUR, 836310 RUR, 794974 RUR, 1060301 RUR, 635734 RUR, 655986 RUR, 664169 RUR, 330106 RUR and 619632 RUR for Glivec, Philachromin FS, Genfatinib, Imatinib-Teva, Imagliv, Imatinib-TL, Imatib, Gistamel, Imatinib, Neopax, respectively (Figure 2). Price of one year of imatinib therapy for a patient with resistant chronic myeloid leukemia (CML) in chronic phase as well as in advanced phase (acceleration phase or blast crisis), in case of daily dose of 800 mg, is 1917477 RUR, 1395519 RUR, 1672620 RUR, 1589948 RUR, 2120601 RUR, 1271469 RUR, 1311972 RUR, 1328337 RUR, 660244 RUR и 1239264 RUR for Glivec, Philachromin FS, Genfatinib, Imatinib-Teva, Imagliv, Imatinib-TL, Imatib, Gistamel, Imatinib, Neopax, respectively (Figure 2). Price of one year of nilotinib (Tasigna) therapy for a patient with resistant chronic myeloid leukemia (CML) in chronic phase as well as in advanced phase (acceleration phase or blast crisis), is 1776915 RUR (Figure 2).

Costs of 1-year course of imatinib or nilotinib therapy were also calculated on the basis of auction prices (in the frame of the reimbursement program for high-cost drugs for imatinib and regional subsidized drug list for nilotinib). Average cost of 1 mg of imatinib was 2.17 RUR, and 1 mg of nilotinib – 6.00 RUR [2,3]. Costs of 1-year imatinib therapy for daily doses of 400 mg and 800 mg for one patient were 316820 RUR and 633640 RUR, respectively; cost of 1-year nilotinib therapy for daily dose of 800 mg for one patient was 1752000 RUR.

Cost-effectiveness analysis results

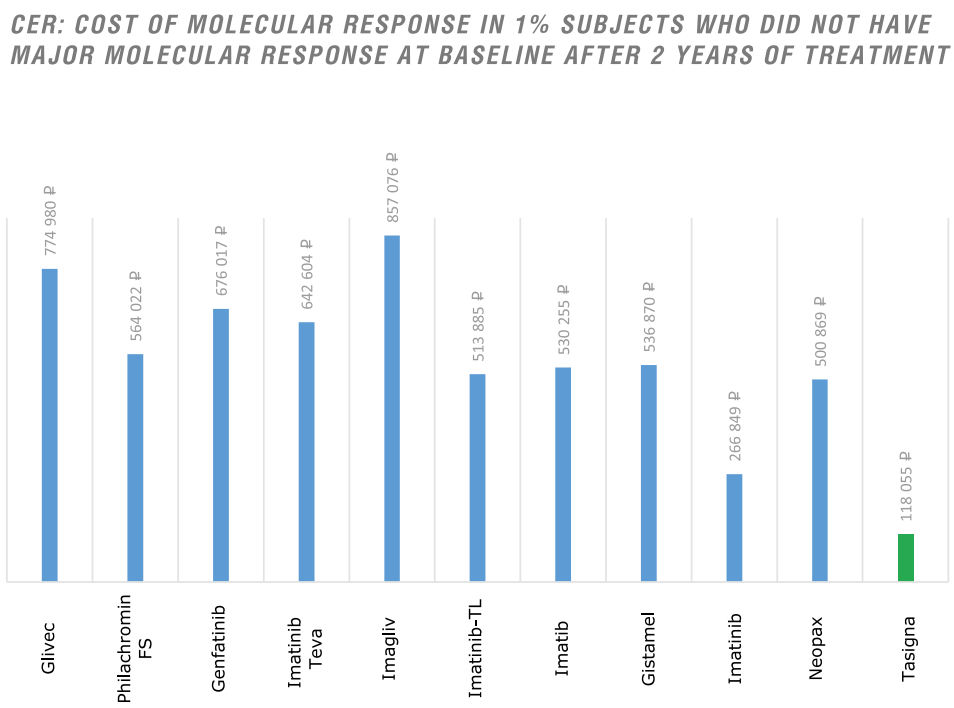
Cost-effectiveness analysis was performed in accordance with abovementioned method, on the basis of molecular response on 1% patients after 2 years and calculated costs (using vital and essential medicines (VEM) prices) of tyrosine kinase inhibitors (TKI) therapy with each drug. According to the results, Tasigna had the lowest cost- effectiveness ratio, i.e., the cost of reaching the therapeutical target was the lowest. The cost- effectiveness ratio (taking into account the discount) was 118055 for Tasigna, and for Glivec, Philachromin FS, Genfatinib, Imatinib-Teva, Imagliv, Imatinib-TL, Imatib, Gistamel, Imatinib, and Neopax, respectively, it was 774980, 564022, 676017, 642604, 857076, 513885, 530255, 536870, 266849 и 500869 (Figure 3). The results of the cost- effectiveness analysis were subjected to single-factor sensitivity analysis with no changes for Tasigna price variations of +/-20%.

