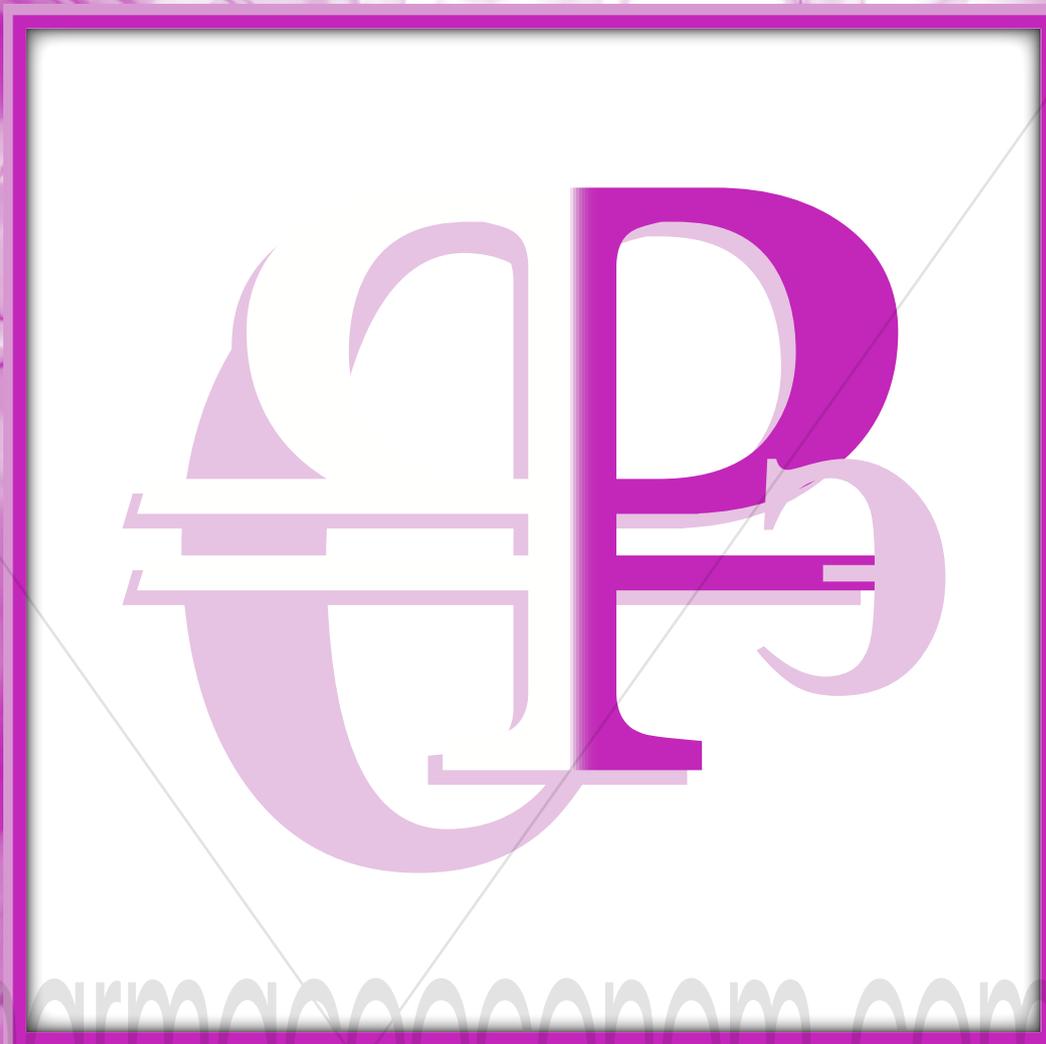


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- **IX НАЦИОНАЛЬНЫЙ КОНГРЕСС С МЕЖДУНАРОДНЫМ УЧАСТИЕМ «РАЗВИТИЕ ФАРМАКОЭКОНОМИКИ И ФАРМАКОЭПИДЕМИОЛОГИИ В РОССИЙСКОЙ ФЕДЕРАЦИИ»**
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- **ОРИГИНАЛЬНЫЕ РОССИЙСКИЕ ФАРМАКОЭКОНОМИЧЕСКИЕ ИССЛЕДОВАНИЯ**

