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PHARMACOECONOMIC ANALYSIS OF TRASTUZUMAB APPLICATION FOR SUBCUTANEOUS ADMINISTRATION COMPARED TO INTRAVENOUS ADMINISTRATION IN THE TREATMENT OF HER2-POSITIVE BREAST CANCER IN REGIONS OF THE RUSSIAN FEDERATION

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Summary: *Breast cancer is a malignant neoplasm that develops from the epithelial cells of ducts and lobules of the glandular parenchyma, which according to the World Health Organization (WHO) is the most common form of cancer among women (16% of all cases) in the world. In 2014, in Kaluga, Lipetsk, Smolensk and Tula regions the mortality from breast cancer reached 3.2%, 3.1%, 4% and 4.7%, respectively. One of the aggressive forms of breast cancer is a HER2positive (HER2+) subtype (14 to 20% of all subtypes), which is treated with targeted therapy. The appearance of trastuzumab for subcutaneous administration has a number of advantages compared to the intravenous formulation. A pharmacoeconomic analysis of treatment of HER2+ breast cancer was performed by comparing trastuzumab in two formulations in Kaluga, Lipetsk, Smolensk and Tula regions. According to the "cost minimization" analysis in the analyzed regions, the use of trastuzumab for subcutaneous administration compared to intravenous administration saves from 29.7 to 34% of funds. The forecasted budget savings as a result of the budget impact analysis for 10 patients is 8,068,360 rubles in Kaluga region, 7,047,430 rubles in Lipetsk region, 6,534,750 rubles in Smolensk region, and 7,188,980 rubles in Tula region for the treatment course with trastuzumab in subcutaneous formulation as compared to the intravenous formulation. The results showed that the use of trastuzumab therapy in the subcutaneous formulation allows treatment of 4 additional patients with HER2+ breast cancer in Smolensk region, and 5 patients in Kaluga, Lipetsk and Tula regions within a fixed budget.*

Keywords: *breast cancer, HER2-positive status, trastuzumab, subcutaneous administration, intravenous administration, pharmacoeconomic analysis, cost analysis, "cost minimization" analysis, budget impact analysis, analysis of lost opportunities , Kaluga region, Lipetsk region, Smolensk region, Tula region.*

Introduction

Breast cancer is a malignant neoplasm that develops from the epithelial cells of ducts and lobules of the glandular parenchyma, which according to the World Health Organization (WHO) is the most common form of cancer among women (16% of all cases) in the world [6,20]. Every year across Russia the prevalence of breast cancer increases, so that from 2004 to 2014 there was an increase of 44% in this indicator (Figure 1) [11].

It should be noted that prevalence of breast cancer has been steadily increasing in various regions of Russian Federation. This study included four subjects of the Russian Federation: Kaluga region, Lipetsk region, Smolensk region, Tula region. The data on mortality and the prevalence of breast cancer in 2014, in particular with HER2+ tumor expression, are presented in Table 1 [11,21].

Patients with HER2-positive breast cancer in combination with obesity have a poor prognosis. Thus, patients with a high body mass index (BMI) are 2.5 times more likely to die of breast cancer within five years compared to patients with a low BMI [28]. It should be noted that the in Russia the adult population with obesity is about 30% and 25% of people have overweight. The prevalence of overweight increases with age reaching the highest incidence in the 60-year-old age group [1]. Thus it is important to consider this factor in pharmacoeconomic analysis, since many drugs used in oncology are calculated based on body weight.

There are innovative drugs currently used in the pharmaceutical market, which have a targeted action on tumor cells. One such drug is trastuzumab, whose application in the treatment of HER2+ breast cancer is included in the recommendations of ESMO, NCCN, AOP, ASCO, St. Gallen and RUSSCO [5,8,9,16]. As of March 28, 2016, trastuzumab is registered in subcutaneous (SC) and intravenous (IV) formulations [13]. Using SC formulation in a fixed dose has a number of advantages compared with IV, such as [7]:

- does not require dose calculation, since it does not depend on body weight;
- does not require a loading dose;
- does not require hospitalization;
- saving on the method of drug administration [26];
– saving time of the medical personnel [26].

