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Research of economic accessibility and costs optimization of chemotherapy treatment schemes of patients with breast cancer in Ukraine

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Abstract
Breast cancer is ranked first in the cancer-related morbidity and mortality rate of malignant neoplasms of the female population around the world. In recent years, approaches to cancer treatment have changed, chemotherapy has become one of the essential component of a comprehensive treatment that is long-lasting and high-value. Considering the high cost of chemotherapeutic treatment schemes and low solvency of the population of the country, it is advisable to conduct a study on the economic availability of chemotherapy schemes for breast cancer patients' treatment and optimizing their costs by minimizing costs in order to offer the most cost-effective therapies.
During the analysis, it was found that the replacement of high-cost medicines in the CMF chemotherapeutic schemes with medicines with the lowest cost of the course dose, which were selected on the basis of the cost-minimization analysis, provides cost savings of $ 48.21 per patient, which allows additional treatment for more patients. The results of the assessment of the socioeconomic availability of chemotherapeutic treatment schemes showed that almost all schemes are poorly available to the Ukrainian patient. Only two schemes: CMF and AC, which have an adequate solvency ratio of 12.12% and 14.8%, are moderately available.

Keywords: breast cancer, adequacy of solvency, economic availability, cost minimization, treatment schemes, malignant neoplasms

1. Introduction
Cancerous diseases today are one of the most common causes of death in a population of people. One in eight deaths in the world is associated with malignant neoplasms (MN). Cancer causes more deaths than AIDS, tuberculosis and malaria taken together, is the second leading cause of death in economically developed countries (after heart disease) and third in developing countries (after heart diseases and gastrointestinal diseases) [2].
According to American Cancer Society, in 2008, women living in economically developed countries were most often diagnosed with breast cancer (BC), colon and lung cancer; in developing countries - breast cancer, cervix and lungs cancer [1]. Breast cancer is ranked first in the mortality of cancer of the female population of the planet (140 countries out of 184). Breast cancer kills one woman out of four suffering from cancer [3].
According to the National Cancer Registry of Ukraine in 2015, there were registered 136,225 new cases of cancer; the general index of morbidity with MN was 375.7 per 100,000 population. The most significant part in the structure of cancer patients is MN: breast, skin, body and cervix, and colorectal cancer (59.9%) [10].
Although the tendency to increase the incidence of BC has continued since the late 1990s, stabilization or reduction of mortality over the past 25 years in some countries of North America and European countries has been maintained. This reduction can be attributed to the early detection of BC by screening (the use of mammography), as well as new approaches to treatment, which today are high-value [4].
Considering the increase in the incidence of BC in Ukraine and the high cost of anti-neoplastic medicines (M), it is advisable to conduct a study on the economic availability of chemotherapeutic schemes for the treatment of patients with BC and optimize their costs by analysis of cost minimization in order to propose the most cost-effective therapies.

2. Materials and methods of research
The methodological basis of research made laws and regulations that outline some aspects of care for patients with breast cancer, namely the Unified Clinical Protocol of Medical Care.

(UCPMC) in patients with BC, MH Ukraine N. 396 of 06.30.2015 [12]. According to the UPMC, the approximate average daily dose, taking into account the body surface area (BSA) of 1.87 m^2 (average height – 167 cm, average women body weight – 75 kg), was calculated using the formula of Montselar [13].

BSA (m^2) = √weight(kg) × height (cm) ÷ 3600

To analyze the socioeconomic availability of anti-neoplastic medicines, an indicator of solvency adequacy ($C_{a.s.}$) was calculated, which shows the share of wages spent on the purchase of one package of medicines and is calculated by the formula:

$$C_{a.s.} = \frac{\overline{P}}{W_{a.w.}} \times 100\%,$$

where $C_{a.s.}$ – solvency adequacy ratio;

P – the cost of the average annual dose of the medicine;

$W_{a.w.}$ – average wage for the period under study.

