

# The Results of the Clinical and Economic Assessment of Drugs Prescriptions to patients with Breast Cancer in the Ukrainian Health Care Institution

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## ABSTRACT:

The economic damage caused by breast cancer includes not only indirect costs, but also direct losses for the provision of medical care. Given that in Ukraine the main payer of expenses is the patient, the issue of cost effectiveness is relevant. The purpose of this work - to estimate efficiency of expenses for pharmacotherapy of patients with breast cancer according to the results of clinical and economic (combined ABC/VEN/frequency) analysis. For VEN analysis current regulatory medical and process documents that determine the provision of medical care to patients with BC, namely the Unified Clinical Protocol of Medical Aid to Patients with BC (Order of the Ministry of Health of Ukraine No. 396 dated 30.06.2015) and the State Formulary of Medicinal Products (2015) were used. The pooled ABC/VEN/frequency analysis was performed. 91 % of drugs in the prescriptions of doctors for the treatment of patients with BC were vital ones. 100% of the financial costs in the costliest group A fall on vital drugs (V category). It was found the high level of compliance of drug prescriptions with current regulatory medical and process documents and high efficiency of the costs of pharmacotherapy for patients with BC in Ukraine. The primary task of the health care system of Ukraine is to implement targeted programs aimed at preventing the impact of risk factors and increasing the economic affordability of sensitive diagnostic tests and modern therapies. This will allow both to reduce the incidence of BC, and diagnose an early stage, the treatment of which is more effective and requires less costs.

**KEYWORDS:** breast cancer, drug prescriptions, clinical and economic analysis, frequency analysis, VEN analysis, ABC analysis.

## INTRODUCTION:

Breast cancer (BC) is the most common cancer among women in both developed and developing countries<sup>1</sup>. The incidence of BC in developing countries is increasing due to an increase in life expectancy and further urbanization<sup>2</sup>. More than 60% of new cases of malignant neoplasms are registered in the countries of Africa, Asia, Central and South America. 70 % of all deaths from cancer occur in these regions. According to forecasts, the number of cases of cancer will continue to grow from 14 million in 2012 to 22 million in the subsequent decades<sup>2,3,4,5</sup>.

One of the most characteristic features of the spread of malignant tumors among women in economically developed countries is a significant increase in the incidence of BC, which ranks first in the structure of cancer pathology. The incidence rate of BC in Ukraine over the past 45 years (1965–2010) has increased from 17.6 to 69.7 cases per 100 thousand female population, and the annual increase of this oncopathology is more than 2%. According to the National Cancer Registry, at the beginning of 2010, 128 thousand women with BC were registered with cancer treatment facilities, in 2011 –16.325, and in 2017 – 14.406 new cases of disease were registered<sup>6,7</sup>.

BC is an important medical and socio-economic problem for society, a reason for the disability of the female population and an increase in labor costs. In Ukraine, among persons, already ill, more than 26.6%, and among the deceased more than 23.6% are able-bodied people, which leads to significant loss of life potential of the female population<sup>6</sup>. The economic damage, inflicted by BC, includes not only indirect costs in the form of social benefits due to the temporary or permanent loss of disability and damage from unfulfilled work and reduced capacity for work, but also direct losses in the form of direct costs for the provision of medical care<sup>8,9</sup>.

Considering that in Ukraine the main payer of expenses is a patient, the issue of costs efficiency is urgent. The introduction of reimbursement and the determination of its volumes are matters of urgency for the health care system of Ukraine. Taking into account the above, the issues of efficiency of costs of pharmacotherapy for patients with BC are very topical for organizers and executive specialists of the Ukrainian health care system.

The purpose of this study was to assess the efficiency of costs of pharmacotherapy for patients with BC based on the results of clinical and economic analysis of drug prescriptions.

## **SUBJECTS AND METHODS:**

Current regulatory medical and process documents that determine the provision medical care to patients with BC, namely the Unified Clinical Protocol of Medical Aid (UCPMA) to patients with BC (Order of the Ministry of Health of Ukraine No. 396 dated 30.06.2015) and the State Formulary of Medicinal Products (2015) were analyzed<sup>10,11</sup>.