PHARMACOECONOMIC ANALYSIS OF KADCYLA (TRASTUZUMAB EMTANSINE) IN THE TREATMENT OF PATIENTS WITH HER2-POSITIVE BREAST CANCER

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Abstract:

Although there have been improvements in the detection and treatment of breast cancer (BC) it remains the most common cancer in women and one of the leading causes of death. In Western Europe and North America, breast cancer is the leading cause of death among women aged 35 to 54 years (20%), and the second leading cause of death in women aged over 55 years exceeded only by cardiovascular diseases. Breast cancer incidence increases with age, beginning from 40 years, with a peak at 60 to 65 years. The objective of this study was to determine, from the pharmacoeconomic point of view, the preferred treatment regimen (Kadcyla, lapatinib + capecitabine, trastuzumab + capecitabine, capecitabine), used in the treatment of HER2-positive breast cancer, on the basis of comparison of cost-effectiveness ratio, safety and life quality. The use of Kadcyla in the treatment of patients with HER2-positive breast cancer resulted in the highest values of life years gained and quality adjusted life years in comparison with lapatinib + capecitabine, trastuzumab + capecitabine, or capecitabine regimen. According to the results of the cost-effectiveness analysis and cost-utility analysis it was found that the therapy with Kadcyla required higher costs to achieve LYG and QALY compared to those of the treatment regimens with the use of lapatinib + capecitabine, trastuzumab + capecitabine, and capecitabine, respectively. Incremental ratios in both analyses are higher than the willingness to pay threshold values for the Russian Federation.

Key words: effectiveness analysis, utility analysis, cost analysis, cost-effectiveness analysis, cost-utility analysis, breast cancer, health technology assessment, Kadcyla, trastuzumab emtansine, lapatinib, capecitabine, trastuzumab, pharmacoeconomics, clinical and economic analysis.

Introduction

Breast cancer (BC) is a malignant tumor that starts in the epithelial cells that line the glandular ducts and lobules [1-4.7]. Although there have been improvements in the detection and treatment of breast cancer (BC) it is now the most common cancer in women and one of the leading causes of death. In Western Europe and North America, breast cancer is the leading cause of death among women aged 35 to 54 years (20%), and the second leading cause of death in women aged over 55 years exceeded only by cardiovascular diseases [8]. Breast cancer incidence increases with age, beginning from 40

years, with a peak at 60 to 65 years. The highest female mortality rates are noted at the age of 40 to 49 years – 27.3%, 50 to 59 years – 25.4%, 30 to 39 years - 20%, and 60 to 69 years - 17%. Female mortality structure changed only at the age of 70 years and older: stomach cancer is the first (15.8%) and breast cancer is the second (12.3%) leading cause of death [8].

In 2013, in Russia there were 57,307 newly diagnosed cases of breast cancer, and in 31.9% of cases the disease was diagnosed at III-IV stage. The total number of patients diagnosed with breast cancer was 562,053 persons. At the same time, the mortality rate remains high during the first year of diagnosis - 3.7% [5].

The objective of this study is to determine, from the pharmacoeconomic point of view, the preferred treatment regimen (Kadcyla, lapatinib + capecitabine, trastuzumab + capecitabine, capecitabine), used in the treatment of HER2-positive breast cancer, on the basis of comparison of cost-effectiveness ratio, safety and life quality.

To achieve this objective, the following tasks were solved:

1. Collection and analysis of clinical practice data regarding the treatment of HER2-positive BC in the treatment groups being compared (Kadcyla, lapatinib + capecitabine, trastuzumab + capecitabine, capecitabine).
2. Selection of the criteria for evaluating the effectiveness of Kadcyla, lapatinib + capecitabine, trastuzumab + capecitabine, capecitabine in the treatment of BC.
3. Cost analysis of the compared regimens used in the treatment of HER2-positive BC.
4. Use of the following methods in this pharmacoeconomic study: cost-effectiveness analysis, cost-utility analysis, budget impact analysis.

