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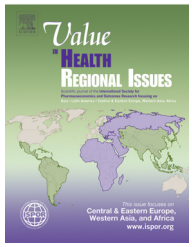

Cost for Treatment of Chronic Lymphocytic Leukemia in Specialized Institutions of Ukraine

Olena Mandrik, PhD[1,2,*], *Isaac Corro Ramos, PhD*[3], *Olga Zalis'ka, PhD*[1], *Andriy Gaisenko, PhD*[4], *Johan L. Severens, PhD*[2,3]

[1]*Danylo Halytsky Lviv National Medical University, Lviv, Ukraine;* [2]*Institute of Health Policy & Management, Erasmus University Rotterdam, Rotterdam, The Netherlands;* [3]*Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, The Netherlands;* [4]*National Cancer Institute, Kyiv, Ukraine*

ABSTRACT

Objective: The aim of this study was to identify, from a health care perspective, the cost of treatment for chronic lymphocytic leukemia in specialized hospitals in Ukraine. **Methods:** Cost analysis was performed by using retrospective data between 2006 and 2010 from patient-file databases of two specialized hospitals (145 patients). Uncertainty was assessed by using bootstrapping and multivariate sensitivity analyses. Linear regression analysis was used to analyze whether patients' characteristics are related to health care costs. In addition, one-way analysis of variance (Welch test) and paired-sample t test were conducted to compare mean costs of treatment between the two hospitals and mean expenses for drugs and in-hospital stay. **Results:** The average annual cost for a patient's drug treatment is 2047 EUR. The cost of hospitalization was significantly lower ($t = 5.026$; significance two-tailed = 0.000) and equal to 541 EUR per person, resulting in total expenditures of 2589 EUR. Mean total costs in the bootstrap analysis were equal to 2584 EUR (median 2576 EUR, 97.5th percentile 3223 EUR; 2.5th percentile 1987 EUR). The regression analysis did not reveal a relation between patients' characteristics and health care costs, although hospital choice was an influential parameter ($\beta = -0.260$; significance = 0.002). Significant difference in mean costs of two analyzed hospitals was also confirmed by one-way analysis of variance (Welch statistics 19.222, $P = 0.000$). **Conclusions:** Drug treatment comprises the largest portion of total costs, but differences between hospitals exist. Because many patients in Ukraine pay out of pocket for in-hospital drugs, these costs are a high economic burden for patients with chronic lymphocytic leukemia.

Keywords: chronic lymphocytic leukemia, cost of treatment, hematologic malignancies.

Introduction

Globally, there are approximately 7.4 million cancer deaths per year, which is approximately 13% of deaths from all causes. Because the population of many countries around the world is aging, it can be expected that cancer incidence will increase [1]. Among oncologic diseases, chronic hematologic malignancies are comparatively rare. In Ukraine in 2010 the officially registered total morbidity rate for patients with diagnosed leukemia was 7.8 per 100,000 people, of which 39.3% did not live a year after diagnosis [2]. Chronic lymphocytic leukemia (CLL) is the most frequent form of leukemia in Western countries, and it accounts for approximately 30% to 40% of all leukemias [3,4]. It is characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Although the median age of patients at diagnosis is higher than retirement age and so has no significant impact on state productivity loss [5], the economic impact of CLL is significant due to long duration and high expenses related to treatment, combined with low cure rates. Nevertheless, early diagnosis and effective treatment of hematologic malignancies shift the indicators of a patient's life expectancy to positive values [6]. For example, in the United States for the time period 1999 to 2005, the 5-year survival rate for leukemia was 82% (79% for CLL), although in the time period 1975 to 1977, this indicator was close to Ukrainian data—35% [7,8].

In-hospital medical care for patients with CLL is generally provided in 35 hematologic departments, based in district hospitals (16), state city hospitals (12), oncologic dispensaries (4), and specialized institutes of the National Academy of Medical Science of Ukraine (3) [2,9]. To the latter group belong two hematologic institutes and the National Cancer Institute, which is a leading state institution additionally responsible for methodological and scientific development in this clinical area. Treatment schemes for patients with CLL are based on a clinical protocol that proposes a number of treatment options for patients with CLL and was first developed and approved under an order of the Ministry of Health of Ukraine in 2010 [10]. State pharmaceutical provision for adult oncologic patients is granted through the national treatment program "Oncology" for the years 2011 to 2016, although governmental financing is insufficient and drug treatment is usually paid out of pocket by patients [11].

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* *Address correspondence to:* Olena Mandrik, Danylo Halytsky Lviv National Medical University, 69 Pekarska Street, Lviv, Ukraine 79010. E-mail: Olena.dem@gmail.com.

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Although CLL has a significant impact on patients' quality of life [12,13], studies exploring economic costs and burden of hematologic malignancies are relatively rare in English-language publications worldwide [14,15]. Possible reasons for this lack of information appear to include the low incidence rate and aged study population (over 60 years old), which make broad, well-designed economic analyses a challenge for most researchers [5,16]. These few cost reviews identified cost drivers for CLL as chemotherapy costs, intravenous immunoglobulin costs, transplantation costs, and costs associated with the differential staining cytotoxicity assay, with the main cost drivers related to the treatment chosen [14–16].