In this regard, it is important to determine the most cost-effective therapy in terms of pharmacoeconomics when comparing trastuzumab SC and IV in the treatment of HER2+ breast cancer at selected regions of Russia, which was the purpose of this study.

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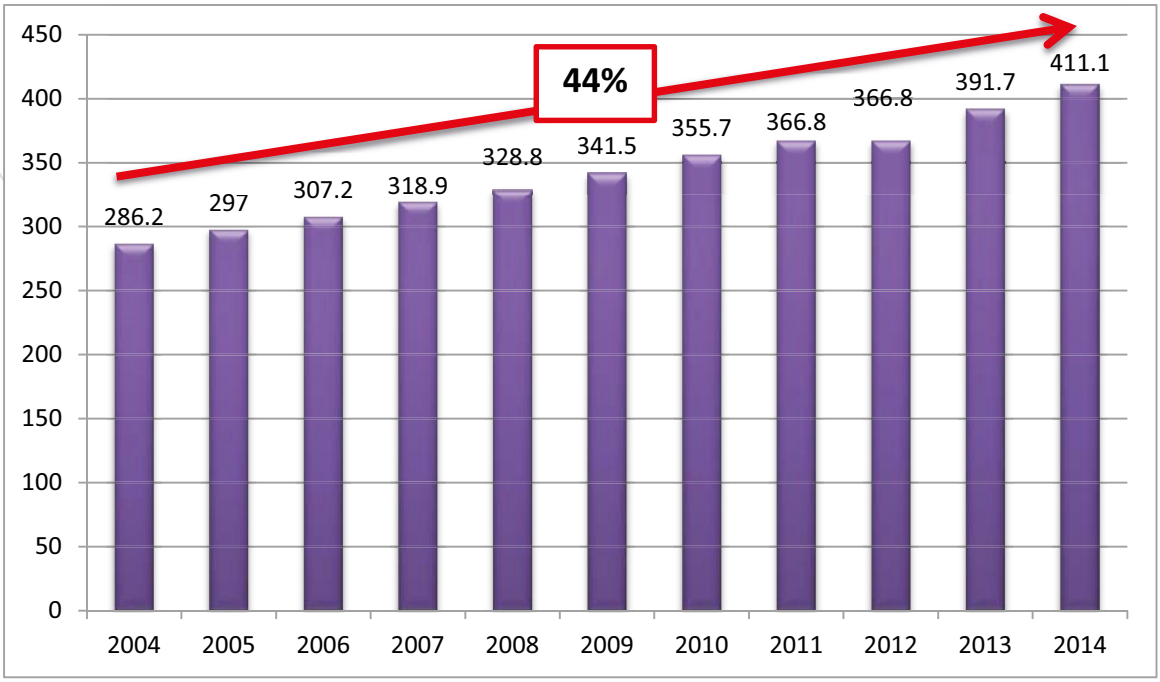

Figure 1. The increased prevalence of breast cancer in Russian Federation per 100 000 inhabitants in the period 2004-2014.

Table 1: Regional data on breast cancer mortality and identification of patients with HER2+ status

Region	Number of breast cancer cases	Mortality, %	Mortality in the first year after diagnosis, %	Number of HER2+ breast cancer cases	Number of HER2+ breast cancer cases, %
Kaluga region	512	3.2	6.8	86	16.8
Lipetsk region	461	3.1	6.1	77	16.7
Smolensk region	469	4.0	6.6	63	13.4
Tula region	717	4.7	10	151	21.1

Materials and methods

During the comparison of using trastuzumab SC and IV formulations in the treatment of HER2+ breast cancer in selected regions of the Russian Federation, a region-specific analytical model created in Microsoft Office Excel was used. The analyzed population is represented by patients with body weight of 80 kg, which is used in the calculation of a single dose of trastuzumab IV.