Effectiveness analysis

On the basis of the information search performed, the criteria of effectiveness and utility were determined to enable pharmacoeconomic assessment of the compared health technologies used in the treatment of patients with HER2-positive BC. In this study, LYG (Life Years Gained) and QALY (Quality Adjusted Life Years) were used as such criteria, respectively. The values presented in Tables 1 and 2 were obtained for the 7-year time frame of the study, on the basis of treatment of one patient.



Table 1 – Results of the effectiveness analysis for the BC treatment regimens compared [15-20].

Effectiveness parameter (LYG)	Kadcyla	Lapatinib + capecitabine	Trastuzumab + capecitabine	Capecitabine
Value during progression-free period, years	1,12	0,86	0,63	0,43
Value after disease progression, years	1,82	1,44	1,25	1,35
Total LYGs	2,94	2,30	1,88	1,78

As seen in the table above, the use of Kadcyla in the treatment of patients with HER2-positive breast cancer resulted in the highest values of life years gained in comparison to lapatinib + capecitabine, trastuzumab + capecitabine, or capecitabine regimen. The use of Kadcyla also increased patient's life years both in the progression-free period and after disease progression. The lowest LYG values (1.78) were obtained in the group of capecitabine. However, with this treatment regimen, survival after disease progression was longer in comparison to the trastuzumab + capecitabine treatment regimen.

Table 2 – Results of the effectiveness analysis for the treatment regimens compared [15-20].

Utility parameter (QALY)	Kadcyla	Lapatinib + capecitabine	Trastuzumab + capecitabine	Capecitabine
Value during progression-free period, years	0,90	0,65	0,47	0,32
Value after disease progression, years	0,97	0,77	0,66	0,72
Total QALYs	1,87	1,42	1,13	1,04

As seen from the table above, the use of Kadcyla in the treatment of patients with HER2-positive breast cancer resulted in the highest values of quality adjusted life years in comparison to lapatinib + capecitabine, trastuzumab + capecitabine, or capecitabine regimen. The use of Kadcyla also increased patient's life quality both in the progression-free period and after disease progression. Similar to the results of the effectiveness analysis, the lowest QALY values (1.04) were obtained in the group of capecitabine. However, with this treatment regimen, life quality after disease progression was higher in comparison to the trastuzumab + capecitabine treatment regimen.

Cost analysis

The total cost included basic pharmacotherapy costs, costs related to the introduction of the treatment regimens compared, and costs associated with the correction of adverse effects due to the use of health technologies being analyzed.

The time frame of this study was 7 years. The discount rate of 3.5% was also used. The obtained results of the cost analysis are presented in Table 3.

Table 3 – Results of the cost analysis for the treatment of HER2-positive BC, rubles

Cost analysis parameter	Kadcyla	Lapatinib + capecitabine	Trastuzumab + capecitabine	Capecitabine
Basic pharmacotherapy costs	7 456 306	2 218 093	912 459	104 876
Treatment regimen introduction costs	1 905	0	1 083	0
Costs associated with the correction of adverse effects due to the use of basic pharmacotherapy	1 535	1 485	1 084	738
Total cost	7 459 746	2 219 578	914 626	105 614

On the basis of the values obtained in the cost analysis, it was concluded that the use of Kadcyla in the treatment of HER2-positive BC requires higher total cost compared to that of lapatinib + capecitabine, trastuzumab + capecitabine, or capecitabine regimen. Besides, the use of Kadcyla resulted in higher costs of each component analyzed: basic pharmacotherapy costs, costs related to the introduction of the treatment regimens compared, and costs associated with the correction of adverse effects due to the use of health technologies being analyzed.

It was also noted that the capecitabine treatment regimen had the lowest cost values (105,614 rubles). In this treatment group, the lowest costs were obtained not only in the calculation of the total value, but also in the analysis of each component.