The value of the average salary was found on the site: www.ukrstat.gov.ua. All trade names (TN) of anti-neoplastic medicines were divided into three categories: high availability, solvency adequacy ratio (Ca.s.) less than 5%, average available - Ca.s. more than 5% and less than 15% and little available - Ca.s. more than 15% [7].

In order to justify the selection of the most cost-effective treatment schemes, we conducted an analysis of cost minimization - the type of pharmacoeconomic analysis intended to justify the choice of medicine with minimal costs, which involves comparing the cost of pharmacotherapy in various medicines, provided they have the same clinical (therapeutic) efficacy [8]. The pre-made ABC / Frequency analysis allowed to determine the treatment scheme, which is most often prescribed and expensive.

ABC analysis is the distribution of Pareto-based medicines into three groups according to the cost of their use:

- Group A – 5-10% M from the whole range, the cost of which is 70-80%;
- Group B – 15-20% M from the whole range, the cost of which is 15-20%;
- Group C – 70-80% M from the whole range, the cost of which is 5-10%.

Frequency analysis is a retrospective assessment of the frequency of use / appointment of one or another / other technology / medicine, which, combined with the cost accounting, allows determination which types of services or medicines have their main share: vital and important medicines for the treatment of a particular disease or to those that are secondary [9].

The objects of our study were the appointment lists of 87 patients with a diagnosis of breast cancer who were treated in a cancer department of one of the country's hospitals.

The analysis of accessibility and optimization of expenses was carried out according to data of the information and retrieval system"Morion".

3. Results and its discussion

According to the Unified clinical protocol for medical care for patients with breast cancer, the choice of treatment method is determined by the stage of the disease, the clinical form of the tumor, the age and the general condition, as well as additional data characterizing the individual properties of the tumor and the body of the woman.

Modern treatment schemes (chemotherapy) can achieve positive results in 50-80% of patients with disseminated BC. The probability of a fatal outcome when performing modern polychemotherapy is not more than 3%. This is due to the improvement of techniques and the use of various anti-neoplastic medicines in treatment schemes. The benefits of chemotherapy, which saves the lives of tens of thousands of patients with BC, are far more common short-term adverse side effects [4]. The most commonly used chemotherapy schemes are the following in the treatment of breast cancer:

Basic schemes:

a. CMF (Cyclophosphamide + Methotrexate + Fluorouracil);
b. AC (Doxorubicinum + Cyclophosphamide);
c. FAC (Cyclophosphamide + Doxorubicine + Fluorouracil).

1. Treatment schemes containing Paclitaxel:
a) P (Paclitaxel);
b) PD (Doxorubicine + Paclitaxel).
2. Treatment schemes containing Docetaxel:
a) D (Docetaxel);
b) DC (Docetaxel + Cyclophosphamide);
c) DD (Doxorubicine + Docetaxel);
d) TAC (Doxorubicine + Cyclophosphamide + Docetaxel);
e) DCap (Docetaxel + Capecitabine).
3. Treatment schemes containing Gemcitabine:
a) G (Gemcitabine);
b) GP (Gemcitabine + Paclitaxel);
c) GD (Gemcitabine + Docetaxel).
4. Treatment schemes containing Vinorelbine:
a) V (Vinorelbine);
b) VG (Vinorelbine + Gemcitabine).
5. Treatment schemes containing Capecitabine:
a) Cap (Capecitabine).

In order to determine the economic availability, a solvency adequacy study (Ca.s.) was conducted for standard chemo-therapeutic schemes for the treatment of patients with BC in accordance with the UCPMC (MH Ukraine N. 396 of 06.30.2015). The indicator of the adequacy of solvency characterizes the dynamics of the ratio of the cost of treatment and the average solvency of the consumer.

According to the UCPMC, the cost and availability of basic chemotherapy schemes were calculated (Fig. 1).