Figure 2. Costs of 1-year imatinib or nilotinib therapy course for one patient, based on upper limit of approved prices.



[1] Calculation was made excluding imatinib 400 mg dosage forms, because, on one hand, these forms are almost not used, and, on the other hand, each mg of the drug is much more expensive in these forms compared to 100 mg dosage forms, which affects the final result significantly.

Figure 3. Cost-effectiveness analysis results



Budget impact analysis results

Budget impact analysis was performed according to abovementioned method. In this article, budget impact analysis results are presented for the time horizon of 1 year. During the analysis, six possible cases were studied, taking into account possibilities of optimization: three cases for upper limits of approved prices, and three cases for auction prices (Table 2). Use of maximum approved prices auction prices was based on the fact that upper limits of approved prices permit to compare treatment alternatives (imatinib and nilotinib) in the frame of comparable prices, because nilotinib currently is not included into the list of the reimbursement program for high-cost drugs); auction prices of imatinib permit to compare obtained results with actual resources of federal budget, offered for the chronic myeloid leukemia (CML) patients. This budget for 2014, taking into account the reimbursement program for high-cost drugs and regional subsidized drug lists, was 4.53 billion RUR [3,17].

According to the Table 2, 1-year budget for imatinib only therapy (Scenario 2) for the subjects with chronic myeloid leukemia (CML), if calculated on the base of upper limits of approved prices, is 6.583 billion RUR. This calculation was performed including actual percentages of imatinib trade names prescribed for the patient in the frame of federal budget in 2014 [3]: 17.59% patients received Glivel, 30.77% patients – Genfatinib, 41.84% patients – Philachromin FS, 4.65% patients – Neopax, 2.72% patients – Imatib, 1.59% patients – Gistamel, 0.84% patients – Imatinib-Teva.

At the same time, in case of conversion of all second-line therapy patients to nilotinib with its theoretic consumption (12.1 packages per patient per year) (Scenario 1), with unchanged distribution in the imatinib purchase, chronic myeloid leukemia (CML) treatment budget is 7.139 billion RUR, which is 8.45% more that in case of Scenario 2. If only 50% of second-line therapy patients are prescribed nilotinib, the budget is 6.861 billion RUR, i.e., 4.23% more than in case of Scenario 2. Nevertheless, a shift from actual imatinib brand names distribution to predicted one, when less expensive brand of imatinib is purchased, in case of conversion of all second-line therapy patient to nilotinib, chronic myeloid leukemia (CML) treatment budget is 5.034 billion RUR, which is 23.52% less that in case of Scenario 2.

Budget impact analysis results with auction prices were the following: 1-year cost of imatinib therapy for all chronic myeloid leukemia (CML) patients (Scenario 2) was 2.929 billion RUR.

In case of conversion of all second-line therapy patients to nilotinib with its theoretic consumption (12.1 packages per patient per year) (Scenario 1), chronic myeloid leukemia (CML) treatment budget is 4.914 billion RUR, which is 1.985 billion RUR more in comparison to Scenario 2 budget. On the other hand, calculation according to Scenario 1 and actual nilotinib consumption (9 packages per patient per year) resulted in 4.115 billion RUR, and if only 50% of second-line therapy patients are prescribed nilotinib, the Scenario 1 budget is 3.522 billion RUR.

Scenario 1 budget calculated on the basis of auction prices was compared with the actual budget for tyrosine kinase inhibitors (TKI) purchase in the frame of reimbursement program for high-cost drugs and regional subsidized drug list. As shown in the Table 2, budgets for all studies situations of nilotinib inclusion as a second-line therapy for chronic myeloid leukemia (CML) patients, in case of actual nilotinib consumption, do not exceed actual costs for cumulative federal budget.

Conclusion

This, nilotinib in comparison with imatinib may be characterized as strictly preferable from the point of view of the cost- effectiveness analysis, as it has lower cost- effectiveness ratio. As the budget impact analysis results demonstrated, conversion of all second-line therapy patients with chronic myeloid leukemia (CML) in Russian Federation from imatinib to nilotinib in case of its theoretic consumption results in an increase of federal budget (compared to Scenario 2) for 1.985 billion RUR. If the actual nilotinib consumption is taken into account, the Scenario 1 budget does not exceed actual costs of chronic myeloid leukemia (CML) treatment in the frame of the reimbursement program for high-cost drugs and regional subsidized drug list.

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[2] The difference between theoretic and actual nilotinib consumption may be explained by the fact that prescription and start of treatment do not take place at the same time for all subjects: different patients receive prescription at different moments of year and, thus, consume unequal amounts of the drug during a calendar year. The difference between theoretic and actual nilotinib consumption may also in part be explained by Grades 3 and 4 adverse events (AEs), which, according to national recommendations [1], require dose modification or therapy interruption. There were no data of actual imatinib consumption available, so Scenario 1 budget in case of actual nilotinib consumption was compared to actual chronic myeloid leukemia (CML) treatment budget.