To carry out the clinical and economic assessment of costs for the therapy of patients with BC, ABC, VEN and frequency analysis were used<sup>12,13,14</sup>.

ABC analysis is the distribution of drugs in accordance with the Pareto principle into three groups according to the amount of expenses for their use: group A – 5-10% of the total amount of drugs prescribed, costs of which make up 70-80%; group B – 15-20% of the total amount of drugs prescribed, costs of which make up 15-20%; group C – 70-80% of the total amount of drugs prescribed, costs of which make up 5-10%<sup>12,13,14</sup>.

In order to ensure the cost efficiency, it is necessary to continuously monitor the use of drugs from group A<sup>14,15</sup>.

The study used a formal VEN analysis – the distribution of drugs into two groups according to their availability in the regulatory documents of the Ministry of Health of Ukraine: UCPMA and the State Formulary of Medicinal Products (2015). In Ukraine, the directions of pharmacotherapy for patients with BC and International Nonproprietary Names (INNs) of drugs are defined in the UCPMA, and the State Formulary of Medicinal Products contains both INNs and trade names (TNs) of drugs. Therefore, V (vital) category was assigned to the drugs if they were included in the UCPMA or the State Formulary of Medicinal Products (2015). Drugs were assigned to N (non-essential) category if they were not included in these documents<sup>12,13,15</sup>.

Frequency analysis is a retrospective assessment of the frequency of drug use, combined with cost estimates, to determine the drugs the share of which is main: vital drugs for the treatment of a particular illness or those that are non-essential. Comparison of the results of the ABC, VEN and frequency analysis (i.e., pooled analysis) has allowed us to estimate how efficiently the financial resources of the health care institution are spent<sup>13,14,15</sup>.

## **RESULTS AND DISCUSSION:**

According to the UCPMA (Order of the Ministry of Health of Ukraine No. 396 dated 30.06.2015)<sup>11</sup>, the choice of the treatment method for BC is determined by the stage of disease, clinical form of the tumor, age and the general condition, as well as additional data characterizing the individual properties of the tumor and the body of a woman.

Directions of treatment for patients with BC, provided by the UCPMA: surgical treatment – mastectomy or organ-preserving surgery; postoperative radiation therapy, adjuvant chemotherapy, neoadjuvant chemotherapy, hormone therapy in the presence of hormone-sensitive tumors (taking into account immunohistochemical studies and age)<sup>11</sup>. Modern pharmacotherapy regimens allow achieving positive results in 50-80% patients with disseminated BC. The probability of death in the execution of modern polychemotherapy is no more than 3%<sup>7</sup>. This is due to the improvement of treatment regimens with the use of antineoplastic drugs, recommended by the current UCPMA, which is based on the principles of evidence-based medicine.

87 medical records of sick women with BC in the average cancer department in the city of Kharkiv, Ukraine, were analyzed. The average age of patients is 62.8 years. Radiotherapy and chemotherapy were performed for all patients. The percentage of women undergoing surgical intervention was 58.62%. The diagnosis of patients was determined according to the TNM International Classification of Malignant Tumors (Fig. 1 a; b)<sup>7</sup>.

**Figure 1 a. Proportion of patients with BC according to the stage of primary tumor (T<sub>1</sub>-T<sub>4</sub>)**

**Figure 1. b. Proportion of patients with BC according to the state of regional lymph nodes (N<sub>0</sub>-N<sub>3</sub>)**

The first stage of clinical and economic analysis was the frequency analysis of pharmacotherapeutic groups. It was established that drugs from 10 pharmacotherapeutic groups were used for the pharmacotherapy of patients with BC (Table 1).

**Table 1: Frequency of drug prescriptions by pharmacotherapeutic groups**

No.	ATCcode	Pharmacotherapeutic group	Frequency of prescriptions	% of the total number of prescriptions	Number of prescriptions per 1patient
1.	L0	Antineoplastic and immunomodulatingagents	366	27.4	4.2
2.	A0	Alimentary tract and metabolism	258	19.3	2.9
3.	N0	Nervous system	243	18.2	2.8
4.	B0	Blood and blood forming organs	180	13.5	2.1
5.	M0	Musculoskeletal system	66	4.9	0.8
6.	C0	Cardiovascular system	63	4.7	0.7
7.	J0	Antiinfectives for systemic use	63	4.7	0.7
8.	H0	Systemic hormonal preparations,excluding re productive hormones andinsulins	48	3.6	0.6
9.	R0	Respiratory system	36	2.7	0.4
10.	D0	Dermatological drugs	12	0.9	0.1

