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**RESULTS OF CLINICAL AND ECONOMIC ANALYSIS OF THE CONSUMPTION OF MEDICINES BY PATIENTS WITH ACUTE LYMPHOID AND MYELOID LEUKEMIA IN UKRAINE**

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***Key words:*** *acute lymphoid leukemia, acute myeloid leukemia, clinical and economic analysis, pharmaceutical providing of patients with leukemia*

The article presents an analysis of the consumption of drugs by patients with acute leukemias in specialized health institutions of Ukraine. A patient with acute lymphocytic leukemia by doctors was made almost twice as prescribing drugs than patients with acute myeloid leukemia. It was found that the structure of consumption of drugs dominated those names, which are necessary for pathogenetic treatment of acute leukemia. Thus, anticancer drugs are one of three leaders as the frequency of medical prescriptions and on the amount of consumption of drugs. More than half of the resources were spent on the consumption of drugs, which are essential to meet the requirements of the legal framework, which regulates the organization of medical and pharmaceutical process providing patients with hematological malignancies. Given the fact that the vast majority of patients belonged to socially vulnerable groups of the population, the introduction of effective mechanisms to compensate for the cost of the high-value of anticancer drugs is presented as the main direction of enhancing the efficiency of pharmaceutical provision patients with hematological malignancies

The issue of rational use of limited resources in health care (HC) are current for any conditions of the economy and society. This is due to progressive growth of requirements of citizens around the world to the effectiveness of medical care (MC) and pharmaceutical providing as the most important indicators that form a social stability in the country.

Research of the rational use of limited resources of HC has become especially actual in conditions of progressive of financial crisis and mass poverty in Ukraine. The declared by state guarantees about providing of effective MC and available medicines for centralized programs are not met in full because of objective reasons. The experience of social-developed countries and the results of numerous scientific studies shows that one of the solutions to complex problems in the domestic HC is the introduction of compulsory medical insurance (CMI). Effectiveness of insurance relations in practical public health depends on the action of a complex of factors and the scientific substantiation of rational models of pharmaceutical providing occupies not the last position. Introduction of methods of clinical and economic analysis (CEA) has particular relevance as modern tools in pharmaceutical providing of patients with leukemia, which are required a full and timely meet the need for high-cost medicines. Thus, the purpose of the work was conducting of CEA of actual consumption of medicines by patients with acute lymphoid and myeloid leukemia who held a chemotherapy (CT) in specialized health care facilities (HCF) of Ukraine.

To achieve the purpose of the work next tasks were identified: to make a statistical evaluation of the totality of patients by various parameters of the research; to conduct a frequency analysis of doctor’s prescriptions by different levels of ATC classification system (http://compendium.com.ua/atc); to calculate and conduct structural analysis of the actual consumption of medicines by patients with acute lymphoid leukemia (ALL) and acute myeloid leukemia (AML); to conduct ABC, VEN and integrated ABC / VEN-analysis of indicator of medicines consumption; to outline the directions for perspective studies towards improving the efficiency of pharmaceutical providing of this group of blood cancer patients.

**Materials and methods.** Randomly two conditional groups of patients with acute forms of leukemia that came to specialized HCF (5 regional oncology clinics of Ukraine throughout 2007-2013) in the acute stage of the pathological process, or in the case of newly detected ALL (I group patients) and AML (second group) were formed. Subsequently, from 267 health cards (HCds) were selected those that have marks about improvement of patient healh in the HCds. Total selected HCds were 169, of which 74 (43.8%) belonged to ALL patients and 95 (56.2%) to the patients with a diagnosis of AML.

The main tools in research methods of CEA became. First, the frequency analysis involves determining of the medicines’ prescriptions frequency according to doctor’s prescriptions lists. According to ABC-analysis of all medicines are divided in terms of their costs into three groups: A - the most expensive drugs (80.0% of the total consumption of medicines over time); B - middlecost (15.0%); C - low-cost medicines (5.0%).