References:
1. National clinical guidelines for the diagnosis and treatment
chronic myeloid leukemia. The team of authors under the leadership of the Acad-Mika V. G. Savchenko. 2014.
2. Turkina A. G. and others, «Russian case for the treatment of chronic myeloid leukemia in routine clinical practice: results of long-term work» Effective pharmacotherapy. 10/2015
3. IMS Health data 2014
4. The state register of medicines [Electronic resource] - Mode of access: http://grls.rosminzdrav.ru. Date of access: 01.2015.
5. Kantarjian Hagop M., Giles Francis J., Bhalla Kapil N. et al. Nilotinib in effective in patients with chronic myelogenous leukemia in chronic phase after Imatinib resistance or intolerance: 24-months follow-up results. Blood 2011; 27:1141-1145
6. Deininger et al., Blood. 2009; 114 [abstract 1126].
7. Switching To Nilotinib In Patients (pts) With Chronic myeloid Leukemia In Chronic Phase (CML-CP) With Suboptimal Cytogenetic Response (CyR) On Imatinib: First Results Of The LASOR Trial. Jorge E. Cortes, Carmino Antonio De Souza, Jose Luis Lopez, Manuel Ayala, Eduardo Bullorsky, Xiaojun Huang, Sandip Shah, K. Govind Babu, Tomasz Sacha, Israel Bendit, Zhizhou Liang, Tina Owugah, Prasanna Kumar Nidamarthy, Tomasz Szczudlo, Carmen Piccolo, and Philipp D. le Coutre. 2013.
8. H.M.Kantarjian, A.Hochhaus, G.Saglio, C.De Souza, I.W.Flinn et all. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, phase 3 randomised ENESTnd trial. Lancet Oncology. 2011; 12:841-5
9. R.A.Larson,A.Hochhaus, T/P/Hughes, R.E.Clark et al. Nilotinib vs imatinib in patients with newly dignosed Ph chromosome-positive chronic myelogenous leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia (2012); 2197-2203.
10. Saglio Giuseppe, Kim Dong-Wook, Issaragrisi Surapol et al. Nilotinib versus Imatinib for Newly Diagnosed Chronic Myelogenous Leukemia. NEJM 2010; 362:2251-2559
11. Saglio G, et al. Blood 2013; 92: 122 (21)
12. Hughes TP, Lipton JH, Leber B, et al. Complete molecular response (CMR) rate with nilotinib in patients (pts) with chronic myeloid leukemia in chronic phase (CML-CP) without CMR after 2 years on imatinib: preliminary results from the randomized ENESTcmr trial of nilotinib 400 mg twice daily (BID) vs imatinib. In: Proceedings from the American Society of Hematology- 53rd Annual Meeting;December 10-13, 2011;San Diego, CA. Abstract 606
13. Khabriev R.u., Kulikov A.Yu., Arinina E.E. Methodological basis of pharmacoeconomic analysis. Moscow: publisher "Medicine", 2011. – 128 pages
14. Yagudina R. I., Novikov V. I., Serpik V. G Information search in conducting pharmacoeconomic research.// Pharmacoeconomics modern pharmacoeconomics and epidemiology No. 3, 2012, pp. 3-7
15. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myelogenous leukemia in chronic phase: 48-month follow-up results of a phase II study. Giles FJ, le Coutre PD, Pinilla-Ibarz J, Larson RA, Gattermann N, Ottmann OG, Hochhaus A, Radich JP, Saglio G, Hughes TP, Martinelli G, Kim DW, Novick S,Gillis K, Fan X, Cortes J, Baccarani M, Kantarjian HM. Leukemia. 2013 Jan;27(1):107-12.
16. Yagudina R.I., Serpik V.G., Sorokovikov I.V. Methodological basics of analysis of "cost-effectiveness", pharmacoeconomics. theory and practice. Vol. 2.No2 – 2014. p. 23-27.
17. Electronic portal of public procurement [Electronic resource] - Mode of access: http://zakupki.gov.ru.
18. The decree of MoH of the Russian Federation of 14 November 2007 No. 704 «On approving the standard of care for patients with myeloid leukemia and other hematological malignancies»

Table 2. Results of the budget impact analysis for one year (total population of patients)

Prices	Level of nilotinib penetration	Tyrosine kinase inhibitors (TKI) consumption	Imatinib purchase optimization	Scenario 1 (nilotinib + imatinib) budget, million RUR	Scenario 2 (imatinib only) budget, million RUR	Change of Scenario 1 budget in relation to Scenario 2 budget, million RUR	Change of Scenario 1 budget in relation to Scenario 2 budget, %	Change of Scenario 1 budget in relation to cumulative tyrosine kinase inhibitors (TKI) purchase budget, %
Approved limit	100%	Theoretic	Actual	7139	6583	391 (additional costs)	8,45	-
	50%			6861	6583	195 (additional costs)	4,23	-
	100%		Optimized	5034	6583	2621 (cost saving)	23,52	-
Auction price	100%	Theoretic		4914	2929	1985 (additional costs)	67,75	additional costs 8,50%
	100%	Actual		4115				cost saving 9,16%
	50%							cost saving 22,25%