The health care system itself, including organization of medical care for oncologic patients, is going through a stage of transformation. Changes include the implementation of a universal reimbursement system to begin in 2016, standardization of medical help with enhanced control on follow-up of clinical protocols, and more strict division between primary, secondary, and tertiary levels of medical help. Considering that the major recipients of the central state budget are specialized institutions (tertiary level of help), the primary aim of this research was to identify the cost of treatment for CLL in specialized hospitals in Ukraine from a health care perspective and to understand whether patient characteristics are related to these costs.

Methods

The study was conducted from a health care perspective, accounting for direct medical costs to illustrate which costs will be paid by the Ministry of Health after the health care system transformation.

Analysis included data from databases of two specialized hospitals—National Cancer Institute and State Institute of Hematology—that receive state financing through the national treatment program "Oncology." These hospital databases were made in the programs Access and Word for the purpose of data storage and included all the information available in hard copies of hospital cards; the data were typed into the hospital databases retrospectively by qualified personnel (hospital assistants). Afterward, data from the two hospital databases were transferred into Excel, and SPSS databases were created for the purpose of data analysis.

The study population included all newly diagnosed and relapsed patients with CLL (145 in total) who were hospitalized during the period from 2006 to 2010 and whose data were recorded in the electronic database. The information derived from the hospital cards (excluding patients' identification information) contained the following data: sex of the patient, age during diagnosis and treatment, number of years a patient lives with the disease, year of treatment, therapies prescribed and duration of treatment, the number of hospitalizations per year, and the duration of hospitalization. Stage of the patient's disease and health state on Eastern Cooperative Oncology Group (ECOG) performance status were excluded from the factor list because data on these parameters were frequently missing.

Costs related only to CLL diagnosis for the last observational year were calculated. These costs included drug expenses and in-hospital costs. The cost of diagnostics, medical procedures, hotel services, and medical personnel is included in the integral in-hospital cost, based on data of the economic department of the National Cancer Institute. These costs reflect the approximate costs for oncologic patients in a specialized hospital and are equal to 16.3 EUR per patient-day [17]. Out-of-hospital health care costs were not calculated because according to the clinical protocol [10], the treatment of patients with CLL should be conducted only in hospital. The average length of hospital stay and drug costs were assessed by retrospective analysis of patient file data.

To assess drug usage, daily defined doses and total amount received during the year were recorded. To calculate drug costs, we used a stepwise approach to determine an average price, depending on the availability of information: tariff in governmental purchases (2010); price, registered in the Ministry of Health; and distributors' price.

Multivariate sensitivity analysis was conducted. Price deviations for the sensitivity test of all drugs were calculated by using the minimum and maximum prices from the available sources (hospital purchases, state registered prices, and distributors' prices). There are no defined general tariffs for hospital stay in Ukraine, which are relatively low in comparison to medical costs in the European countries and may vary from 3.4 to 19.2 EUR [17–19]. All statistical analyses were performed in IBM SPSS Statistics 20 (SPSS, Inc., Chicago, IL), and bootstrapping (1000 replications) was performed in Microsoft Excel 2010. To analyze whether choice of the hospital and age and sex of a patient have an impact on total health care costs, logarithmic data transformation was performed on nonnormally distributed costs and a linear regression analysis was applied. Because of frequently missing data for the parameter "stage of the disease," as a proxy for disease progression we included "number of years a patient is living with the disease" in the linear regression analysis. Based on Cook's distance (0.028571), which measures the effect of deleting a given observation and so allows to define data points with large residuals, we excluded six outliers to improve the residuals plot and model validity. One-way analysis of variance (Welch test) was conducted to compare mean costs of treatment in the two hospitals involved (asymptotically F distributed). Paired-sample t test was used to compare difference in mean expenses for drugs and in-hospital stay.

Results

Overall, data of 113 patients from the first hospital (State Hematology Institute) and of 32 patients from the second hospital (National Cancer Institute) were analyzed. Patients were aged 40 to 85 years (mean age 62.9 years, mean age during diagnosis 60.3 years, SD 9.8 years). From the sample, 27.6% (40) of the patients were newly diagnosed. Because of limited sample size, the distribution of patients by sex was not equal in different age groups, with the total proportion of men being equal to 60.7% (88 men).

Values of the cost items (drugs) and cost deviations for the sensitivity test are presented in Table 1. As can be seen in Table 1, the highest cost per milligram was for fludarabine, vincristine, and rituximab. Rituximab and fludarabine (if Fludara was prescribed) had the highest price per average daily dose, equal to 312.03 EUR for fludarabine and 237.93 EUR for rituximab. Because drug expenditures depend not only on cost per item but also on total volume used, we present cost-items utilization and characteristics of population using it in Table 2. Data are presented for items that were used by more than 3% of patients. Cyclophosphamide, fludarabine, and vincristine were prescribed to most of the patients. Characteristics of the study population using specific cost items showed a significant difference in the percentage of men prescribed cyclophosphamide, mitoxantrone, and chlorambucil in comparison to other drugs. No significant difference in the patients' age was observed, although on average the age of patients receiving alemtuzumab was lower and of those receiving chlorambucil was higher. From Table 2 it also may be observed that the injectable form of fludarabine is prescribed significantly more than the oral form.

