№1 Том4 2016

Фармакоэкономика
теория и практика

www.pharmacoeconom.com

Pharmacoeconomics
theory and practice

№1 Volume4 2016

- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ФАРМАКОЭКОНОМИЧЕСКОГО МОДЕЛИРОВАНИЯ
- 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

PHARMACOECONOMIC ANALYSIS OF LAPATINIB TREATMENT IN METASTATIC BREAST CANCER WITH HER2+ OVEREXPRESSION

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Abstract: *According to the World Health Organization, breast cancer is the most common form of cancer in women worldwide. The steady increase in the prevalence of breast cancer, followed by an increase in the state budget expenditures on drug supply for this category of patients, determines the relevance of pharmacoeconomic evaluation of treatment of HER2-positive breast cancer using a combination of lapatinib and capecitabine and trastuzumab emtansine monotherapy.*

A subgroup analysis of the therapeutic outcomes in patients with HER2+ breast cancer conducted by the EMILIA study failed to find a statistically significant difference in median overall survival in patients receiving either trastuzumab emtansine or a combination of lapatinib and capecitabine as second-line treatment, or in patients with non-visceral metastases. Analysis of overall survival of the entire population of patients in the EMILIA study revealed that trastuzumab emtansine is more effective than a combination of lapatinib and capecitabine. Despite this, NICE does not recommend treatment with trastuzumab emtansine due to high cost of treatment.

The EMILIA study results were used as a basis for pharmacoeconomic models for HER2+ breast cancer therapy, using such methods of pharmacoeconomic analysis as budget impact analysis, cost-effectiveness analysis, and cost-minimization analysis for these subgroups of patients.

Result of budget impact analysis revealed that the use of the lapatinib and capecitabine combination can reduce health system expenditures by 3,985,271 rubles per patient per year or by 5,851,484 rubles over three years per one patient, which allows treating 4 additional patients given the fixed budget. Cost-effectiveness ratio of lapatinib + capecitabine equals to 869,705 rubles and 3,461,960 rubles with LYG and QALY as efficacy endpoints, respectively, which identifies this therapy as cost-effective in pharmacoeconomic terms. Cost-minimization analysis of lapatinib+capecitabine patient groups in the second-line treatment, and a group of patients with non-visceral metastases showed that the use of this treatment may reduce costs by 78% in comparison with trastuzumab emtansine.

Keywords: breast cancer, HER2+ tumor expression, pharmacoeconomic analysis, lapatinib, capecitabine, trastuzumab emtansine, efficacy analysis, cost analysis, cost-effectiveness analysis, cost-utility analysis, life years gained, LYG, quality-adjusted life years gained, QALY, analysis, cost-minimization analysis, budget impact analysis

Introduction

According to the World Health Organization (WHO), breast cancer (BC) is the most common form of cancer in women worldwide (16% of all cancer cases). Every year ca. 1.25 million cases of breast cancer are diagnosed worldwide [19]. From 2004 to 2014 a steady increase in breast cancer morbidity has been observed in Russia; it now accounts for 11.4% of cases in the structure of cancer prevalence (Figure 1). 61,376 patients with newly diagnosed breast cancer were registered in Russia in 2014, and 8,237 (13.4%) of them have HER2-positive status (Figure 2). Furthermore, in 30.9% of women breast cancer was detected for the first time at advanced stages (3 and 4), which is primarily due to a delay in seeking medical care. The mortality rate of patients in the first year after diagnosis remains high. However, starting from 2004-2014, there has been a decrease in breast cancer mortality from 11.5% to 7.3%, due, in part, to emergence of innovative targeted drugs [11,20,21].

At the moment, one of such drugs is lapatinib, reversible tyrosine kinase inhibitor, which, according to the instructions for medical use, is indicated to patients with HER2-positive breast cancer in combination with capecitabine [1,15]. The use of lapatinib in combination with capecitabine is included in the ESMO, NCCN, AOP, and RUSSCO recommendations, which indicate that this regimen significantly increases the time to progression of the disease [2,4,6,18]. There is another drug on the pharmaceutical market, trastuzumab emtansine, a conjugate of humanised monoclonal antibody (IgG_1) against the human epidermal growth factor type 2 (HER2) receptor and an inhibitor of tubulin polymerisation (DM1) [16]. This drug is used to treat HER2+ breast cancer, but due to its high cost it is not recommended by the NICE, and therefore it seems appropriate to consider the rational choice of drug regimens in terms of pharmacoeconomic analysis [5,33].

The aim of the study is to identify the preferable therapy for treatment of HER2+ breast cancer by comparing a combination of lapatinib and capecitabine with trastuzumab emtansine in patients who have received prior therapy with trastuzumab.

Description of the model

This study compared two alternatives: lapatinib + capecitabine and trastuzumab emtansine for the treatment of breast cancer patients with HER2-positive status. The developed decision-making analytical model in Microsoft Office Excel allows real-time changes in the input data that influence the final outcome of the study.

The time horizon of the study is 3 years. The analyzed population includes patients who have received prior therapy with trastuzumab, with a mean weight of 70 kg and an average surface area of the body of 1.74 m2, which is required to calculate the average daily dose of medication for the treatment of HER2+ breast cancer 12,14,35].