Cost-effectiveness analysis

The cost-effectiveness analysis (CEA) is used to assess the cost of an effectiveness unit of the respective health technologies being compared [6, 10]. This type of pharmacoeconomic analysis permits comparison of health technologies not only on the basis of total cost values, but also using cost-effectiveness ratio calculation. The cost-effectiveness ratio is calculated according to the formula:

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

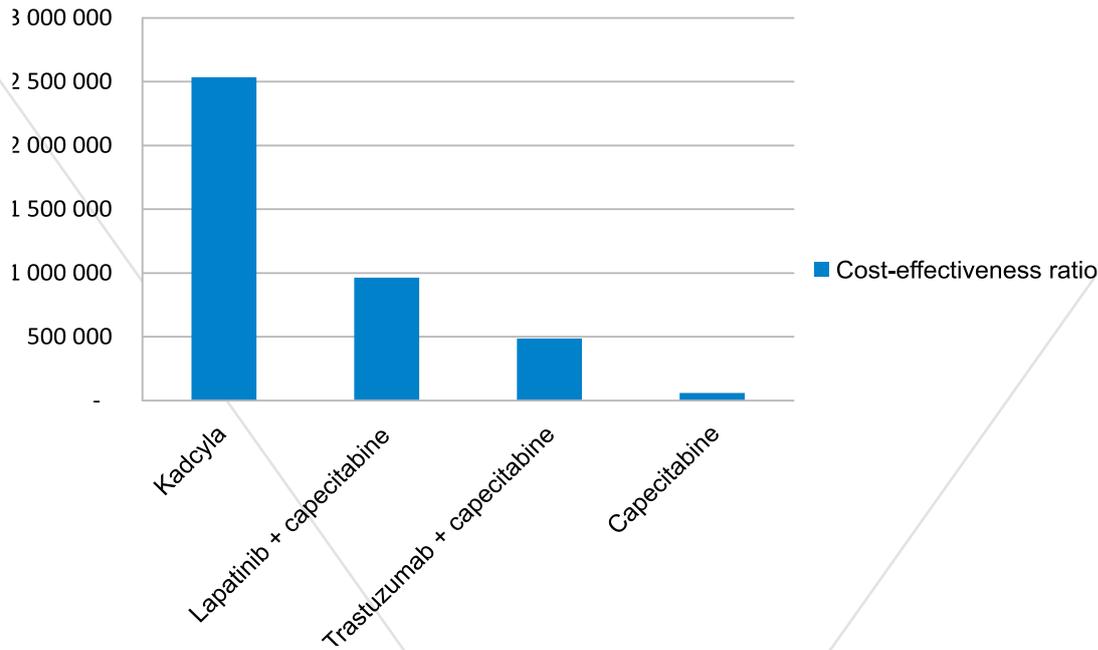
where: CER is the cost-effectiveness ratio;
Cost is the cost of the technology studied, rubles;
Ef is the effectiveness of the technology studied.

Therefore, in this study, the cost-effectiveness ratio values were calculated for the treatment of HER2-positive breast cancer using Kadcyla, lapatinib + capecitabine, trastuzumab + capecitabine, or capecitabine treatment regimen. LYG values were used as the effectiveness criterion (Table 4, Fig. 1).

Table 4 – Results of the cost-effectiveness analysis (effectiveness criterion – Life Years Gained)

Parameter	Kadcyla	Lapatinib + capecitabine	Trastuzumab + capecitabine	Capecitabine
Costs, rubles	7 459 746	2 219 578	914 626	105 614
LYG	2,94	2,30	1,88	1,78
Cost-effectiveness ratio	2 534 090	964 642	486 603	59 471

Figure 1. Cost-effectiveness ratios per one patient



As seen from the results above, the capecitabine regimen has the lowest cost per one life year gained. However, along with the highest costs, the use of Kadcylya also shows the highest effectiveness expressed as maximum values of life years gained for the alternatives being compared.

Then the incremental cost-effectiveness ratios were calculated for the health technologies being compared. For the most effective treatment regimen (with Kadcylya), the following results per one LYG were obtained: 8,151,824 rubles compared to the lapatinib + capecitabine regimen, 6,150,597 rubles compared to the trastuzumab + capecitabine regimen, and 6,297,111 rubles compared to capecitabine.