Comparison of a certain prevailing direction of pharmacotherapy with those recommended for BC by the UCPMA indicates that, on the whole, they coincide. So, the determined main directions of therapy of patients with BC are generally compliant with the requirements of the current clinical protocol UCPMA. More than 27.4% prescriptions of drugs are related to chemotherapy – the main direction of treatment: one patient received four antineoplastic drugs. Drugs (ATC code – A0) to correct side effects from the gastrointestinal tract (vomiting and nausea) accounted for 19.3% prescriptions and almost three drugs were prescribed to each patient.

Drugs, which doctors prefer in their prescriptions, were established by the results of the frequency analysis by INNs (Fig. 2.).

**Figure 2. Drugs leaders (TOP 10) among INNs**

The top ten drug leaders in terms of the frequency of prescriptions consisted of the following INNs (Fig. 3): Fluorouracil (99 prescriptions), Cyclophosphamid (84 prescriptions), Doxorubicin (57 prescriptions), Methotrexat (54 prescriptions) – these are antineoplastic drugs, Ondansetron (66 prescriptions) – antiemetic, which was used to correct adverse reactions of chemotherapy, Diazepam (63 prescriptions), Fentanyl (60 prescriptions) to provide an analgesic therapy; Natrii chloridum (57 prescriptions), which was used as a solvent for chemotherapeutic agents, Ceftriaxon (42 prescriptions) – antimicrobial drug of the III generation cephalosporins group, which was used to prevent post-operative infections, Dexamethasone (42 prescriptions), which was used to correct neutropenia. Thus, during the frequency analysis by INNs, it was established that the first three leaders in frequency were chemotherapeutic agents: Fluorouracil, Cyclophosphamid and antiemetic Ondansetron.

At the next stage of the study, in order to determine the efficiency of drug prescriptions, we conducted a formal VEN analysis, that is an assessment of the compliance of drug prescriptions with the current regulatory medical and process documents. According to the results obtained, from 98 drugs by TNs, prescribed for the treatment of BC, the State Formulary included 87 drugs, that is 88.78% of all drugs, and they were assigned to V category, and 13 drugs (11.22%) were assigned to N category due to their absence in the document. V category included antineoplastic drugs: Methotrexat, 5-Fluorouracil, Ftorolek, Gemcitabin, Etoposide, etc. N category included metabolic agents: Mildronate, Mildrocard, Actovegin, Riboxin; hepatoprotectors: Glutargin, Hepadif, which were used to correct adverse reactions.

Comparison of the results of the frequency and VEN analysis (Fig. 3) shows that almost 91% of all prescriptions are drugs of V (vital) category and almost 9% – drugs of N (non-essential) category.

**Figure 3. Results of the compared frequency and VEN analysis:**

proportion of the prescriptions of vital (V) and non-essential (N) drugs

So, 91% of drugs in the prescriptions of doctors for the treatment of patients with BC are vital ones, indicating a high level of efficiency of prescriptions and their compliance with the current regulatory documents of Ukraine.

The next stage of our work was to assess the efficiency of costs based on the results of the ABC analysis, assuming the allocation of drugs into three groups by costs. Results of the ABC analysis are shown in Fig. 4.

#### Figure 4. Results of the ABC analysis for INNs

The results of the ABC analysis showed that 14 INNs belonged to group A, amounting to 17.5% of the total number of INNs and 20.1% of the total number of prescriptions (Fig. 5).

percentage of V drugs prescriptions in group A, %

#### Figure 5. Results of the ABC analysis for INNs: group A

The costs of group A drugs accounted for 81.81% of the total cost of the BC therapy. All drugs from 14 INNs of group A belong to V category. So all drugs amounting to 26.82% of the total number of prescriptions are vital in the costliest group A (81.8% of costs).

