



CLINICAL AND ECONOMIC EVALUATION OF THE USE OF FULVESTRANT COMPARED WITH CHEMOTHERAPY FOR THE TREATMENT OF PATIENTS WITH LOCALLY PROGRESSIVE OR METASTATIC ER (+) HER2 (-) BREAST CANCER: UKRAINIAN REALITIES

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Abstract

Use of fulvestrant an estrogen receptor antagonist is complicated by its high cost. Actual treatment practice of metastatic breast cancer in Ukraine is chemotherapy (ChT) including CMF regime (cyclophosphamide + methotrexate + fluorouracil).

Methods of research. Pharmacoeconomic evaluation of fulvestrant (500 mg once monthly) therapy versus CMF ChT was conducted. The cost-effectiveness analysis with time horizon of 1 year were analyzed. Direct costs were taken into account with discount rate of 3% includes cost of medical products, cost of medical devices, adverse events (AEs) of 3-4 degree of severity (febrile neutropenia, diarrhea, vomiting). Additional calculation includes patients staying at hospital during basic therapy and AEs treatment. Indirect costs were not taken into account because all patients were at retirement age and GDP losses were insignificant. Prices for medicines and medical products are used in accordance with the data of the existing registers of wholesale prices. The cost of staying patients is determined by the official website of the private clinic "Boris". The cost of AEs treatment were calculated based on additional search strategy in Pubmed data base. The incremental cost-effectiveness ratio (ICER) for fulvestrant compared to CMF ChT was calculated according to the formula: total treatment costs (fulvestrant) - total treatment costs (CMF)/clinical efficacy (fulvestrant) - clinical efficacy (CMF). As a measure of the clinical efficacy the indicator of overall survival (overall survival, OS) was used.

Results. The total direct cost of fulvestrant treatment is 217906.54 UAH compare with 258969.23 UAH CMF treatment. The overall survival of patients in fulvestrant treatment is 1.875 years, and CMF is 1.5 years. ICER = - 109497,84 UAH for one additional life year saved.

Conclusion. Fulvestrant treatment (500 mg once monthly) for locally advanced or metastatic ER (+) HER2 (-) breast cancer in postmenopausal women with recurrence or progression of the disease after the application of the first line of hormonal therapy (nonsteroid antiestrogens and aromatase inhibitors) and in the absence of the visceral crisis is cost-effective therapy in compared with CMF ChT with clinical benefits.

Key words: fulvestrant, CMF chemotherapy, breast cancer, cost-effectiveness, budget impact.

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer and the leading cause of death among women worldwide, with approximately 1.7 million cases and 521.9 thousand deaths worldwide according to 2012 data. It is also the most commonly diagnosed cancer in most countries (140 out of 184) and accounts for 25% of cancers and 15% of cancer deaths in women worldwide.. BC mortality rates in low- and middle-income countries are high due to late diagnosis and limited access to treatment [24].

The principles of modern treatment of metastatic breast cancer (m-BC) are based on individual selection of therapy taking into account the biological characteristics of the tumor. The main goal of treatment is to achieve remission of the disease and its continuation for the longest possible period. It is very important to preserve the quality of life of patients [9].

Endocrine therapy is the therapy of choice for the treatment of hormone-dependent BC. Its effectiveness is not inferior to the effectiveness of chemotherapy (CT), and the frequency and severity of adverse events (side effects) are much lower than with CT. Currently, there are several groups of drugs that affect hormone receptors: antiestrogens, aromatase inhibitors, luteinizing hormone releasing factor agonists, progestins [Errore. L'origine riferimento non è stata trovata.].

Fulvestrant is a synthetic selective dysregulator of estrogen receptors (ER). Unlike tamoxifen, which has a partial agonist effect, and aromatase inhibitors, which reduce the amount of estrogen available to tumor cells, fulvestrant competitively binds to ER and blocks it. [25]. This leads to complete inhibition of the passage of estrogen signals through the receptors. Fulvestrant is devoid of cross-resistance with other endocrine therapy drugs [14, 23, 31, 33]. This allows the widespread use of fulvestrant in patients with hormone-dependent BC and opens the possibility for longer control of the disease.