Cost-utility analysis

In the course of this pharmacoeconomic study, the cost-utility analysis was performed on the basis of treatment of one patient with HER2-positive BC. The results of cost-utility analysis (CUA) and incremental cost-utility ratio analysis (ICUR) are expressed as the respective ratios which are calculated according to the following formulas [9, 11]:

$$CUR = DC/Ut,$$

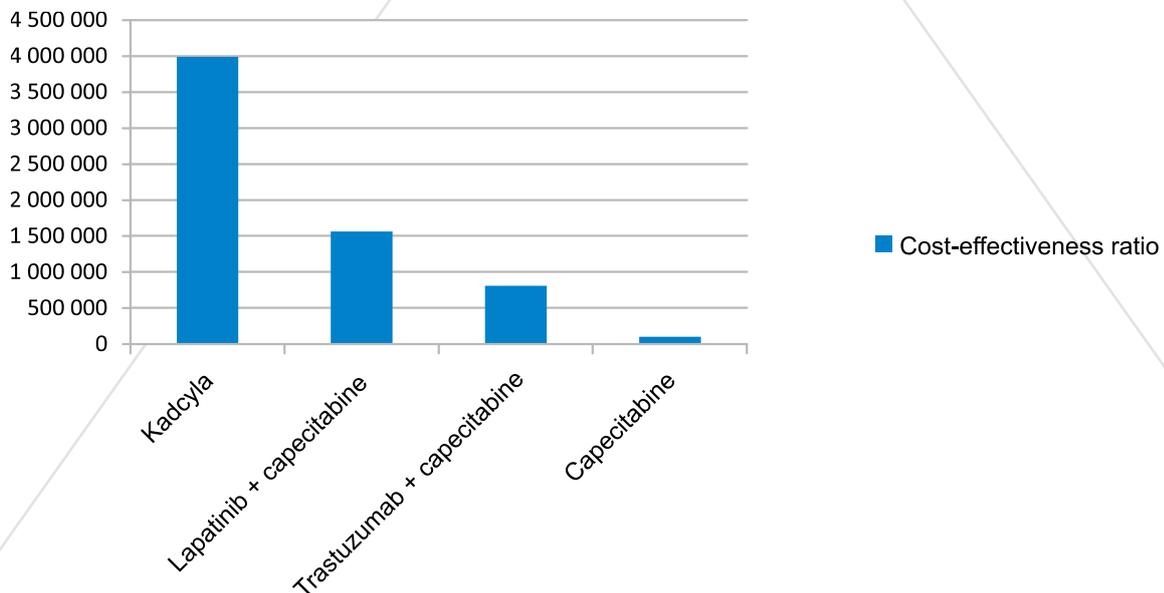
$$ICUR = (DC1 - DC2)/(Ut1 - Ut2),$$

where CUR is the cost-utility ratio (cost per one utility unit - QALY);
ICUR is the incremental cost-utility ratio (incremental cost per one additional utility unit);
DC1 are direct costs of the first treatment option;
DC2 are direct costs of the second treatment option;
Ut1 and Ut2 are utility values of the first and second treatment options (QALY value).
Therefore, in this study the cost-utility ratio values were obtained for the regimens of HER2-positive BC treatment being compared. QALY values were used as the utility criterion (Table 5, Fig. 2).

Table 5 – Results of the cost-utility analysis (utility criterion – QALY)

Parameter	Kadcylya	Lapatinib + capecitabine	Trastuzumab + capecitabine	Capecitabine
Costs, rubles	7 459 746	2 227 197	919 173	109 501
QALY	1,87	1,42	1,13	1,04
Cost-utility ratio	3 989 169	1 563 083	809 403	101 552

Figure 2. Cost-utility ratios per one patient





As seen from the results above, the capecitabine regimen has the lowest cost per one QALY. However, along with the highest costs, the use of Kadcyła also shows the highest utility expressed as maximum QALY values for the alternatives being compared.

Then the incremental cost-utility ratios were calculated for the health technologies being compared. For the treatment regimen showing the maximum utility (with Kadcyła), the following results per one QALY were obtained: 11,683,769 rubles compared to the lapatinib + capecitabine regimen, 8,906,925 rubles compared to the trastuzumab + capecitabine regimen, and 8,835,356 rubles compared to capecitabine.