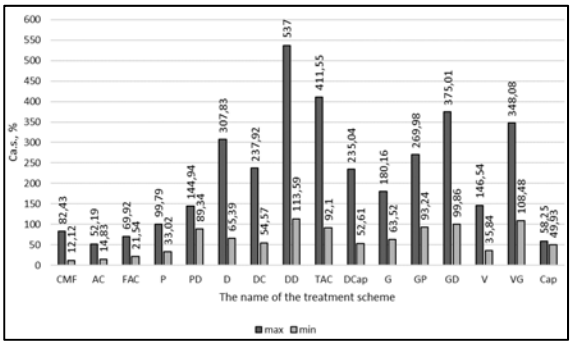

Fig 1: Indicator of solvency adequacy (Ca.s.) of standard chemo-therapeutic schemes of breast cancer treatment

As a result of the calculations, it has been established that virtually all standard chemotherapy schemes for the treatment of patients with BC are poorly available, but two schemes

have been identified, the solvency index of which is less than 15%:

1. Scheme CMF (Cyclophosphamide + Methotrexate + Fluorouracil) with a minimal cost of TN for one treatment course:
- Endoxan 1 g. (Baxter AG, Switzerland, powd. for inj. prep.1 g bot., №1);
- Methotrexate-Teva (Teva, Israel, sol. for inj. 100 mg/ml bot. 10 ml, №1);
- Fluorouracil Medac (Medac, Germany, sol. for inj. 50 mg/ml bot. 100 ml, №1), the solvency adequacy ratio (Ca.s) of which is 12,12%.
2. Scheme AC (Doxorubicinum + Cyclophosphamide):
- Oncodox 50 (Cipla, India, lioph. p. for inj. 50 mg bot., №1);
- Endoxan 1 g (Baxter AG, Switzerland, powd. for inj. prep.1 g bot., №1) the solvency adequacy ratio (Ca.s) – 14,8%.

There were highlighted chemotherapeutic schemes with indicator Ca.s. more than 200%, namely the following:

- *scheme D* (Docetaxel 100 mg/m^2 i/v) with TN: Taxoter (Sanofi, France, conc. sol for inf. 20 mg bot. 1 ml, №1), Ca.s. - 307,83 %;
- *scheme DC* (Docetaxel 75 mg/m^2 i/v + Cyclophosphamide – 600 mg/m^2 i/v, 1 day) with TN: Taxoter (Sanofi, France, conc. sol for inf. 20 mg bot. 1 ml, №1); Endoxan 200 mg (Baxter AG, Switzerland, powd. for inj. prep.1 g bot., №1), Ca.s. - 237,92 %;
- *Scheme DD* (Doxorubicine 50 mg/m^2 i/v + Docetaxel 75 mg/m^2 i/v, 1 day) with TN:
- Adriblastine fast soluble (Pfizer Inc., USA, lioph. powd. for inf. 10 mg bot., sol. amp. 5 ml, №1); Taxoter (Sanofi, Франція, conc. sol for inf. 20 mg bot. 1 ml, №1), Ca.s. - 537%;
- Adriblastine fast soluble (Pfizer Inc., USA, lioph. powd. for inf. 10 mg bot., sol. amp. 5 ml, №1); Docetaxel "Ebewe" (Sandoz, Switzerland, conc. sol. for inf. prep. 20 mg bot. 2 ml, №1), Ca.s. - 281,49%;
- *scheme TAC* (Doxorubicine 50 mg/m^2 i/v + Cyclophosphamide – 500 mg/m^2 i/v + Docetaxel 75 mg/m^2 i/v) with TN: Adriblastine fast soluble (Pfizer Inc., USA, lioph. powd. for inf. 10 mg bot., sol. amp. 5 ml, №1); Endoxan 200 мг (Baxter AG, Switzerland, powd. for inj. 1 g bot., №1); Taxoter (Sanofi, France, conc. sol for inf. 20 mg bot. 1 ml, №1), Ca.s. - 411,55%;
- *scheme DCap* (Docetaxel 75 mg/m^2 i/v + Capecitabine 1000 mg/m^2, twice a day, orally, 1 day) with TN: Taxoter (Sanofi, France, conc. sol for inf. 20 mg bot. 1 ml, №1); Xeloda (Roche, Switzerland, coat. tabl. 150 mg blister, №60), Ca.s. - 235,04 %.
- *scheme GP* (Gemcitabine 1250 mg/m^2 i/v + Paclitaxel 175 mg/m^2 i/v) with TN: Gemzar (Eli Lilly, USA, lioph. powd. for inf. 200 mg bot., №1); Paclitaxel "Ebewe" (Sandoz, Switzerland, conc. sol. inf. sol. 30 mg bot. 5 ml), Ca.s. - 269,98 %.
- *sheme GD* (Gemcitabine 1000 mg/m^2 i/v + Docetaxel 75 mg/m^2 i/v, 1 day) with TN:
- Gemzar (Eli Lilly, USA, lioph. powd. for inf. 200 mg bot., №1); Taxoter (Sanofi, France, conc. sol for inf. 20 mg bot. 1 ml, №1), Ca.s. - 375,01%;
- Gemcitabine "Ebewe" (Sandoz, Switzerland, conc. sol. for inf. 1000 mg bot. 100 ml, №1); Docetaxel "Ebewe" (Sandoz, Switzerland, conc. sol. for inf. 20 mg bot. 2 ml, №1), Ca.s. - 233,95%.
- *scheme VG* (Vinorelbine 30 mg/m^2 i/v + Gemcitabine 1000 mg i/v 1, 8 days) with TN:
- Vinorelbine "Ebewe" (Sandoz, Switzerland, conc. for inf. sol. 10 mg bot. 1 ml, №1); Gemzar (Eli Lilly, USA, liophil. for inf. 200 mg bot., №1), the indicator of adequacy of solvency of which is 348,08%.
- Vinorelsin (Actavis Group, Ireland, conc. for inf. 10 mg/ml bot. 5 ml, №1); Gemcitabine "Ebewe" (Sandoz, Switzerland, conc. sol. for inf. 1000 mg bot. 100 ml, №1), Ca.s. - 234,08%.