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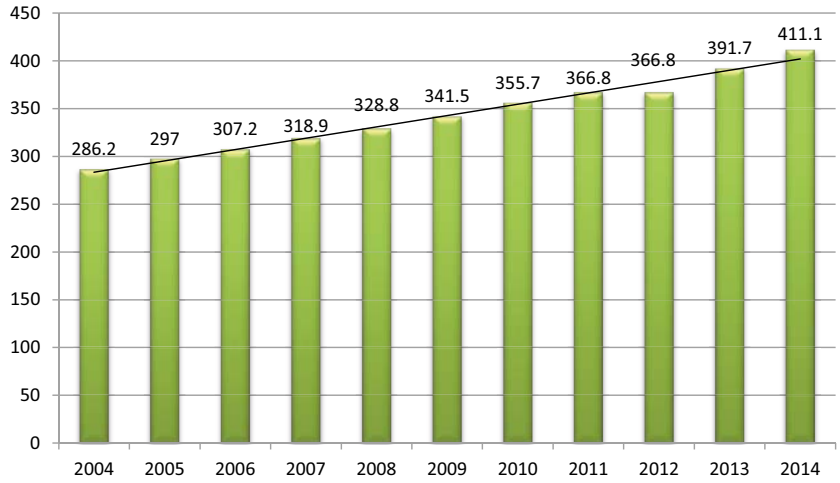

Figure 1. The prevalence of BC in Russia from 2004 to 2014 (per 100,000 population)

Analysis of effectiveness

At the first stage of pharmacoeconomic assessment the analysis of effectiveness has been conducted which captured literature review in centralized scientific medical library (CSML), PubMed, Medline, ClinicalTrials databases and Internet by key words such as Pharmacoeconomics, breast cancer, HER2+ status, lapatinib, capecitabine, trastuzumab emtansine, life years gained, quality-adjusted life years gained, LYG, QALY.

Based on the results of the identified clinical trials three populations were considered separately: a) the total population; b) patients who received lapatinib + capecitabine or trastuzumab emtansine as second-line therapy; c) patients with non-visceral metastases [35].

Total population. Based on the results of the information search, we selected a clinical trial that compared lapatinib + capecitabine and trastuzumab emtansine in the treatment of HER2+ BC from the available publications [35]. This study evaluated the overall survival of patients with a follow-up period of 36 months.

We have also discovered published results of a study by A.Yu. Kulikov et al. (2015), based on a global model, which formed the basis of further analysis of effectiveness [3]. In this study we developed an adapted model using the Kaplan–Meier method for calculation of effectiveness criteria over three years [29,31,32,34]. The criteria of effectiveness / utility were determined as a result. The study endpoints included: life years gained (LYG) and quality-adjusted life years (QALY) for the compared therapies in the treatment of HER2-positive BC [23]

Tables 1 and 2 show the results of an effectiveness /utility analysis which were obtained based on the treatment of one patient over three years [3].

Table 1. The results of an effectiveness analysis for the compared treatment regimens over three years

LYG	Lapatinib+ capecitabine	Trastuzumab emtansine
Progression-free period, years	0.8	1.01
Period after progression, years	1.07	1.15
Final LYG values	1.87	2.16

Table 2. The results of a utility analysis for the compared treatment regimens over three years

QALY	Lapatinib+ capecitabine	Trastuzumab emtansine
Progression-free period, quality-adjusted years	0.61	0.81
Period after progression, quality-adjusted years	0.57	0.61
Final QALY results	1.18	1.42

As Table 1 shows, the use of lapatinib + capecitabine regimen for the treatment of HER2+ breast cancer allowed to reach 0.8 LYG in the progression-free period and 1.07 after progression of the disease, with the total of 1.87 LYG over three years, whereas in case of trastuzumab emtansine the LYG value was 1.01 in the progression-free period, and 1.15 after progression of the disease, giving 2.16 LYG in total.

Table 2 presents the QALY values, which for lapatinib and capecitabine combination therapy were 0.61 for the progression-free period and 0.57 after progression of the disease, with a total of 1.18 QALY. For trastuzumab emtansine the QALY value was 0.81 in the progression-free period and 0.61 after the progression of the disease, with a final value of 1.42.

Despite the greater efficiency, NICE does not recommend trastuzumab emtansine for inclusion in standards of treatment due to high cost of therapy.

Second-line chemotherapy in metastatic HER2+ breast cancer

According to the data of a clinical trial (S. Verma, 2012), in addition to the total population of patients with metastatic breast cancer (mBC) with HER2+ status, another group of patients was singled out - those receiving second-line therapy who accounted for 36% of the total population. The study selected median overall survival as criterion of effectiveness. It demonstrated a lack of statistically significant difference between the compared groups. Thus, we may conclude that relatively similar effectiveness criteria may allow us to use cost minimization analysis [35].

HER2+ breast cancer with non-visceral metastases. Cost minimization analysis should be conducted under equal effectiveness criteria. According to the clinical trial that compared the treatment effectiveness (effectiveness criteria: median overall survival) with lapatinib + capecitabine and trastuzumab emtansine in non-visceral metastatic HER2-positive breast cancer demonstrated relatively similar effectiveness due to lack of statistically significant differences [35].