When VEN-analysis in determining the possible inclusion of medicinec in groups we used a formal approach. Thus, to the group V medicines that were part of the National list of basic medicines and medical products (Resolution of CMU from 25.03.2009. №333 (http://www.ua-tenders.com), the Budget list of medicines (Resolution of CMU from 05/09/1996 p. №1071 «On procedure of procurement of drugs by establishments and health institutions financed from the budget" amended in accordance with the orders of the Ministry of Health of Ukraine of 27.08.2010 №631, 26.04.2011 №170, 5.03.2012 №79, 7.03.2013, №105 (http://www.apteka.ua)., State Formulary of the drug that corresponded to years of treatment (http: //www.dec. gov.ua/), and protocols of medical aid of the specialty "Hematology" (ICD-10: С91.0, С91.5 ICD-10: С92.0, С92.4, С92.5, С93.0, С94.0, С94.2) were attributed.

To the group E - the names of medicines, that were absent in the National list of basic medicines and medical products and present in all other documents, and to the group N all other names of medicines were included [1,3,5]. The integrated ABC / VEN-consumption analysis was carried out as in the value terms, so and in quantitative terms by the international non-proprietary name (INN) of drugs. As a result of CEA of consumption of drugs by patients with ALL and AML we have built several matrix projection in which each drug at INN received status, such as A / V, A / E, A / N, B / V, B / E, C / V, C / E [1,3].

Calculations of drug consumption had been conducted in average retail prices, which were determined by the method that was proposed by domestic scientists organizers [2].

Processing of statistical data was carried out using spreadsheet Microsoft Office Excel 2010 and standard applications applied statistical analysis Statistica 6.0 (software license V.7. English - V.6 Russia K 892818) [4].

**Results and discussion.** At the first stage of research we analyzed the patients together on various parameters (age, sex, social status, place of residence, presence of comorbidities). It was founded that in the first and second groups more than half of patients belonging to women (42 patients or 56.8% of ALL group and 55 patients or 57.9% of AML group). Analyzing a set of patients at their place of residence it was revealed that the vast majority of patients were townspeople (I group - 91.7% and in the second group - 86.7% of patients). In the first group the share (%) of employees amounted to 41.67% and in group II - 37.8%. Overall the % of the most vulnerable segments of the population (pensioners, currently unemployed, disabled of I and II groups) were 58.33% (ALL) and 62.2% (AML). The largest number of patients with ALL was presented in the age group of 31 to 40 years (16 patients or 21.5%), and the AML - from 61 to 70 years (24 - 25.3%).

Leukemia as a systemic disease is characterized by availability of burdensome history of patients. Thus, 64 patients (86.5%) of I group and 81 (85.3%) of the II analyzed group than primary analysis had a wide range of related diseases. The first position in the frequency of display in the HCds of I group patients took coronary heart disease, and in the II group - hypertensive heart disease. It should be noted that in the second group of patients, there are more pathological health problems (202 pathologies) compared with patients with group I (144 pathologies).

Further, an analysis of the frequency of medicines prescriptions to I and II patients group had been conducted. Totally for patients of I group had been used 120 names of medicines by INN and had been made 4983 doctor’s prescriptions, in terms of for one patient prescriptions were 67 medicines. In the second group 132 medicines by INN had been prescribed by doctors 2722 times, that per AML patient amounted to an average of 29 doctor’s prescriptions . As you can see, the frequency of medicines prescriptions that was calculated for one patient with ALL was 2.3 times higher than in patients with AML.

Analyzing the frequency of medicines prescriptions for the first and second levels of ATC classification system, we have identified three leading pharmacotherapeutic groups of medicines. Thus, the first level of classification theI group of patients three leaders by the number of prescriptions were: L- Antineoplastic and immunomodulating agents (28.0% of all prescriptions for patients); B- Medications of Blood and blood forming organs (25.59%); A- Medications influencing on the digestive system and metabolism (21.37%). For the II group of patients the first three positions of the prescribed drugs had took: B - Medications of Blood and blood forming organs (27.19%); A - Medications influencing on the digestive system and metabolism (18.88%); L - Antineoplastic and immunomodulating agents (18.08%). That is, only 3 of the 13 groups of drugs, which are presented in ATC classification had place in prescriptions for patients with ALL 74.96% and 64.15 AML% of total doctor’s prescriptions .