The results of assessing the socioeconomic availability of standard chemotherapy schemes, which are formed with TN with a minimum cost of course dose, have shown that practically all schemes are low available for patients with BC in Ukraine. Only 2 schemes: CMF (Cyclophosphamide + Methotrexate + Fluorouracil) with the use of TN: Endoxan (Baxter AG, Switzerland, powd. inj. 1 g bot., №1); Methotrexate- Teva (Teva, Israel, sol. for inj. 100 mg/ml bot. 10 ml, №1); Fluorouracil Medac, (Medac, Germany, sol. for inj. 50 mg/ml bot. 100 ml, №1) and AC (Doxorubicine, Cyclophosphamide) with the use of TN: Oncodox 50 (Cipla, India, lioph. for inf. sol. 50 mg bot., №1); Endoxan (Baxter AG, Switzerland, powd. for inj. sol. 1 g bot., №1), solvency adequacy rate which is respectively 12.12% and 14.8% is medium available.

Considering the difficult economic situation in Ukraine, the high cost of chemotherapy schemes for the treatment of patients with BC and the low solvency of the population of the country, it is expedient to optimize the cost of antineoplastic medicines by replacing high-dose medicines with medicines with a minimum cost of course dose. Such medicines were identified as a result of the analysis of “cost minimization”.

Based on the results of a pre-performed ABC / frequency analysis and comparison of its results, it has been found that the most commonly prescribed treatment scheme was the CMF (Cyclophosphamide + Methotrexate + Fluorouracil) scheme, therefore, optimizing the cost of treatment is appropriate especially for it.

According to the results of the frequency analysis, the following medicines were included in the CMF scheme [5]:

- 5-Fluorouracil (Ebewe Pharma, Austria, conc. for inf. sol. 500 mg amp. 10 ml, №5) or Ftorolek (Pharmstandard-Biolik Ukraine, Kyiv, sol. for inj. 50 mg/ml bot. 10 ml, №10;
- Methotrexate (Ebewe Pharma Austria, sol. for inj. 50 mg amp. 5 ml, №5);
- Endoxan (Baxter Oncology Germany, powd. for inf. sol. 200 mg bot., №1)

According to the results of the analysis, minimization of costs” among the TN fluorouracili medicine with a minimum cost of the course dose is Fluorouracil Medac (Medac, Germany, sol. for inj. 50 mg/ml bot. 100 ml, №1), among TN methotrexati - Methotrexate-Тева (Teva, Israel sol. for inj. 100 mg/ml bot. 10 ml, №1), among TN cyclophosphamidi - Endoxan (Baxter AG, Switzerland, powd. for inj. sol. 1 g bot., №1) [6].