Cost analysis

Progression-free period

The studied regimens are indicated in HER2-positive mBC and are prescribed according to the instructions for medical use and both international and Russian clinical guidelines for the period before progression of the disease. The cost structure in the progression-free period consisted of the cost of primary pharmacotherapy (lapatinib + capecitabine - study group, trastuzumab emtansine - comparison group), the cost of medical services and medications included in the standards of care, and therapy management costs (based on the dosage form and the need for hospitalization), as well as the costs of managing adverse effects.

At the first stage of the cost analysis we determined the cost of primary pharmacotherapy, which in the case of the study group was the cost of combination therapy with lapatinib and capecitabine for the treatment of HER-positive mBC. According to the instructions for medical use the daily dose of lapatinib for mBC is 1,250 mg. Based on the cost of a lapatinib package (250 mg tablets - 130,041 rubles), according to the results of public procurement for the period of 01.01.2015 - 31.12.2015, the average price of the daily dose was 4,644 rubles. The cost of one year and three years of treatment calculated based on this price were equal to 1,695,176 rubles and 5,085,528 rubles, respectively [17].

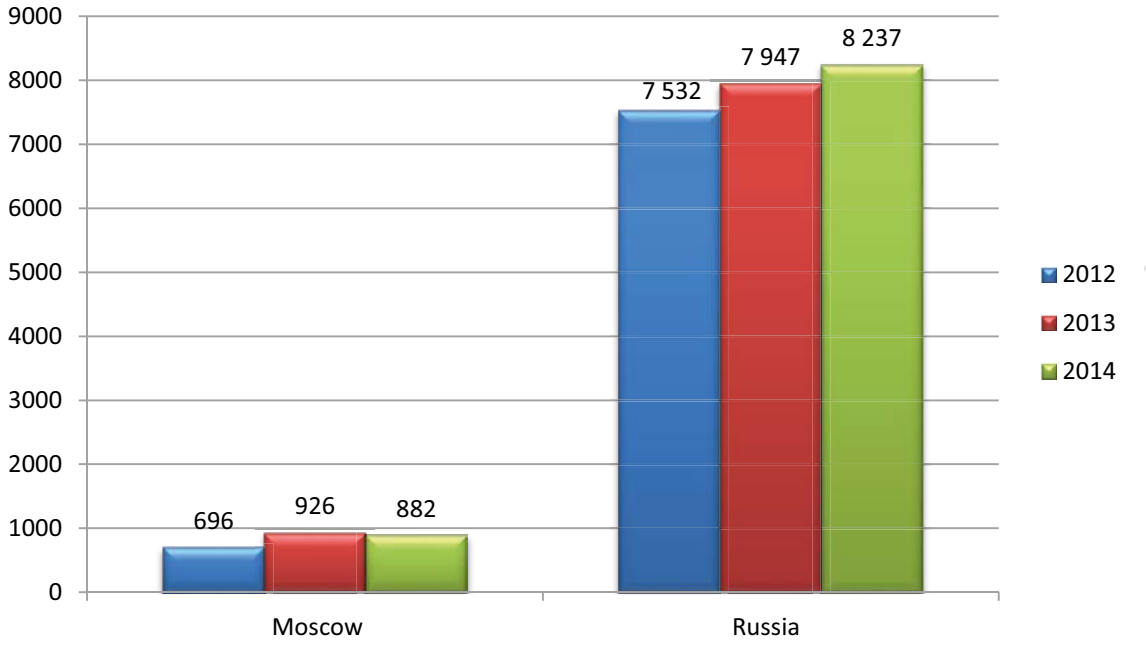

Figure 2. Number of diagnosed cases of HER2+ breast cancer in Moscow and in Russia

The daily dose of capecitabine is 3,480 mg per day for 14 days followed by a seven-day break (243 administrations per year). Taking into account the annual healthcare budget, calculation cost of treatment per year as well as over a three-year period has been prepared, which is the average period of follow-up of patients in the clinical trial. Thus, the cost of capecitabine is 200,600 rubles for one year and 601,800 rubles for three years (Table 3).

The price of one package of trastuzumab emtansine, based on the results of state procurement for the period of 01.01.2015-31.12.2015, was 169,768 rubles (lyophilisate 100 mg) and 267,914 rubles (160 mg) [17]. The cost of a daily dose, which was based on the price of 100 mg and 160 mg trastuzumab emtansine bottles, was 437,682 rubles. According to the instructions for medical use, the drug is administrated as 1 i.v. drip infusion every 3 weeks (21-day cycle), which adds up to 17 administrations a year. Therefore, the cost of treatment with trastuzumab emtansine for one year is equal to 7,607,337 rubles, which corresponds to 22,822,011 rubles for the treatment of one patient over a three-year time horizon (Table 3).

Table 3. The cost of the primary pharmacotherapy

BC treatment scheme		Daily dose, mg	Cost per 1 mg, RUB	Yearly cost, RUB
Lapatinib+-capecitabine	Lapatinib	1,250	3,7	1,895,776
	capecitabine	3,480	0,24	
Trastuzumab emtansine		252	1,686	7,607,337

The range of medical services, as well as the list of concomitant drugs in the Russian Federation is determined by the standard of care [7].

The cost of providing medical services was calculated based on their prescription frequency and treatment regimen. The cost of medical services was calculated on the basis of the fee schedules of in the Territorial Compulsory Medical Insurance Fund (TCMIF) in Moscow [13]. The cost of medical services per patient was 8,180 rubles per year and 24,541 rubles over three years of treatment of a patient receiving lapatinib + capecitabine and for a patient treated with trastuzumab emtansine. The cost of medical services for the regimens under study are comparable due to the use of the standard of specialized medical care for each patient with breast cancer.