About the second level ATC classification, three groups of leaders in patients with ALL were: L01 - Antineoplastic and immunomodulating agents (27.09% of total medicines prescriptions ); B05-Blood substitutes and perfusion solutions (21.07%); C01- Drugs for the treatment of heart disease (5.83%). Patients with AML often received drugs from the following groups: B05-Blood substitutes and perfusion solutions (21.16%); L01- Antineoplastic and immunomodulating agents (17.78%); J01- Antibacterial for systemic use (9.26%). Comparing the frequency of prescriptions of different groups of drugs it can be said about the pathogenetic character of the therapy that was conducted for patients with acute leukemia at HCF, especially for intensive courses of chemotherapy using active perfusion solutions. In addition, an important place in the treatment of patients was paid to eliminate the side effects of drugs, the effects of the pathological process and treatment of comorbidities that threaten the lives of patients.

According to the INN, patients with ALL mostly were prescribed with such name of medicines (first three positions): sodium chloride sol. for inf. 0.9% 200 ml (528 prescriptions or 10.60% of all in the group); rheosorbilactum sol. for inf., bottles 200 ml (180 abo3,61%); sodium chloride sol. for inf. 0.9% 400 ml (177 or 3,55%). For patients with AML three leaders were: sodium chloride sol. for inf.. 0.9% 200 ml (362 prescriptions or 13.30% of the group on frequency); mildronat sol. for inj. 10% , amp. 5 ml and profile pkg., № 10% (108 or 3.97%); cytosar liofil. pow. for inj. 100 mg vial. with solu. in amp. 5 ml, № 1 (80 or 2.94%). An interesting analysis of frequency of prescriptions of anticancer drugs (AD). Thus, patients with ALL often were appointed with drugs of vincristine (96 prescriptions or 6.89% of prescriptions of AD). The second position was taken drugs of cytarabine (69 prescriptions , or 4.95%, respectively), and the third - mercaptopurine (57 prescriptions or 4.09%). In patients with AML undisputed leader in terms of prescriptions became cytarabine (1116 prescriptions or 23.58%), followed by a significant margin was submitted idarubicin (32 appointment or 6.5%) and doxorubicin and tretionin (by appointment 24 or 4.88% each respectively).

For I group of patients the overall rate of consumption of medicines was 2,251,437.93 UAH (US $ 281,781.97 by NBU rate that effect at the time of treatment), and group II - 1,736,304.6 UAH or 35,266.83 USD. In terms of consumption per ALL patient it was 30,424.84 UAH (3,807.86 USD), and AML - 18,276.89 UAH (2,287.47 USD). In the structure of consumption of drugs for the I group of patients occupied the first three positions of the following drugs: Cyclophosphan (cyclophosphamide by INN) pow. for sol. for inj. 200 mg vial (425,385.0 UAH or 18.89% of the total consumption of the drugs); Epreks (erythropoietin) 2000 UA/ ml. amp. (219,603.30 UAH or 9.75%); Vifend (voriconazole) tab. 200 mg №14 (210195,0 UAH or 9.34%). For patients with AML the largest share in consumption (first three positions) the following drugshad: Cytosar (cytarabine) liofil. pow. for inj. 100 mg vial. with sol. in amp. 5 ml, № 1 (357,634.80 UAH or 20.60%); Zavedos (idarubicin) cap. 10 mg vial, №1 (217150,24 UAH or 12.51%); Meronem (Meronem) pow. for sol. 1000 mg vial., № 10 (75419.96 UAH or 4.34%).