Budget impact analysis

Budget impact analysis involves the assessment of all types of expenditure associated with the introduction of a new treatment regimen in relation to all types of expenditure associated with the already existing treatment regimen [2]. Costs are calculated according to the following formula:

$$BIA = Cost1 - Cost2, \text{ where}$$

Cost1 is the total cost of the first treatment option (rubles);

Cost2 is the total cost of the second treatment option (rubles);

BIA is the budget impact analysis (rubles).

According to the results of the budget impact analysis it was found that for the Kadcyła treatment regimen the difference in the required budgetary funds was 5,240,168 rubles compared to the lapatinib + capecitabine regimen, 6,545,120 rubles compared to the trastuzumab + capecitabine regimen, and 7,354,132 rubles compared to capecitabine for the treatment of one patient with HER2-positive BC (7 year time frame).

Results

1. As a result of the cost analysis performed, the following costs of BC treatment were obtained (time frame - 7 years): 7,459,746 rubles in Kadcyła group, 2,219,578 rubles in lapatinib + capecitabine group, 914,626 rubles in trastuzumab + capecitabine group, and 105,614 rubles in capecitabine group.

2. The results of the cost-effectiveness analysis showed that the cost-effectiveness ratios (effectiveness criterion – Life Years Gained, LYG) were as follows (time frame – 7 years): 2,534,090 rubles in Kadcyła group, 964,642 rubles in lapatinib + capecitabine group, 486,603 rubles in trastuzumab + capecitabine group, and 59,471 rubles in capecitabine group. For the most effective treatment regimen (Kadcyła), the following incremental cost-effectiveness ratios were obtained: 8,151,824 rubles compared to the lapatinib + capecitabine regimen, 6,150,597 rubles compared to the trastuzumab + capecitabine regimen, and 6,297,111 rubles compared to capecitabine.

3. According to the results of the cost-effectiveness analysis it was found that the cost-utility ratios (utility criterion – QALY) were as follows (time frame - 7 years): 3,989,169 rubles in Kadcyła group, 1,563,083 rubles in lapatinib + capecitabine group, 809,403 rubles in trastuzumab + capecitabine group, and 101,552 rubles in capecitabine group. For the treatment regimen showing the maximum utility (Kadcyła), the following incremental cost-utility ratios were obtained: 11,683,769 rubles compared to the lapatinib + capecitabine regimen, 8,906,925 rubles compared to the trastuzumab + capecitabine regimen, and 8,835,356 rubles compared to capecitabine.

4. According to the results of the budget impact analysis it was determined that for the Kadcyła treatment regimen the difference in the required budgetary funds was 5,240,168 rubles compared to the lapatinib + capecitabine regimen, 6,545,120 rubles compared to the trastuzumab + capecitabine regimen, and 7,354,132 rubles compared to capecitabine for the treatment of one patient with HER2-positive BC (7 year time frame).

Discussion

According to the estimates with regard to the total number of patients with metastatic BC, HER2-positive metastatic breast cancer, probabilities of the first and second therapy line administration, and previous treatment with trastuzumab and taxanes, a total of 2,501 patients in the Russian Federation need treatment with Kadcyła, which will require the expenditure of 18,656,824,939 rubles for the treatment over 7 years.

Monotherapy with Kadcyła® is effective in the difficult-to-treat group of patients with HER2-positive metastatic breast cancer when disease progression is detected during the adjuvant therapy including trastuzumab or taxane drugs or during 6 months following its completion, i.e. when the standard adjuvant therapy is ineffective.

According to the estimates with regard to the total number of patients with BC, HER2-positive BC, probabilities of adjuvant therapy administration

and disease progression during the standard adjuvant therapy including trastuzumab and taxane drug or during 6 months following its completion, a total of 177 patients in the Russian Federation need treatment with Kadcyła for this indication, which will require the expenditure of 1,320,375,056 rubles for the treatment over 7 years. Today, there are no other drug treatment options approved in Russia for use in this category of patients.

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