The costs of concomitant drugs included stepwise calculation of the cost of a unit of activity followed by the cost of the total cumulative dose over a course of treatment with each drug included in the standard of specialized medical care for patients with breast cancer [7]. The average cost of concomitant drugs for one case of breast cancer per year was 17,249 rubles for each of the two groups under study, which corresponds to 51,748 rubles over three years of treatment.

In addition, costs of the administration of therapy have been calculated, which included the cost of drug administration and patient hospitalization. These costs were calculated only for trastuzumab emtansine because its route of administration is i.v. drip over a long period time, which requires medical supervision and incurs consumable (i.v. system) costs.

Taking into account that lapatinib and capecitabine are administered orally in tablet form, their application does not incur additional labor costs for medical staff for the use of this combination.

According to Moscow TCMIF, the cost of intravenous administration is 77 rubles, while the average cost of a day hospital/hospitalization is 418 rubles. [13]. Consequently, each administration of trastuzumab emtansine incurs additional costs compared to the lapatinib + capecitabine regimen in the amount of 495 rubles per patient, which corresponds to 8,603 rubles per year and 25,810 rubles over three years.

At the next stage of the analysis the costs of management of adverse events (AEs) of grades 3 and 4 have been calculated. To determine the treatment regimen for each AE we performed an information search for treatment standards and recommendations, and also obtained expert opinion. The frequency of AEs was taken into account in each treatment group [8-10,13] . Based on the data obtained we calculated the AE management costs, which are presented in Table 4.

Table 4. The costs of managing adverse events in the groups under study

No.	AE	Lapatinib + capecitabine		Trastuzumab emtansine	
		Frequency, %	Costs, RUB	Frequency, %	Costs, RUB
1.	Diarrhea	20.7	34	1.6	3
2.	Hand-foot syndrome	16.4	64	0	0
3.	Vomiting	4.5	5	0.8	1
4.	Neutropenia	4.3	3,053	2.0	1,420
5.	Hypokalemia	4.1	9	2.2	5
6.	Fatigue	3.5	11	2.4	8
7.	Nausea	2.5	3	0.8	1
8.	Stomatitis	2.3	5	0.2	0
9.	Thrombocytopenia	0.2	93	12.9	5,980
10.	Increased AST	0.8	15	4.3	83
11.	Increased ALT	1.4	27	2.9	56
12.	Anemia	1.6	41	2.7	70
		TOTAL	**3,361**	**TOTAL**	**7,627**

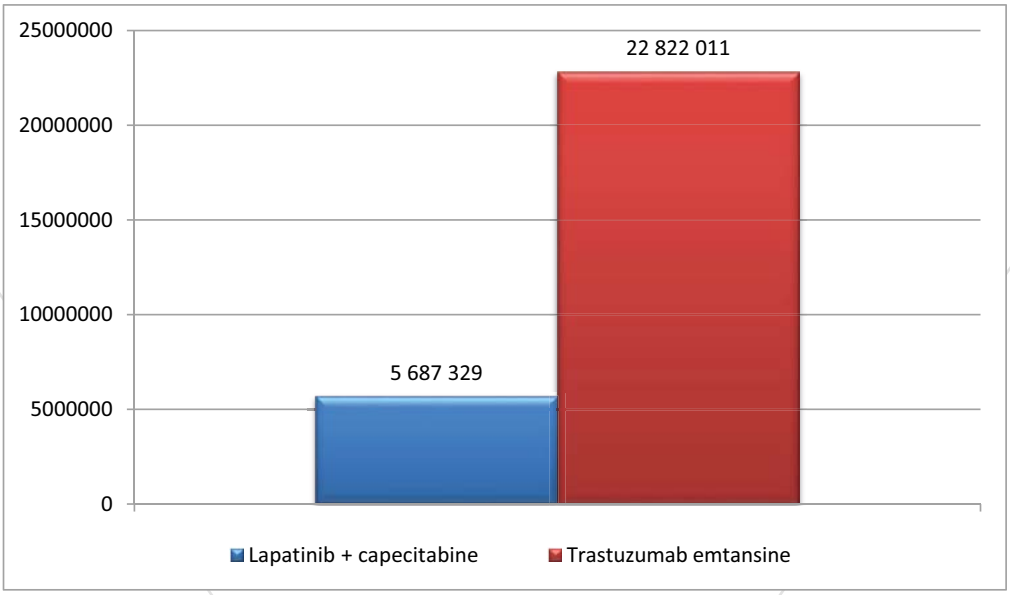

Figure 3. Cost of the primary pharmacotherapy for one patient over three years

Table 4 demonstrates that the costs of management of adverse events in the lapatinib + capecitabine treatment group were lower at 1,120 rubles, while in the group treated with trastuzumab emtansine they were 2,542 rubles. The cost of management of adverse events over three years are 3,361 rubles for therapy with lapatinib + capecitabine and 7,627 rubles for trastuzumab emtansine.

The total costs in the progression-free period were 1,922,326 rubles per one year of treatment for the group of patients who received lapatinib + capecitabine, and 7,643,912 rubles for patients who received trastuzumab emtansine. Table 5 presents the results of the cost analysis for the treatment of one case of HER2-positive mBC over one and three years of treatment, respectively.