10 INNs out of 14 INNs of group A are antineoplastic drugs: Fluorouracil, Paclitaxel, Cyclophosphamid, Doxorubicin, Carboplatin, Gemcitabin, Methotrexat, Docetaxel, Cisplatin, Mitomycin. The most commonly prescribed among them were the following: Fluorouracil (99 prescriptions), Cyclophosphamid (84 prescriptions), Doxorubicin (57 prescriptions), Methotrexat (54 prescriptions); and less prescribed – Cisplatin (12 prescriptions), Paclitaxel (9 prescriptions), Carboplatin (9 prescriptions), Docetaxel (6 prescriptions), Mitomycin (6 prescriptions), Gemcitabin (3 prescriptions). The latter three drugs are very expensive. Group A also included Disodium folinate, used to eliminate the toxic effects of antitumor therapy; drugs from Bisphosphonates group – Acid zoledronic, which is an inhibitor of osteoclastic bone resorption and is used to treat metastases; Dexketoprofen – nonsteroidal anti-inflammatory drug with a pronounced analgesic effect; Gelofusine – Blood substitutes and plasma protein fractions.

Medium-cost group B (14.9% of costs) includes 16 INNs, amounting to 20 % of the total number of INNs and 38.1% of the total number of prescriptions. Thirteen drugs (81.25%) out of 16 INNs of group B belong to V category. Three INNs belong to N category: Meldonium, hemoderivative from calf blood (Actovegin), Arginin – metabolic agents. The majority of drugs (81.25%), accounting for 89.97 % of the total number of prescriptions in group B, are vital. The ratio of expenses for the drugs of V and N categories– 5.82/1. The most part of expenses falls on vital drugs.

The least expensive group C (3.3% of the total costs) included 50 INNs, amounting to 62.5% of the total number of INNs and 41.8% of the total number of prescriptions. Forty-two of 50 INNs of group C belong to V category, that is the majority. Eight INNs belong to N category: Diphenhydramin, Hydrogen peroxide 0.15%, Piracetam and others.

The ABC analysis showed that the funds were used quite efficiently. Comparison of ABC, VEN and frequency analysis shows that the main funds are spent on vital drugs, which accounted for most of prescriptions.

A detailed analysis of the costliest group A showed that it consisted of V category drugs, which were practically leaders in the frequency of prescriptions (Fig. 6.)

#### Figure 6. Allocation of costs (%) of the drugs in the costliest group A

Among the pharmacotherapeutic groups, the first place in terms of costs (89% of the total costs of group A) is taken by drugs for chemotherapy Antineoplastic and immunomodulating agents– (L0). These are such INNs as Fluorouracil, Paclitaxel, Cyclophosphamid, Doxorubicin, Docetaxel, Cisplatin, Mitomycin, Carboplatin, Gemcitabin, Methotrexat. The second place in terms of costs (5.6% of the total costs of group A) is taken by drugs affecting the musculoskeletal system (M0), such as Dexketoprofen (analgesic), Acid zoledronic. The third place in terms of costs (5.4% of the total costs of group A) is taken by Disodium folinate and Gelofusine.

#### CONCLUSIONS:

1. It was found that 91 % of drugs in the prescriptions of doctors for the treatment of patients with BC were vital ones, indicating a high level of compliance of drug prescriptions with current regulatory medical and process documents in Ukraine. However, among antineoplastic drugs there are no modern drugs of the latest generations, such as Trastuzumab, Bevacizumab, Fulvestrant, which are used for the targeted therapy and are safer than chemotherapy.

2. The results of the pooled ABC/VEN/frequency analysis indicate the high efficiency of the costs of pharmacotherapy for patients with BC, since 100% of the financial costs in the costliest group A fall on vital drugs (V category).
3. Taking into account the very high cost of antineoplastic therapy for patients with BC growing in accordance with the stage of the disease, the presence of metastases and complications, the primary task of the health care system of Ukraine is to implement targeted programs aimed at preventing the impact of BC development risk factors and increasing the economic affordability of sensitive diagnostic tests and modern therapies. This will allow both to reduce the incidence of BC, and diagnose an early stage of the disease, the treatment of which is more effective and requires less financial costs. And moreover it is necessary to introduce a system of reimbursement of costs for the pharmacotherapy of BC given that the use of antineoplastic drugs of the latest generation is economically unaffordable to the Ukrainian patient.

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