It is founded that in I group of patients’ consumption of AD was equal to the value of 1,089,345.18 USD (14720.88 UAH / person.), representing 48.38% of the total consumption of medicines. In the II group of patients the proportion of the costs of AD consumption were comparatively higher and amounted to 58.44% (1,014,695.94 UAH or 10681.01 UAH / person.) (Table 1).

As a result, ABC-analysis had been founded that in the structure of consumption of medicines by ALL patients in group A there were 15 names on INN or 28 trade names of medicines (1786807.5 UAH), B – 15 medicines or 28 trade names of drugs (352,278.63 UAH) , C - 90 medicines by INN or 110 trade names of medicines (112,351.80 UAH). From AD in the group A were represented: 7 medicines by INN or 12 trade names of drugs (1,044,871.65 UAH); group B - 2 medicines in 2 brand names (43,530.36 UAH); C -1 INN in 3 trade names (943.17 UAH).

Table 1

**Analysis of patients with leukemias consumption of drugs from the group L01 - anticancer drugs**

|  |  |  |
| --- | --- | --- |
| ATC groups of drugs by ATC classification system  (code, name of the group), INN of drugs | Structure of consumption | |
| Consumption, UAH  (ALL/AML) | Питома вага %,  (ALL/AML) |
| 1 | 2 | 3 |
| **L01 – Anticancer drugs**  **L01Alkylating agents** | | |
| **L01AA Analogs of nitrogen mustard:**  **L01AA01 Cyclophosphamide:** | 432237,00/25654,40 | 39,68/2,53 |
| **Total by group**: | **432237,00**/**25654,40** | **39,68/2,53** |
| **L01B Antimetabolites:** | | |
| **L01BA Structural analogs of folic acid:**  L01BA01 **Methotrexate** | 943,17/30,60 | 0,09/0,003 |
| **L01BB Structural analogues of purine:**  L01BB02 **Mercaptopurine** | 47838,00/1700,00 | 4,39/0,17 |
| **L01BC Structural analogs of Pyrimidine:**  L01BC01 **cytarabine** | 106452,00/464150,00 | 9,77/45,74 |
| **Total by group**: | **155233,17/465880,60** | **14,25/45,91** |
| **L01C Vegetable alkaloids and other drugs** | | |
| **L01C Vinca alkaloids and its analogues:**  L01CA02 **Vinkristyn**: | 159173,85/- | 14,61/- |
| **L01CB Derivatives of podofillotoxine:**  L01C B01 **Etoposide** | 47130,00/25578,00 | 4,33/2,52 |
| **Total by group:** | **206303,85/25578,00** | **18,94/2,52** |
| **L01D Antineoplastic antibiotics** | | |
| **L01DBAntracycline:**  L01DB01 Doxorubicin | 187944,00/108483,00 | 17,25/10,69 |
| L01DB02 daunorubicin | 28680,96/- | 2,63/- |
| L01DB06 idarubicin | 14849,40/301296,84 | 1,36/29,69 |
| L01DB07 mitoxantrone | -/34399,62 | -/3,39 |
| **Total by group:** | **231474,36/444179,46** | **21,24/43,77** |
| **L01X Others anticancer drugs** | | |
| L01XX Others antineoplastic drugs:  L01XX14 Tretinoyin | -/52988,00 | -/5,22 |
| **Total by group:** | **-/52988,00** | **-/5,22** |
| **L03 Immunostimulators:**  **L03A Immunostimulators**: | | |
| **L03AB Interferons:**  L03AB11 peginterferon alfa -2a | 64096,80/- | 5,88/- |
| **L03AX Other immunostimulators:**  L03AX21Other drugs | -/415,48 | -/0,04 |
| **Total by group:** | **64096,80/415,48** | **5,88/0,04** |
| **Total:** | **1089345,18**/**1014695,94** | 100/100 |

To the group A for patients with AML were included 11 drugs under INN of 25 trade names (1,375,919.00 UAH), B - 12 drugs or 28 trade names (273,159.60 UAH), and to the group C - 109 drugs by INN or 131 trade name of medicines (87,226.0 UAH). AD were represented in all three groups of drugs, so the group A included four drugs under INN (7 trade names, 927363.92 UAH), group B - three drugs under INN (5 trade names 85,632.02 UAH), and the group C - only 1 drug (1700.0 UAH).