Table 5. The total cost of treatment per one and three patient-years

Costs, RUB	1 year		3 years	
	Lapatinib + capecitabine	Trastuzumab emtansine	Lapatinib + capecitabine	Trastu-zumab emtansine
Primary pharmacotherapy, RUB	1,895,776	7,607,337	5,687,329	22,822,011
MS, RUB	8,180	8,180	24,541	24,541
CD, RUB	17,249	17,249	51,748	51,748
Administration, RUB	0	8,603	0	25,810
AE management, RUB	1,120	2,542	3,361	7,627
Total costs, RUB	1,922,326	7,643,913	5,766,978	22,931,736

Note: PP, Primary pharmacotherapy; MS, medical services; PD, concomitant drugs; AE, adverse events.

Figures 3 and 4 show the results of cost analysis of treatment per patient over three years of therapy, which include the cost of the primary pharmacotherapy, medical services, concomitant drugs, administration, and management of adverse events in the group of patients who received lapatinib + capecitabine and the comparison group which received trastuzumab emtansine.

Period after progression of the disease

According to the instructions for medical use of the study drugs, they should be discontinued after the onset of disease progression. Patients with progressing disease should be treated with other anti-cancer drugs under medical supervision. Due to a large variety of treatment regimens and lack of statistical data on the frequency of their use, it was assumed that patients were prescribed therapy with drugs included in the standard of care [7]. The costs after disease progression also include the costs of managing adverse events whose frequency is based on the data from the clinical trial which are provided above [35].

Table 6 shows the results of cost analysis after disease progression for one and three years.

Table 6. Cost after disease progression

Costs, RUB	1 year		3 years	
	Lapatinib+ capecitabine	Trastuzumab emtansine	Lapatinib + capecitabine	Trastuzumab emtansine
Medical services	8,180	8,180	24,541	24,541
Concomitant drugs	50,090	50,090	150,269	150,269
AE management	1,120	2,542	3,361	7,627
Total	59,390	60,812	178,171	182,437

Note: AE - adverse events

According to the data presented in Table 6, the total costs after disease progression were about 59,390 rubles per year and 178,171 rubles over three years in the group that had previously received lapatinib + capecitabine and 60,812 rubles per year and 182,437 rubles over three years for the group previously treated with trastuzumab emtansine.

Therefore, the cumulative costs of treating one patient with HER2+ mBC in the progression-free period and after disease progression are shown in Table 7 for one and three years of treatment.

Table 7. Total survival-adjusted discounted costs per patient

Costs, RUB	1 year		3 years	
	Lapatinib+ capecitabine	Trastuzumab emtansine	Lapatinib + capecitabine	Trastuzumab emtansine
Primary pharmacotherapy	1,118,508	5,096,916	1,426,989	7,229,321
Medical services	7,444	7,771	30,864	34,328
Concomitant drugs	26,206	25,582	164,269	178,989
Administration, RUB	0	5,764	0	24,527
AE management	1,120	2,415	4,226	10,668
Total	1,153,177	5,138,449	1,626,349	7,477,833

Note: AE - adverse events

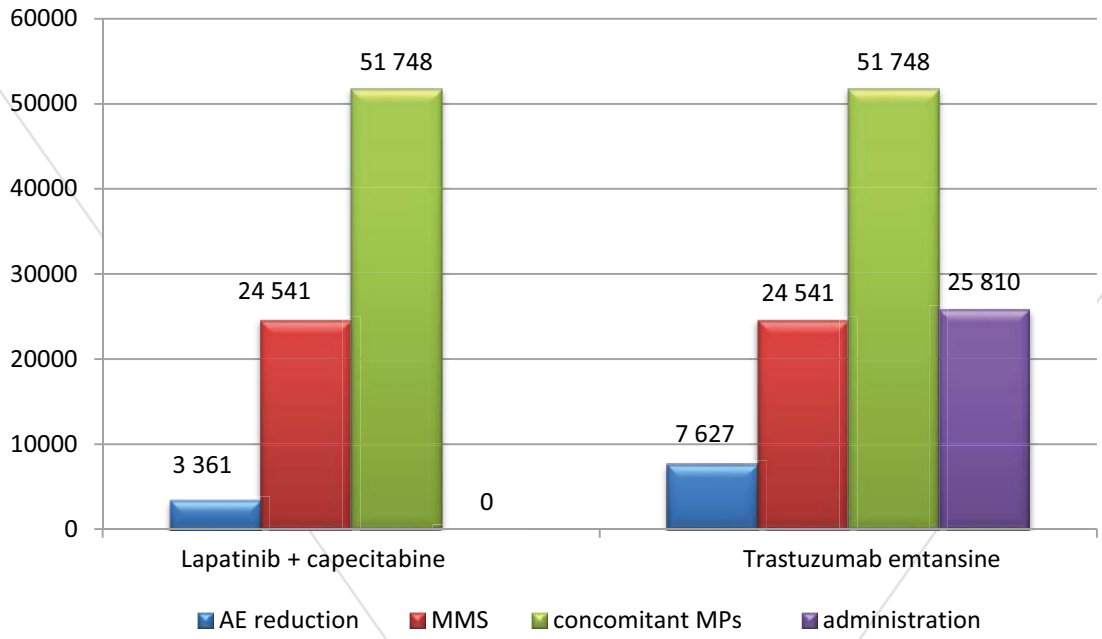

Figure 4. Cost of treatment of one patient over three years

Due to the long-term character of the evaluation (3 years), WHO-recommended discount rate of 3% should be applied according to the ISPOR guidelines for pharmacoeconomic forecasts [28,30].