In the first stage of the study the costs analysis has been performed, which included the calculation of direct costs associated with the treatment of HER2+ breast cancer. When calculating the cost of drugs the data from trastuzumab prescribing information was used along with maximum wholesale prices including VAT for each considered subject of the Russian Federation according to the prices register for vital and subcutaneous drugs as of March 28, 2016. The basic pharmacotherapy is held once every 3 weeks with trastuzumab SC (600 mg) in one group and with trastuzumab IV (440 mg and 150 mg) in the compared group. One-year adjuvant treatment course consists of 18 injections of trastuzumab, which when used in the SC formulation are administered in a fixed dose, which corresponds to the use of one vial at each administration[4]. Trastuzumab IV dose is measured based on the patient weight and applied according to the following regimen: the first dose is a loading dose (8 mg/kg or 640 mg), and subsequent 17 doses are maintenance doses (6 mg/kg or 480 mg) [2,3]. Due to the different cost of SC and IV administration, the cost of the medicinal product administration is calculated by multiplying the cost of administration by the number of doses per course. Further, in calculating the costs for medical personnel, the data of Russian sites from a multicenter study PrefHER (sub research "Time & Motion") (2014) were used, which showed the difference in the administration time between SC and IV formulations [26]. Hence, taking into account the average salary of medical personnel, the cost of this expenditure item was determined using formulas 1 and 2 [14].

$$Cost_{min}=P/N/n/60, \text{ where} \quad (1)$$

$Cost_{min}$ – cost of one working minute of a nurse/doctor, rubles;
P – nurse/doctor salary, rubles per month;
N – number of working days per month;
n – number of working hours per day;
60 – minutes per hour.

$$Cost_{mp}=(z*Cost_{nurse1}+(100-z)*Cost_{doctor1})*t, \text{ where} \quad (2)$$

$Cost_{mp}$ – cost of services provided by medical personnel, rubles;
$Cost_{nurse1}$ – cost of one working minute of a nurse, rubles;
$Cost_{doctor1}$ – cost of one working minute of a doctor, rubles;
z – share of procedure performed by a nurse;
(1-z) – share of procedure performed by a doctor;
t – procedure time, min

Application of trastuzumab IV requires long-term observation of medical personnel after the procedure, which explains the need for patient hospitalization or day-time staying that involves additional costs compared with SC formulation (formula 3).

$$Cost_{st} = (q*Cost_{day} + (100-q)*Cost_{h})*v, \text{ where} \quad (3)$$

Costst – cost of day-time staying/hospitalization, rubles;
$Cost_{day}$ – cost of day-time staying in oncology department, rubles;
$Cost_{h}$ – cost of hospitalization in oncology department, rubles per day;
q – share of patients in day-time staying;
(1-q) – share of hospitalized patients;
v – number of intravenous administrations.

Total costs for the treatment of patients with HER2+ breast cancer were determined by adding up the cost of basic pharmacotherapy, administration, medical personnel and hospitalization/day-time staying. The costs associated with standard medical care for patients with breast cancer (diagnosis, treatment and additional pharmacotherapy), as well as costs for HER2 expression testing were not taken into account due to the fact that they are the same in both comparison groups [10].

Due to the same clinically proven efficacy and safety of trastuzumab SC and IV, at the next stage of the study it was expedient to perform the cost minimization analysis, which shows the cost difference if alternatives are used and is calculated according to formula 4 [22,27].

$$CMA = DCiv - DCsc, \text{ where} \quad (4)$$

CMA – the cost difference between the compared drugs, rubles;
DCiv – direct costs of treating HER2+ breast cancer with trastuzumab IV, rubles;
DCsc – direct costs of treating HER2+ breast cancer with trastuzumab SC, rubles.

To complete the assessment of the financial implications of trastuzumab IV replacement with an innovative method (trastuzumab SC) of treating HER2+ breast cancer the *budget impact analysis* has been performed, which takes into account all types of costs for each treatment (formula 5) [24,25].

$$BIA = Cost_{iv} - Cost_{sc}, \text{ where} \quad (5)$$

BIA – result of budget impact analysis, rubles;
Costiv – the total economic effect of trastuzumab IV application, rubles;
Costsc – the total economic effect of trastuzumab SC application, rubles.