An important feature of medicines consumption is the presence in the first rungs of ABC analysis antitumor action of drugs. Thus, for group of patients with ALL - it cyclophosphamide, and for the group of patients with AML - cytarabine. From one perspective, this fact indicates the main direction in the conduct of treatment, namely conducting courses of intensive chemotherapy, and from the other – is a material proof of the need to introduce effective mechanisms of compensation for the cost of consumption of drugsin conditions of shortage of funds in the HC and poverty of the population.

According to VEN-analysis of consumption of medicines it is established the following. The group V in ALL patients included 35 titles on medicines by INN (1,244,045.28 UAH), of which 7 INN were for AD (14 trade names 981,718.02 UAH); E - 65 drugs (870,116.10 UAH), of which for AD - 3 by INN (3 trade names 107,627.16 UAH), and the group N - 20 medicines (137,276.55 UAH).

In the treatment of HML 44 doctors used medication of 44INN from group V (966640,76 UAH), of which 6 medicines by INN (9 trade names, 312,798 UAH) accounted for anticancer drugs group action. In the group E were 68 medicines (710,223.72 UAH), of which three medicines by INN (5 trade names) related to AD (194,342.23 UAH). The group N was presented by 20 medicines (59,440.12 UAH). As you can see, on both samples of patients in the consumption were no drugs of antitumor action in the group N.

Value in consumption between drugs V, E and N for patients with ALL was 55: 39: 6, and for patients with HML - 56: 41: 3, more than half of medicines that were spent on pharmaceutical provision of patients with ALL and AML belonged to the group of vital medicines.

The results of the integrated ABC / VEN-analysis are presented in Table 2 and 3.

As we can see according to the matrixes, the largest amount of resources in both groups of patients accounted for consumption of drugs with the status of A / V, and the lowest - the status of C / V (ALL) and C / N (HML). That is, in the structure of consumption of drugs in both groups of patients drugs that have vital importance for the requirements of the regulatory framework and related to high-cost or have high rates or frequency setting, occupied 45.03% (AML) and 48.05% (ALL ). Interesting is the fact that HCF in the treatment of patients with AML was not used any drug in the status B / N.

Table 2

**Matrix of integrated ABC / VEN-analysis of consumption of drugs by patients with ALL and AML**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **ALL** | | | | | | | | | | |
| Group of АВС-  analyses | **V (vital) drugs** | | | **Е (essential) drugs** | | | **N (non-essential) drugs** | | | Сorrelation  in consumption  of drugs by groups  V:E:N |
| Quantity of drugs | Amount of consumption  (UAH) | Specific weight in expenditure (%) | Quantity of drugs | Amount of consumption  (UAH) | Specific weight in expenditure (%) | Quantity of drugs | Amount of consumption  (UAH) | Specific weight in expenditure (%) |
| ***ALL*** | | | | | | | | | | |
| **А** | 8 | 1081740,12 | 86,95 | 6 | 661858,53 | 76,07 | 1 | 43209,12 | 31,48 | 61:37:2 |
| **В** | 6 | 139370,79 | 11,21 | 7 | 146286,09 | 16,82 | 2 | 66621,78 | 48,43 | 40:41:19 |
| **С** | 21 | 22934,37 | 1,84 | 52 | 61971,48 | 7,12 | 17 | 27445,65 | 19,99 | 20:56:24 |
| **Total:** | **35** | **1244045,3** | **100** | **65** | **870116,1** | **100** | **20** | **137276,5** | **100** | **55:39:6** |
| ***AML*** | | | | | | | | | | |
| **А** | 5 | 781878,26 | 80,89 | 4 | 547343,96 | 74,93 | 1 | 44040,96 | 86,52 | 57:40:3 |
| **В** | 7 | 157663,74 | 16,31 | 5 | 115495,92 | 18,29 | 0 | - | - | 58:42:0 |
| **С** | 32 | 27098,76 | 2,8 | 59 | 47383,84 | 6,78 | 19 | 15399,16 | 13,48 | 27:55:18 |
| **Total:** | **44** | **966640,76** | **100** | **68** | **710223,7** | **100** | **20** | **59440,1** | **100** | **56:41:3** |