Thus, Table 7 shows that the total discounted cost per patient was 1,626,349 rubles for combination therapy with lapatinib and capecitabine and 7,477,833 rubles for trastuzumab emtansine over three years.

Cost-effectiveness analysis

Cost-effectiveness ratios (CER) which reflect the cost of one unit of effectiveness of the investigated regimens and allow to determine the preferable therapy were obtained as a result of a cost-effectiveness analysis [26]. CER values for therapeutic regimens under study (combination of lapatinib and capecitabine and monotherapy with trastuzumab emtansine) over three years are shown in Table 8 and in Figure 5.

Table 8. Cost-effectiveness ratios for the regimens under study

Parameter	Lapatinib+ capecitabine	Trastuzumab emtansine
Costs, rubles	1,626,349	7,477,833
LYG	1.87	2.16
Cost-effectiveness ratio	869,705	3,461,960

The cost-effectiveness ratio is 869,705 rubles for the treatment with lapatinib + capecitabine, and 3,461,960 rubles for the therapy with trastuzumab emtansine. This means that the use of lapatinib in combination with capecitabine is the cost-effective treatment from the point of view of pharmacoeconomics [25].

Cost-utility analysis

At the next stage of the pharmacoeconomic study we performed a cost-utility analysis, whose results are expressed as the cost-utility ratio (CUR), which determines the cost of one quality-adjusted year of life gained [24]. The values of CUR for the use of lapatinib in combination with capecitabine in comparison with trastuzumab emtansine are presented in Table 9 and in Figure 5.

Table 9. Cost-utility ratios (three-year horizon)

Parameter	Lapatinib+ capecitabine	Trastuzumab emtansine
Costs, rubles	1,626,349	7,477,833
QALY	1.18	1.42
Cost-utility ratio	1,378,262	5,266,080

The presented results demonstrate that the cost of a quality-adjusted year of life gained is lower for combination therapy with lapatinib and capecitabine compared with trastuzumab emtansine.

The cost-utility ratio is 1,378,262 rubles for lapatinib and capecitabine and 5,266,080 for trastuzumab emtansine. Despite the QALY value for lapatinib in combination with capecitabine, a lower CUR value suggests that the use of lapatinib in combination with capecitabine is the cost-effective treatment for HER-positive mBC from the pharmacoeconomic point of view. [22]

Budget impact analysis

This analysis allows prediction of the impact on the health budget and calculation of the economic effect that can be expressed as cost savings or increased costs after transition from the comparison therapy to the alternative therapy [25,27].

The results of the budget impact analysis for the full course of treatment for 100 HER2-positive mBC patients are presented in Table 10 (Figure 6).

Table 10. The total cost of treatment of one patient with metastatic HER2+ breast cancer over one and three years

	Costs	Total costs, rubles	Cost savings associated with the use of L+C instead of TE, rubles	Cost savings associated with the use of L+C instead of TE
1 year	Lapatinib + capecitabine	115,317,721	398,527,137	78%
	Trastuzumab emtansine	513,844,858		
3 years	Lapatinib + capecitabine	162,634,884	585,148,420	78%
	Trastuzumab emtansine	747,783,304		

Note: L + C - lapatinib + capecitabine, TE - trastuzumab emtansine.

The results of the budget impact analysis demonstrate that the transition from trastuzumab emtansine to lapatinib + capecitabine is associated with budget savings of 3,985,271 rubles per patient for one year of therapy, and 5,851,484 rubles over three years, reducing the costs by 78%. When calculating the cost of treatment of 100 patients over three years, the total savings would constitute 585,148,420 rubles, which, within a fixed budget, enables treatment of 60 additional 3 patients.