The result of the budget impact analysis is expressed in monetary units, which determine the budget savings or the need for additional budget funds when using the evaluated technology [23]. In conducting this analysis, calculation of patient transfer from trastuzumab IV to trastuzumab SC was performed for 10 people in each of the analyzed regions. Based on the data obtained in the budget impact analysis, the indicators of "lost opportunities" in the treatment with the most expensive drug were calculated according to the following formula:

$$Q = \Delta C / C^{low}, \text{ where} \quad (6)$$

Q – lost opportunities;
ΔC – cost savings when using less expensive drug, rubles;
C^{low} – cost of treatment with less expensive drug, rubles.

The result of the "lost opportunities" analysis is shown as the number of patients, which can be additionally treated within a fixed budget when switching patients from more expensive to less costly therapy [12].

Baseline data

To do the pharmacoeconomic analysis calculation it is required to know trastuzumab cost of both formulations, cost of SC and IV administration, cost of hospitalization and day-time staying at oncology department, as well as the average monthly salary of the doctor and nurse. This study compared the use of trastuzumab SC and trastuzumab IV in the treatment of HER2+ breast cancer with in Kaluga, Lipetsk, Smolensk and Tula regions, which affects the value of the baseline data. According to the information search performed, the Table 2 was formed with the baseline data for each test region.

Table 2. Baseline data by regions of the Russian Federation [14,15,17-19]

Expenditure item, rub.	Kaluga region	Lipetsk region	Smolensk region	Tula region
Trastuzumab IV 440 mg	85 198,99	82 060,48	85 734,83	86 117,58
Trastuzumab IV 150 mg	28 639,33	27 584,33	28 819,45	28 948,11
Trastuzumab SC 600 mg	85 198,99	82 060,48	85 734,83	86 117,58
IV administration	456	120	719,42	450
SC administration	174	80	150	130
Hospitalization	16 676	8 005,8	5 286	7 065
Day-time staying	11 875	11 927	5 286	10 990
Nurse service	22 968	18 254	18 295	21 928
Doctor service	40 610	32 901	30 929	39 159

Results

Based on the results of pharmacoeconomic study of using trastuzumab SC compared to trastuzumab IV in patients with HER2+ breast cancer in the Kaluga, Lipetsk, Smolensk and Tula regions, the costs per patient per treatment course for alternatives were shown in Table 3. Also based on the results of cost minimization analysis, the cost savings for each region were determined, both by general and specific items of expenses, when transferring patients from IV to SC formulation (Table 3).

Table 3. Results of the cost analysis and cost minimization analysis for the treatment course of one patient in the investigated region of the Russian Federation

Costs, rub.	Subcutaneous administration	Intravenous administration	Cost savings when switching to trastuzumab SC
Kaluga region			
Trastuzumab	1 533 582	2 077 729	544 147
Administration	3 132	8 208	5 076
Medical personnel	794	1 448	654
Hospitalization/ day-time staying	0	256 959	256 959
Total	**1 537 508**	**2 344 344**	**806 836**
Lipetsk region			
Trastuzumab	1 477 089	2 001 191	542 102
Administration	1 440	2 160	720
Medical personnel	639	1 165	526
Hospitalization/ day-time staying	0	179 395	179 395
Total	**1 479 168**	**2 183 911**	**704 743**
Smolensk region			
Trastuzumab	1 543 227	2 090 796	547 570
Administration	2 700	12 950	10 250
Medical personnel	614	1 121	507
Hospitalization/ day-time staying	0	95 148	95 148
Total	**1 546 541**	**2 200 016**	**653 475**
Tula region			
Trastuzumab	1 550 116	2 100 130	550 014
Administration	2 340	8 100	5 760
Medical personnel	762	1 391	629
Hospitalization/ day-time staying	0	162 495	162 495
Total	**1 553 218**	**2 272 116**	**718 898**

Thus, Table 3 shows that using trastuzumab SC results in saving of 806,836 rubles in Kaluga region, 704,743 rubles in Lipetsk region, 653,475 rubles in Smolensk region, and 718,898 rubles in Tula region per patient per treatment course.

As seen in Figure 2, switching of 10 patients in Kaluga region from trastuzumab IV to SC demonstrated budget savings in the amount of 8,068,360 rubles for the treatment course of HER2+ breast cancer, reducing costs by 34%. Analysis of "lost opportunities" showed that the saved money allow to provide treatment for 5 additional patients within the fixed budget.