Estrogen receptor positive BC is sensitive to hormone therapy, but eventually develops resistance. Switching to another type of endocrine therapy when resistance develops may bypass this problem and delay the need for cytotoxic chemotherapy.

Indications for the use of fulvestrant are locally progressive or metastatic ER (+) HER2 (-) BC in the postmenopausal period with recurrence or progression of the disease after the use of first-line hormone therapy (antiestrogens and aromatase inhibitors). The widespread use of fulvestrant in Ukraine is complicated by its high cost, and very often in real practice, if there are indications for its use, traditional chemotherapy regimens are used, most often – CMF regimen (cyclophosphamide + methotrexate + fluorouracil). [Errore. L'origine riferimento non è stata trovata.].

Aim of this study was to pharmacoeconomically evaluate the use of fulvestrant (500 mg 1 g/month) compared with CMF chemotherapy regimen (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², fluorouracil 600 mg/m²) for the treatment of patients with locally progressive or metastatic ER (+) HER2 (-) BC in the postmenopausal period with recurrence or progression of the disease after the use of first-line hormonal therapy (antiestrogens and aromatase inhibitors) and in the absence of visceral crisis.

Methods

There was used method of pharmacoeconomic analysis «cost-effectiveness» [Errore. L'origine riferimento non è stata trovata.]. Research horizon – 1 year. Only direct costs were taken into account, by taking into account the discount rate of 3%: the cost of the annual course of treatment with comparable schemes; the cost of medical devices (MD) and additional means (AM), to use and perform administration of drugs; the cost of treatment of SE (febrile neutropenia (FN) 3-4 degrees of severity), gastrointestinal SE of 3-4 degrees (diarrhea and vomiting), as well as the cost of hospital stay during the main therapy and treatment of SE. Indirect costs were not taken into account because all patients of retirement age and GDP losses were considered to be insignificant. The pharmacoeconomic assessment took into account the presence of drugs in the National List of Essential Medicines and in the register of wholesale prices at the time of the analysis [1, Errore. L'origine riferimento non è stata trovata.], as it was assumed that the procurement of medicines will take place from the budget. The cost of hospital stay of

patients is determined according to the official website of the private clinic «Boris» [22]. The cost of therapy of SE and management of patients in case of their

occurrence was calculated by taking into account the frequency, which was determined according to the search strategy in the Pabmed databases.

The incremental cost-effectiveness (ICER) when using fulvestrant in comparison with HT CMF was calculated by the formula: total treatment costs (fulvestrant) – total treatment costs (CMF)/clinical efficiency (fulvestrant) – clinical efficacy). The overall survival was used as an indicator of clinical effectiveness of the studied schemes (overall survival, OS).

Results

Calculation of the cost of the annual course of treatment with fulvestrant in patients with locally progressive or metastatic ER (+) HER2 (-) breast cancer

In the list of wholesale prices [4] fulvestrant (trade name Fazlodex, Astra Zeneca UK Limited, Great Britain) is given only in one dosage of 250 mg/5 ml № 2 worth 15791.96 UAH. Based on the purpose of the study, for pharmacotherapy of patients with locally progressive or metastatic (LPr/M) ER (+) HER2 (-) BC it is necessary to use 2 ampoules of the drug of 250 mg to obtain the required dose. The annual course of therapy requires 13 doses of fulvestrant 500 mg each (Table 1).

When calculating the total cost of therapy with fulvestrant, we took into account the cost of MD and AM for parenteral administration of the drug: medical latex sterile gloves, medical masks, cotton wool, syringes, blood transfusion systems, that for 13 courses of treatment requires 108.94 UAH.

Calculation of the cost of SE treatment with fulvestrant. According to the scientific literature [11], when using fulvestrant, approximately 1% of patients develop febrile neutropenia (FN) or neutropenia of 4th degree of severity, also known gastrointestinal SE: vomiting and diarrhea. Therefore, it was advisable to take into account the cost of SE pharmacotherapy.