Table 3

**Matrix projection of integrated ABC / VEN-analysis of consumption of drugs by patients with acute forms of leukemias**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Groups of analyses | The share of drugs from the group **V** | | The share of drugs from the group **E** | | The share of drugs from the group **N** | |
| ALL | AМL | ALL | AМL | ALL | AМL |
| The share of drugs from the group **A** | **48,05** | **45,03** | 29,39 | 31,52 | 1,92 | 2,54 |
| The share of drugs from the group **B** | 6,19 | 9,08 | 6,50 | 6,65 | 2,96 | 0,00 |
| The share of drugs from the group **C** | **1,02** | 1,56 | 2,75 | 2,73 | **1,22** | 0,89 |

**Conclusions**

1. The analysis of HCds of patients with ALL and AML allows to found that more than three quarters of patients (86.5% and 85.3%, respectively) than the main diagnosis had a wide range of diseases. The first position in the frequency display in the HCds of the I group of patients took coronary heart disease, and in the II group - hypertension.
2. . While in specialized HCF for the treatment of I group patients doctors used 120 medicines and made 4983 prescriptions (67 prescriptions per patient), and patients with AML - 2722 prescriptions (29 per patient) using 132 medicines by INN names.
3. An important characteristic of pharmaceutical providing for patients is the presence of three leaders of the frequency of prescriptions - drugs from the group L-neoplastic and immunomodulating agents (ALL - 28.0%, AML - 18.88% of total prescriptions by groups of patients, respectively).
4. Organizing of data of frequency analysis of doctor’s prescriptions for patients with ALL and AML and relevant protocols of the MC makes it possible to assert that the overwhelming majority of doctors used drugs of pathogenetic therapy. The top-three leading drugs in both groups of patients were taken the medications of antitumor action (I group - vinkristyn → mercaptopurine → cytarabine, and II group - idarubicin → cytarabin → tretionin).
5. Consumption of medicines by ALL patients amounted to UAH 2,251,437.93 (30,424.84 UAH / patient), and the AML - UAH 18,276.89 (30,424.84 UAH / patient). The share of AD costs was for patients with ALL 48.38% and AML - 58.44%.
6. The first three positions by the amount of consumption of medicines were held the following drugs: ALL - Cyclophosphane (cyclophosphamide for INN) → Epreks (erythropoietin) → Vifend (voriconazole) → mercaptopurine; AML - cytosar (cytarabine) → Zavedos (idarubicin) → Meronem (Meronem).
7. An important characteristic of the consumption of medicines, which is determined according to the ABC-analysis is the presence in the first rungs of action of anticancer drugs (I group patients - cyclophosphamide; II group - cytarabine).
8. It is proved that more than half of the resources spent on pharmaceutical providing of patients accounted for drugs from the group V, which can be assessed as positive. Thus, the ratio between the consumption of drugs V, E and N was: in I group - 55: 39: 6, and for patients with AML 56: 41: 3.
9. It is established that in both groups of patients most costs were spent on drugs consumption with the status of A / V, and the least - C / V (ALL) and the status of C / N. (AML). In the treatment of AML was not used any drug with the status B / N.
10. An important direction of future research is the development of theoretical and applied approaches to developing of effective models of reimbursement of cost of drugs consumption on different groups of blood cancer patients, especially in acute leukemias, which by vital indicators require timely, valuable providing with available medicines.