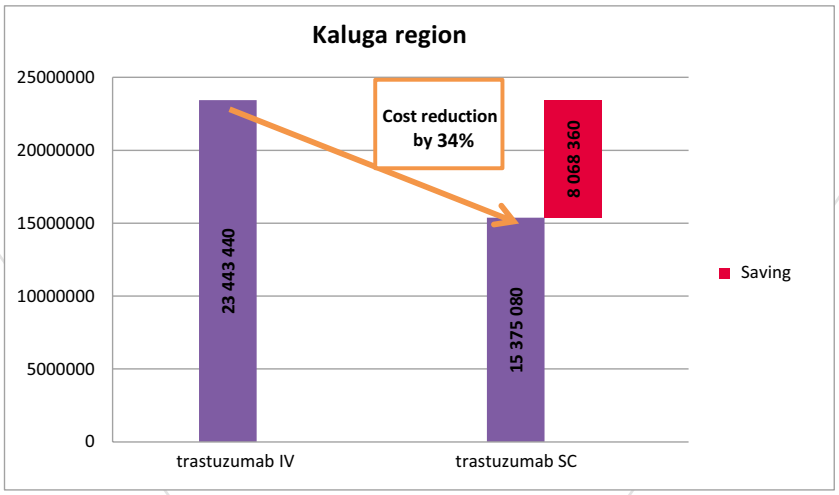

Figure 2. Results of budget impact analysis for the treatment course of patients with HER2+ breast cancer in Kaluga region

Budget impact analysis in Lipetsk region showed that money savings when switching 10 patients from trastuzumab IV to trastuzumab SC will amount to 7,047,430 rubles (reducing costs by 32%) for the treatment course. It the scope of the fixed budget it allows to provide trastuzumab SC treatment for 5 additional patients (Figure 3).

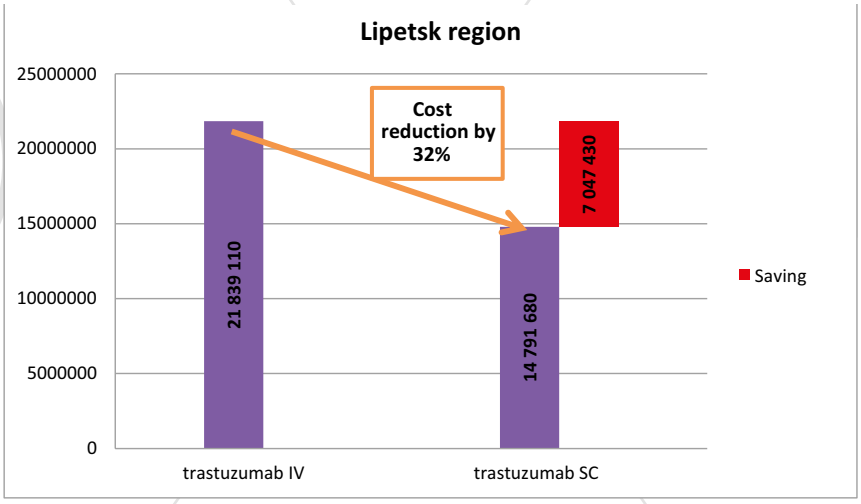

Figure 3. Results of budget impact analysis for the treatment course of patients with HER2+ breast cancer in Lipetsk region

The results of budget impact analysis in Smolensk region showed that switching of 10 patients from trastuzumab IV to trastuzumab SC demonstrated the money saving of 6,534,750 rubles for the treatment course. It the scope of the fixed budget it allows to provide trastuzumab SC treatment for 4 additional patients (Figure 4).