The results of calculating the cost of the CMF scheme with the proposed TN and with consideration the average course of dose and frequency of appointment, established in accordance with the appointment lists, are given in Table 1 [11].

For the medicines that were included in the retrospective analysis of appointment lists for patients with BC, the cost of the course dose was calculated, taking into account the frequency of appointments and the cost of the CMF treatment scheme. The analysis showed that it is advisable to replace these medicines with medicines with the lowest cost of course dose.

The total cost of treatment for all patients (n = 87) using the CMF scheme with prescribed medicines was USD 44167.47, and per patient: 44167,47 USD / 87 = 507,67 USD.

Table 1: Cost optimization for the CMF chemo-therapeutic scheme for the treatment of patients with breast cancer.

No.	TN, manufacturer, dosage form	Average course dose mg	The cost of the average course dose, USD	Frequency of appointments	The cost of the course dose considering frequency, USD	Cost of the treatment scheme, USD
Designated scheme						
1.	5-Fluorouracil (Ebewe Pharma, Austria, conc. for inf. sol. 500 mg amp. 10 ml, №5)	6082,5	92,27	60	5535,89	12222,52
	Methotrexate (Ebewe Pharma Austria, sol. for inj. 50 mg amp. 5 ml, №5)	289,44	33,78	54	1823,92	
	Endoxan (Baxter Oncology, Germany, powd. for inj. 200 mg bot., №1)	3706,25	101,31	48	4862,71	
The proposed scheme for cost optimization						
2.	Fluorouracil Medac, (Medac Germany, sol. for inj. 50 mg/ml bot. 100 ml, №1)	6082,5	61,97	60	3718,37	8028,02
	Methotrexate-Teva (Teva Israel, sol. for inj. 100 mg/ml bot. 10 ml, №1)	289,44	2,73	54	147,45	
	Endoxan (Switzerland, Baxter AG, powd. for inj. sol. 1 g bot., №1)	3706,25	86,71	48	4162,20	

When replacing a medicine in the scheme of CMF for medicines with the lowest cost of the course dose, the estimated cost of the scheme will be 8028.02 USD, which, in terms of the total set of patients, is: 44167,47 USD – 12222,524 USD + 8028,02 USD = 39972,97 USD, but in terms of one patient is 39972,97 USD / 87 = 459,46 USD, saving is 507,67 USD - 459,46 USD = 48,21 USD. Replacement of high-cost medicines in the basic scheme CMF chemotherapy medicines at the lowest cost term doses, which were determined by the analysis of "cost minimization", provides cost savings in the amount of 48,21 USD per patient, per 1000 patients respectively is 48212,83 USD.

4. Conclusions

1. During the frequency analysis of pharmacotherapeutic groups, it was found that chemotherapy with the use of CMF schemes (Cyclophosphamide + Methotrexate + Fluorouracil) was the leading direction in the treatment of patients with breast cancer.
2. The results of the assessment of the socioeconomic availability of chemotherapeutic schemes for the treatment of patients with breast cancer, which were formed with TN medicines with a minimum cost of course dose, showed that practically all schemes are low available to the Ukrainian patient. Only two schemes: SMF and AC, which solvency adequacy rate is respectively 12.12% and 14.8%, are available to the average patient with breast cancer in Ukraine.
3. According to the results of the analysis of "minimization of expenses", the TN of chemotherapeutic medicines, which requires the lowest costs of the payer: a patient or a health care institution, were determined. Based on the above data, the treatment schemes for patients with breast cancer with the minimum cost of treatment were formed.

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