According to the clinical guidelines for the treatment of FN, patients should receive granulocyte colony-stimulating factor (G-CSF) - a glycoprotein that regulates the formation of functionally active neutrophils and their release into the blood from the bone marrow. Already in the

first 24 hours after administration, the drug significantly increases the number of neutrophils in the peripheral blood with a slight increase in the number of monocytes. Treatment or prevention of severe infectious complications in FN is carried out by parenteral administration of carbopenems and antifungal drugs. The treatment protocol includes glucocorticosteroids (dexamethasone) and β -lactam antibiotics, including meropenem [19]. The cost of pharmacotherapy of FN together with the cost of medical devices and additional means for parenteral administration of drugs per 1 patient per year is 7725.24 UAH.

In order to determine the frequency of gastrointestinal SE (diarrhea and vomiting) during treatment with fulvestrant, a research and analysis of relevant literature sources was performed, as a result of which the PALOMA study was selected. [11]. According to this study, the incidence of diarrhea and vomiting of 3 degrees of severity during treatment with fulvestrant is 1% [11]. It was determined that the cost of pharmacotherapy of gastrointestinal SE together with the cost of medical devices and additional means by which to perform manipulations and parenteral administration of drugs, while taking into account the probability of occurrence per 1 patient is 271.87 UAH.

The cost of hospital stay of the patient during therapy with fulvestrant. According to the information from the official website of the private clinic "Boris" [22], the cost of staying patients in the hospital during therapy (1 hour) is 148 UAH., For 1 day (for the treatment of SE) - 3340 UAH.

The total cost of treatment of patients with fulvestrant for one year (13 courses), table. 2.

Calculation of the cost of the annual course of treatment of LPr/M ER (+) HER2 (-) BC according to the CMF scheme (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m²) of the chemotherapeutic drugs, the first edition of the National List of Essential Medicines included: cyclophosphamide at a dose of 1 vial of 500 mg, methotrexate 50 mg and fluorouracil at a dose of 250 mg (Table 3).

To obtain the required dose of cyclophosphamide (1038 mg) it is necessary to take 3 vials of 500 mg, ie the cost of the course dose of cyclophosphamide is 1377.39 UAH. (459,13 × 3).

To obtain the required dose of methotrexate (69.2 mg) you need 2 vials of 2 ml (25 mg/ml), and their cost will be 195.76 UAH ($97,98 \times 2$). To obtain the required dose of 5-fluorouracil (1038 mg) you need 2 vials of 10 ml (50 mg/ml) at a price of UAH 238.93, ie the cost is UAH 477.86. ($238,93 \times 2$).

It is known that in case of CT intolerance, the dose of drugs is reduced to 80%, which was taken into account when calculating the cost.

The cost of 12 courses of treatment of patients with LPr/MER(+) HER2(-) BC CMF scheme are given in table.4.

When performing CMF chemotherapy, maintenance therapy is required to prevent the development of SE, the cost of which is given in table. 5.

Calculation of costs for SE pharmacotherapy according to the CMF scheme. It is known that CT of cancer and, in particular BC, is accompanied by the development of a number of SE that require additional pharmacotherapy. The most threatening SE with chemotherapy are neutropenia and subsequent infectious complications, the severity of which depends on the scheme, intensity and dosage of CT, the presence of a history of radiation or cytotoxic therapy, comorbidities. The most serious SE with CT requiring pharmacotherapy are neutropenia, in particular FN and grade 3-4 neutropenia, which require treatment with colony-stimulating growth factors. Under conditions of neutropenia, there are usually bacterial and fungal infections, which also require pharmacotherapy with broad-spectrum antibiotics (meropenem) and systemic antifungal drugs (amphotericin B).