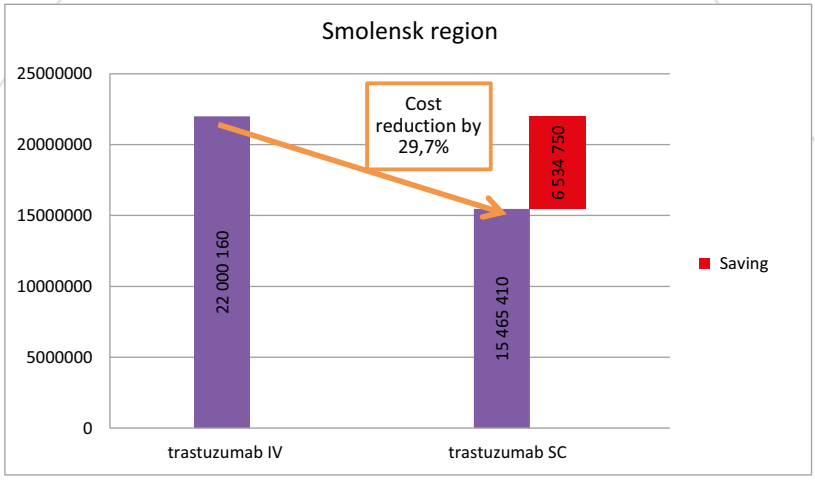

Figure 4. Results of budget impact analysis for the treatment course of patients with HER2+ breast cancer in Smolensk region

Figure 5 shows the results of budget impact analysis in Tula region showing that budget savings when switching of 10 patients from trastuzumab IV to SC will amount to 7,188,980 rubles (reducing costs by 31.6%) for the treatment course of HER2+ breast cancer. It the scope of the fixed budget it allows to provide treatment for 5 additional patients.

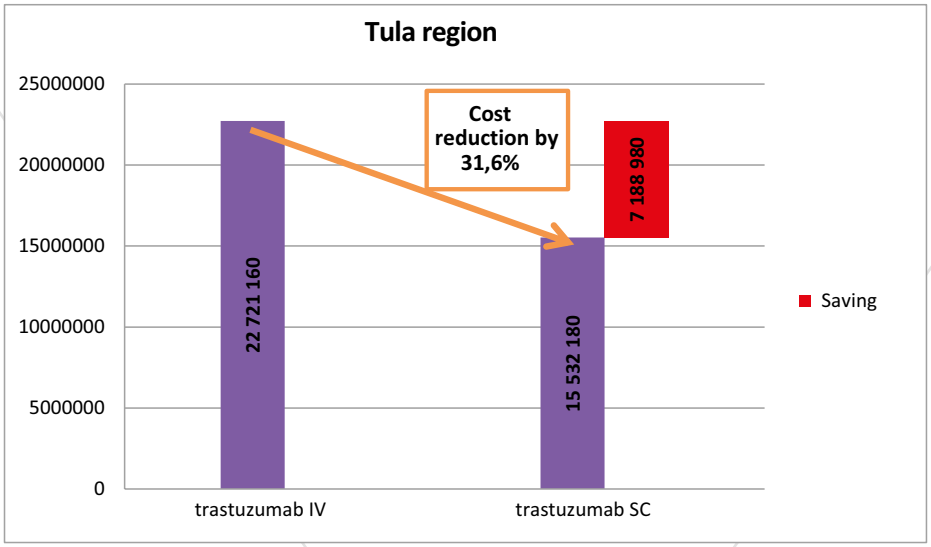

Figure 5. Results of budget impact analysis for the treatment course of patients with HER2+ breast cancer in Tula region

Conclusions

Breast cancer is a malignant neoplasm that causes high mortality, including during the first year after breast cancer diagnosis (Kaluga region – 6.8%, Lipetsk region – 6.1%, Smolensk region – 6.6%, Tula region – 10%), and currently requires treatment with the targeted drugs [11].

Trastuzumab SC therapy has a number of advantages compared to IV formulation such as fixed dose, no hospitalization for administration, and saving medical personnel time.

According to the results of pharmacoeconomic analysis for Kaluga, Lipetsk, Smolensk and Tula regions it was concluded that the treatment of HER2+breast cancer with trastuzumab SC compared to trastuzumab IV allows to save budget funds (from 29.7% to 34%), as well as to provide treatment for 4 additional patients in Smolensk region, and 5 patients in Kaluga, Lipetsk and Tula regions with the targeted drug in SC formulation within the fixed budget.

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