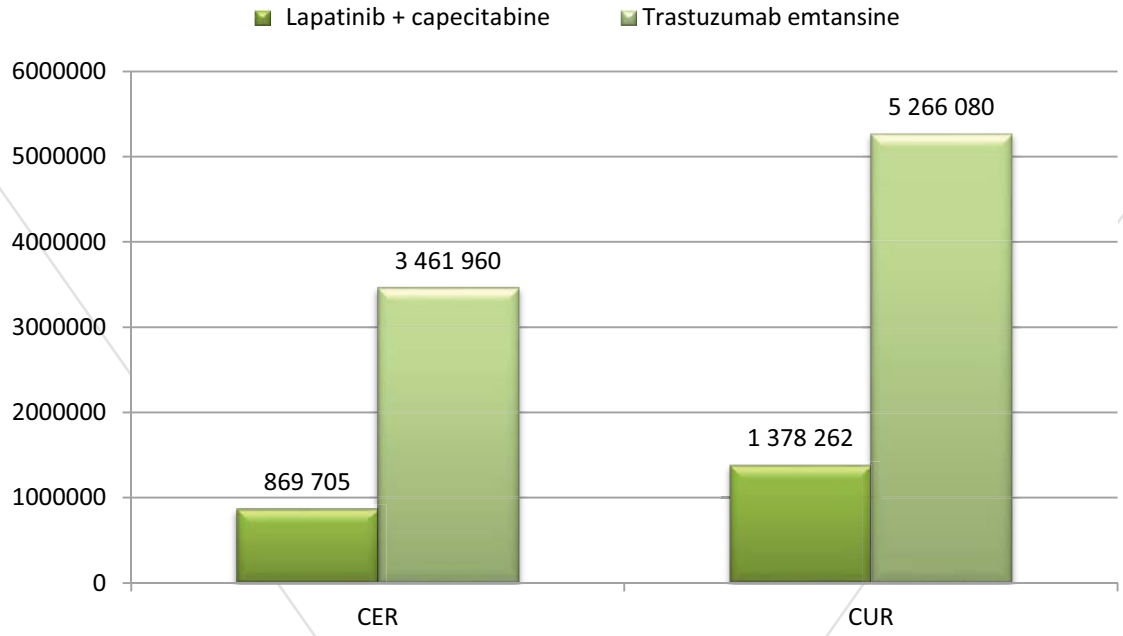

Figure 5. Cost-effectiveness/utility ratios for the compared health technologies, using quality-adjusted years of life gained per patient as the utility criterion

Cost-minimization analysis

Second-line chemotherapy in HER2+ mBC

The cost-minimization analysis demonstrated that the use of combination therapy with lapatinib + capecitabine is associated with budget savings compared to trastuzumab emtansine. Lapatinib + capecitabine therapy provide savings of about 143,469,769 rubles for every 36 patients out of 100 per year and 210,653,431 rubles over three years, which corresponds to a cost reduction of 78% (Table 12) [35].

The number of patients receiving second-line therapy for HER2+ mBC is 36% of the total population, which is equivalent to 2,965 patients based on the 2014 epidemiological data. One-time prescription of combination therapy with lapatinib + capecitabine to this group of patients is associated with budget savings of 17,349,650,666 rubles over three years in comparison with trastuzumab emtansine monotherapy. Therefore, within a fixed budget of the health system, transferring this group of patients from trastuzumab emtansine to lapatinib + capecitabine allows to treat 10,688 additional patients.

HER2+ BC with non-visceral metastases.

The group of patients with non-visceral metastases was singled out in this pharmacoeconomic study. It constituted 32.5% of the total population [30]. This means that the treatment efficacy is similar in 33 out of every 100 patients, and therefore the use of the least expensive treatment is warranted. Thus we conducted a cost-minimization analysis, which demonstrated that for every 33 out of 100 HER2-positive mBC patients with non-visceral metastases, the use of lapatinib + capecitabine therapy leads to savings of 193,098,979 rubles over three years, which corresponds to a 78% reduction in the costs (Table 11).

Sensitivity analysis

Sensitivity analysis identifies the most important parameter whose change can significantly affect the outcome of the study. In this paper we studied the variability of the total cost and cost-effectiveness ratios based on changes in the prices of various components.

A two-factor sensitivity analysis has been used, which included simultaneous change in the key parameter of cost of combination lapatinib + capecitabine and trastuzumab emtansine. The range of price fluctuations was set to ± 10% [13]. Table 12 demonstrates how the final results change depending on fluctuations in the cost of therapy with lapatinib + capecitabine and trastuzumab emtansine within ± 10%.

Table 12. The results of a sensitivity analysis for simultaneous changes in the price of the primary pharmacotherapy in the compared groups

Coefficient	Therapy	-10%		+10%
CER	Lapatinib + capecitabine	773,257	869,705	935,462
	Trastuzumab emtansine	3,248,987	3,461,960	3,960,414
CUR	Lapatinib + capecitabine	1,225,416	1,378,262	1,482,470
	Trastuzumab emtansine	4,942,121	5,266,080	6,024,291

The sensitivity analysis presented in Table 13 shows that the results of the cost-effectiveness/cost-utility pharmacoeconomic analyses are stable in case of simultaneous 10% increase in the cost of lapatinib + capecitabine therapy and 10% reduction in the cost of trastuzumab emtansine, since CER/CUR values for lapatinib + capecitabine remain lower than CER/CUR values for trastuzumab emtansine over this entire range.

Results

The analysis of effectiveness/utility of treating HER2-positive mBC patients determined the effectiveness criteria for the progression-free period and after progression of the disease, which are represented by the LYG and QALY indicators. The use of lapatinib in combination with capecitabine allowed to achieve 0.8 LYG in the PFP and 1.07 after progression of the disease, with a total of 1.87 LYG over three years, while LYG value in the use of trastuzumab

Table 11. The results of a cost-minimization analysis for HER2+ mBC patients

Population	Number of patients 100	Time horizon	L+C, RUB	TE, RUB	Economy under L+C instead of TE, RUB
2nd line chemotherapy	36	1 year	41,514,380	184,984,149	143,469,769
		3 years	58,548,558	269,201,989	210,653,431
HER2+advanced Breast Cancer with non-visceral metastasis	33	1 year	38,054,848	169,568,803	131,513,955
		3 years	53,669,512	246,768,490	193,098,979

Note: L+C – lapatinib + capecitabine, TE – trastuzumab emtasine.