An analysis of the scientific literature in the Pubmed database on the application of the HT CMF regime was performed. The search strategy was conducted by keywords: breast cancer, metastatic breast cancer, chemotherapy, effectiveness, adverse events, overall survival, time to progression. From 40 abstracts, 6 complete publications with information on FN/neutropenia of 3-4 degrees, diarrhea and vomiting of 3-4 degrees with the use of ChT CMF were selected (Table 6).

Calculation of costs for the treatment of FN, diarrhea and vomiting when using the CMF scheme

Febrile neutropenia leads to prolonged hospital stay, increased treatment costs, and reduced quality

of life for patients [27]. The cost of pharmacotherapy of FN and gastrointestinal SE (diarrhea and vomiting) by using the CMF scheme, as well as the cost of medical devices and additional means by which manipulations and parenteral administration of drugs for the treatment of SE and their costs were calculated in the same way as for fulvestrant treatment regimens.

The cost of hospital stay of patients during ChT CMF. As a basis for the calculation, we took the cost of the patient's stay in a private clinic «Boris»: 1 hour - 148 UAH, 1 day - 3340 UAH. It has been suggested that CMF chemotherapy with concomitant medications will last for 3 hours and that FN treatment will require hospital stay for 14 days [22]. The cost of hospital stay for CT is 5328 UAH. ($148 \text{ UAH} \times 12 \text{ courses} \times 3 \text{ hours}$). The cost of the patient's stay in the hospital during the treatment of neutropenia/FN, taking into account the probability of the event is UAH 60 600,96. ($3340 \text{ UAH} \times 14 \text{ days} \times 12 \text{ courses} \times 0,108$).

The cost of the patient's stay in the clinic during the treatment of diarrhea, taking into account the probability of the event and medications (infusion therapy, loperamide, attributes, octreotide) is 29 739,36 UAH. ($3340 \text{ UAH} \times 7 \text{ days} \times 12 \text{ courses} \times 0,106$). The cost of the patient's stay in the clinic during the treatment of vomiting (infusion therapy, tropiston), taking into account the probability of the event is 7238,45 UAH. ($3340 \text{ UAH} \times 7 \text{ days} \times 12 \text{ courses} \times 0,0258$).

The total cost of pharmacotherapy of patients with LPr/M ER (+) HER2 (-)BCr using the CMF scheme are given in table. 7.

Comparison of the cost structure (Fig. 1) For the studied m-BC therapy regimens shows that when using fulvestrant 92% of the costs fall on the main therapy (the cost of fulverant). In the cost structure for the use of ChT CMF, the cost of the main scheme is only 12%, and 88% of the cost is the cost of therapy, SE and hospital stay.

Determination of incremental cost-effectiveness (ICER) when using fulvestrant compared with the scheme ChT CMF. According to the Stockler study [26], it was established that the overall survival with CMF is on average 18 months, ie 1.5 years (Table 8). According to the assessment [17] of the use of fulvestrant 500 mg at metastatic BC, the overall survival (OS) is 22.5 months, ie 1,875 years.

Discussion

The costs of the main schemes of therapy with fulvestrant and CMF are very different: 205 295,48 UAH. for fulvestrant (tab. 1) and UAH 24 612,12. for the CMF circuit (Table 4). In general, the fulvestrant treatment regimen is more effective and safer (the incidence of SE (FN/neutropenia 3-4 degrees and vomiting and diarrhea 3-4 degrees) is 1%, respectively, against 10.8%, 2.58% and 10, 6% when using the CMF scheme). Comparison of the cost structure (Fig. 1) for the studied m-BC therapy regimens shows that when using fulvestrant then 92% of the costs fall on the main therapy (the cost of fulvestrant). In the structure of costs for the use of HT CMF costs for the main scheme is only 12%, and 88% of the cost is the cost of maintenance therapy, SE and hospital stay due to their occurrence, ie most of the money is spent not on the main treatment scheme, but on correction of adverse reactions, which significantly reduce the quality of life of patients [30, 32]. Given the cost of SE treatment and the cost of staying in the clinic during treatment, as well as the significant cost of maintenance therapy for CT, aimed at preventing the occurrence of SE, the ChT CMF scheme is more expensive.

The results of the pharmacoeconomic analysis shows that the use of fulvestrant in comparison with CMF chemotherapy is less expensive by 41 061,69 UAH, while helping to prolong the overall survival of patients by 0,375 years (4.5 months) and save 109 497,84 UAH for one additional year of the patient's saved life.

In the health care system of Ukraine, the use of fulvestrant (500 mg 1 time/month) compared with the CMF chemotherapy (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², fluorouracil 600 mg/m²) for the treatment of patients with locally progressive or metastatic ER (+) HER2 (-) BC in the postmenopausal period with recurrence or progression of the disease after the first line of hormonal therapy (antiestrogens and aromatase inhibitors) and in the absence of visceral crisis is dominant – less expensive and more effective.

Conclusions

Use of fulvestrant (500 mg 1 g/month) compared with CMF chemotherapy (cyclophosphamide 600

mg/m², methotrexate 40 mg/m², fluorouracil 600 mg/m²) in the treatment of locally advanced or metastatic ER (+) HER2 (-) BC in postmenopausal women with recurrence or progression of the disease after first-line hormone therapy (nonsteroidal estrogen antagonists and aromatase inhibitors) and in the absence of visceral crisis is clinically justified in terms of the frequency of adverse reactions and long-term adverse reactions.

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Table 1. The cost of the annual course of treatment of 1 patient with LPr/M ER (+) HER2 (-) BC fulvestrant

INN	Product form	Packaging cost, UAH	Cost of annual course of treatment (13 doses of 500 mg), UAH.
Fulvestrant (Fazlodex, Astra Zeneca UK Limited, UK)	amp. 250 mg/5 ml № 2	15791,96	205295,48

Table 2. The total cost of treatment of patients with LPr/M ER (+) HER2 (-) BC with fulvestrant for one year

Types of costs	UAH
The cost of treatment with fulvestrant, including the cost of MD	205404,43
The cost of staying in the clinic during treatment with fulvestrant	1924,00
The cost of treatment of FN/neutropenia 3-4 degrees together with MD and AM, which perform IV manipulation in FN and taking into account the frequency (1%)	7725,24
The cost of hospital stay during FN treatment	6078,80
The cost of treatment of gastrointestinal SE of 3-4 degrees in the hospital with taking into account the frequency (1%)	271,87
The cost of hospital stay during treatment of gastrointestinal SE	3039,40
Total	224443,74
Total with taking into account the discount rate of 3%	217906,54

Table 3. Minimum wholesale prices for cyclophosphamide, methotrexate and 5-fluorouracil and their dosage for the average statistical body surface area (BSA)

INN	Price of package, UAH	The dose of the drug per 1 m ² BSA, mg/m ² iv, 1 day	The dose of the drug based on the average BSA of 1,73 m ² , mg
Cyclophosphamide/Endoxan® 500 mg, flac. 500 mg № 1	459,13	600	1038
Methotrexate/Methotrexate-Teva, 25 mg/ml flac. 2 ml №1	97,98	40	69,2
Fluorouracil/5-Fluorouracil "EBEVE" 50 mg/ml, flac. 10 ml №1		600	1038

Table 4. The cost of treatment of patients with LPr/MER (+) HER2 (-) BC according to the scheme CMF

INN	The cost of 1 course, UAH.	The cost of 12 courses, UAH.	The cost of 1 course, with taking into account the dose reduction to 80%, UAH.
Cyclophosphamide/Endoxan® 500 mg, flac. 500 mg № 1	1377,39	16528,68	13222,944
Methotrexate/Methotrexate-Teva, 25 mg/ml flac. 2 ml №1	195,76	2349,12	1879,296
Fluorouracil/5-Fluorouracil "EBEVE" 50 mg/ml, flac. 10 ml №1	477,86	5734,32	4587,456
Total	2051,01	24612,12	19689,70
The cost of medical devices and additional means for use of the CMF scheme	194,00	2328,04	
The cost of treatment with CMF together with the cost of MD and AM, to perform parenteral administration of drugs	2245,01	26940,16	