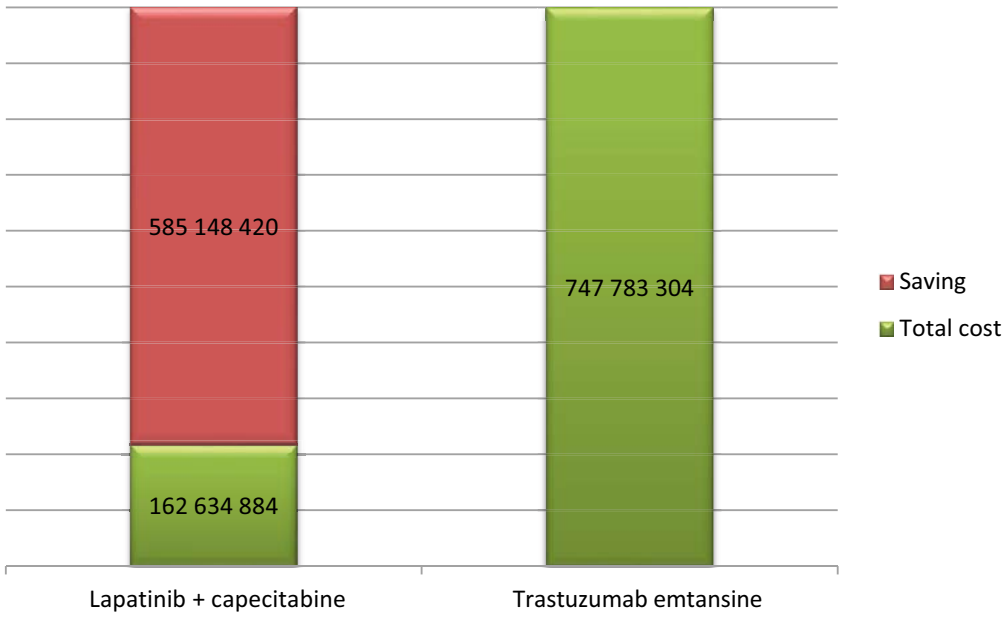

Figure 6. The total cost of treatment of one patient with HER2+ mBC over three years

emtansine was 1.01 for PFP and 1.15 after the progression of the disease, with a final figure of 2.16 LYG. The QALY value for the combination of lapatinib and capecitabine was 0.61 in the PFP and 0.57 after disease progression, giving a total of 1.18 QALY; for trastuzumab emtansine the values were 0.81 for PFP, 0.61 after disease progression, and 1.42 QALY in total.

The cost analysis yielded the total cost of treatment of one patient per year, which included a transition from a "progression-free" state to "after disease progression" state; it constituted 1,153,177 rubles for lapatinib + capecitabine and 5,138,449 rubles for trastuzumab emtansine (after discounting). The total costs over three years were 1,626,349 rubles and 7477833 rubles, respectively.

The cost-effectiveness ratios obtained from the cost-effectiveness analysis were 869,705 rubles for lapatinib + capecitabine and 3,461,960 rubles for trastuzumab emtansine, respectively.

The cost-utility ratios obtained from the cost-utility analysis were 1,378,262 rubles for lapatinib + capecitabine and 5,266,080 rubles for trastuzumab emtansine, respectively.

Predicted budget savings per patient calculated based on the results of the budget impact analysis were 3,985,271 rubles per year and 5,851,484 rubles over three years, or 585,148,420 rubles per 100 patients over three years of treatment. The results demonstrated that lapatinib + capecitabine therapy reduces treatment costs by 78% as compared to trastuzumab emtansine, and a transition of 100 patients from trastuzumab emtansine to lapatinib + capecitabine allows treating 360 additional patients within a fixed budget.

The sensitivity analysis showed that with concurrent changes in the primary pharmacotherapy in both groups (range of [-10; 10]%), the CER index would be 935,462 rubles and 3,248,987 rubles for lapatinib + capecitabine and trastuzumab emtansine, respectively. Under the same conditions, the cost-utility parameter was 1,482,470 rubles and 4,942,121 rubles for lapatinib in combination with capecitabine and trastuzumab emtansine, respectively. Therefore, the sensitivity analysis confirmed stability of the study results.

The cost-minimization analysis for patients receiving second-line chemotherapy demonstrated that the use of lapatinib + capecitabine in 36 patients out of 100 allows saving 143,469,769 rubles per year and 210,653,431 rubles over three years of treatment, which corresponds to a 78% cost reduction versus trastuzumab emtansine.

The results of the cost minimization analysis performed for a groups of patients with non-visceral metastases demonstrated that the use of lapatinib + capecitabine in 33 patients out of 100 provides budget saving in the amount of 131,513,955 rubles per year and 193,098,979 rubles over three years of treatment, which corresponds to a 78% cost reduction.

Conclusion

The conducted pharmacoeconomic analysis of treatment of HER2-positive BC compared the treatment regimens of lapatinib + capecitabine and trastuzumab emtansine.

Based on the results of the pharmacoeconomic analysis, it was concluded that the use of lapatinib in combination with capecitabine is superior to trastuzumab emtansine in HER2+ BC in the second-line treatment and in patients with nonvisceral metastases in terms of healtheconomics due to lower annual treatment costs and cost savings which create the possibility of treating more patients. The lapatinib + capecitabine therapy is preferable from a pharmacoeconomic point of view.

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