Table 5. Calculation of the cost of maintenance therapy using the CMF scheme

Accompaniment therapy	Unit price, UAH	Duration of therapy/dose	The cost of 1 course of CT, UAH..	The cost of 12 courses of CT, UAH.
Neupogen (Neupogen® 30 million IU (300 µg)/0.5 ml)	1038,68	300 mcg / day, 4 days after a course of CT	4154,72	49856,64
Tropisetron (Tropisetron 1 mg/ml, amp. 5 ml № 5)	312,00	once before CT	312,00	3744,00
Tropisetron (Tropisetron, caps. 5 mg № 5)	78,24	5 mg per day 5 days after CT	78,24	938,88
Dexamethasone (Dexamethasone tab. 0.5 mg № 10)	25,73	8 mg 2 times / day, 3 days	247,01	2964,12
Dexamethasone (Dexamethasone 4 mg/1 ml 1 ml № 25)	209,59	20 mg iv once before CT	41,90	502,80
Loperamide-Zdorovia (Loperamide, tab. 2 mg № 20)	7,29	16 mg per course	2,88	34,56
Total cost of pharmacotherapy			4836,75	58041,00
Cost of MD for maintenance therapy			59,56	714,72
Total			4896,31	58755,72

Table 6. References used to establish the frequency of SE in the application of chemotherapy according to the CMF scheme

N°	Authors, article title	Diarrhea of 3-4 degree, %	Vomiting of 3-4 degree, %	FN/neutropenia of 3-4 degree, %
1	Stockler M. R., Harvey V.J., Francis P.A. et al., 2011 [26]	5,5	2,8	35
2	Cameron D.A., Massie C., Kerr G., Leonard R.C.F., 2003 [26]	-	-	10
3	Fisher B., Anderson S., Tan-Chiu E., Wolmark N. et al., 2001 [26]	3	2	4
4	De Placido S., De Laurentiis M., De Lena M., et al., 2005 [12]	0,9	3,5	4,4
5	Engelsman E., Klijn J.C.M., Rubens R.D. et al. 1991 [15]	33	-	2,4
6	Fountzilas G., Pectasides D., Christodoulou C. et al., 2006 [18]	-	2	9
Calculated indicators of SE frequency		10,6 (95% DI 4,15; 25,35)	2,58 (95% DI 1,87; 3,28)	10,8 (95% DI 1,02; 20,58)

Table 7. The total cost of pharmacotherapy of patients with LPr/M ER (+) HER2 (-) BC using the CMF scheme

Name	UAH
The cost of ChT CMF including 12 courses without dose reduction taking into account the frequency of events 0.76	18705,21
The cost of ChT CMF taking into account the dose reduction by 80% taking into account the frequency of events 0.24	4725,53
The cost of medical devices for course of CT	2328,04
Cost of maintenance therapy to prevent SE together with MD	58755,72
Cost of treatment of FN taking into account the probability of SE and MD	77486,36
Cost of vomiting treatment taking into account the probability of SE and MD	193,60
Cost treatment of diarrhea taking into account the probability and MD	1637,08
The cost of hospital stay for ChT CMF	5328
The cost of hospital stay for the treatment of FN*	60600,96
The cost of hospital stay for the treatment of vomiting*	7238,45
Cost of hospital stay for diarrhea treatment*	29 739,36
Total	266 738,31
Total taking into account the discount rate of 3%	258 969,23

Table 8. The results of the analysis of «cost-effectiveness»

Treatment schemes	Total costs, UAH.	Cost difference, UAH.	Performance index, overall survival (years)	Difference in survival rate (years)	ICER, UAH for one additional year of saved life
Fulvestrant	217906,54		1,875	0,375	-109497,84
CMF	258 969,23	41061,69	1,5		

Figure 1. The cost of treatment of patients with LPr/M ER (+) HER2 (-) BC fulvestrant (a) and CMF scheme (b)