Table 1 – Price values of the drugs for the cost and sensitivity analyses.

Drugs*	Base-case price (EUR per mg)	Range used in sensitivity analysis (EUR per mg)	Source†
Alemtuzumab (inj.)	0.4500	–	Tariff in governmental purchases 2010
Bleomycin (inj.)	1.5100	1.5100–1.6300	Distributors' price
Chlorambucil	0.0080	0.0080–0.2290	Tariff in governmental purchases 2010
Cyclophosphamide (Adriablastine)	1.0600	0.6700–1.4500	Price, registered in the MOH
Cyclophosphamide (other generics)	0.0077	0.0010–0.0120	Tariff in governmental purchases 2010
Dexamethasone (inj.)	0.0200	0.0040–0.0840	Price, registered in the MOH
Dexamethasone (po)	0.0002	–	Price, registered in the MOH
Doxorubicin (inj.)	0.1300	0.1300–0.4400	Tariff in governmental purchases 2010
Etoposide phosphate (po)	0.1000	0.0980–0.1000	Price, registered in the MOH
Fludarabine (Fludara inj.)	3.7400	3.2200–3.7400	Tariff in governmental purchases 2010
Fludarabine (Netran inj.)	0.7700	–	Tariff in governmental purchases 2010
Fludarabine (Netran po)	0.1500	–	Tariff in governmental purchases 2010
Fludarabine (other generics)	2.7800	0.7600–3.3700	Price, registered in the MOH
Methylprednisolone (inj.)	0.1100	0.0140–0.1100	Price, registered in the MOH
Methylprednisolone (po)	0.0260	0.0220–0.0300	Price, registered in the MOH
Mitoxantrone (inj.)	0.3800	0.3800–3.8300	Tariff in governmental purchases 2010
Prednisolone (inj.)	0.0160	0.0130–0.0170	Price, registered in the MOH
Prednisolone (po)	0.0072	0.0072–0.0077	Price, registered in the MOH
Rituximab (inj.)	2.0300	1.3500–2.9600	Tariff in governmental purchases 2010
Vincristine (inj.)	3.6700	2.8600–4.0600	Tariff in governmental purchases 2010
Vinblastine (inj.)	0.6300	0.4000–0.6300	Price, registered in the MOH

inj., injection; MOH, Ministry of Health; po, *per os* (by mouth).

* Trade name is indicated if the product was prescribed specifically by it.

† To value the use of the drugs from a health care perspective, we used a stepwise approach to determine an average price, depending on the availability of information: tariff in governmental purchases (2010); price registered in the MOH; distributors' price.

The average annual cost for a patient's drug treatment is 2047 EUR. The average cost of in-hospital stay is 542 EUR per person, resulting in total expenditures of 2589 EUR. Results indicate that expenses for drugs significantly exceed hospitalization costs ($t = 5.026$; significance two-tailed $= 0.000$).

Mean total cost in the bootstrap analysis was 2584 EUR (median 2576, 97.5th percentile 3223 EUR; 2.5th percentile 1987 EUR). Sex of the patient, number of years a patient lives with the disease, and age at the time of hospitalization had no significant impact on health care costs per patient. Hospital choice ($\beta = -0.260$; significance $= 0.002$), however, was a strong determinant of health care costs. One-way analysis of variance also showed a significant difference in mean costs between the two hospitals involved (Welch statistics 19.222, $P = 0.000$).

The results of the multivariate sensitivity analysis showed that in the best-case (lowest cost) scenario, the average annual spending on drug treatment of a patient with CLL is 1659 EUR, and in the worst-case scenario, it is 2332 EUR. The deviation of drug costs does not exceed 12% on the negative side and 19% on the positive side. The annual cost of hospitalization ranges from 251 to 597 EUR per person and depends on the type of hospital at which a patient is treated.

Discussion

A literature review was conducted in the database PubMed to explore whether our results were consistent with results from studies in other countries and to understand whether factors that impact the cost of other cancer conditions are similar to those affecting CLL. The search was limited to a 10-year period of English-language articles studying multiple cancer conditions. The literature review showed that the major factors influencing the cost of cancer conditions are related to patients' characteristics, such as stage at diagnosis and stage at treatment, degree of comorbidity, age and gender of a patient, and tumor site. Lal et al. [20], Longo et al. [21,22], and Yabroff et al. [23] recorded increased costs due to higher stage of the disease during treatment. Akushevich et al. [24], in a retrospective analysis on oncologic patients in the United States, determined that the highest costs exist in the period of treatment immediately after diagnosis. Yabroff et al. [23] also recorded that both the first stage and the last stage of the disease at the time of treatment are associated with higher costs. The results of the studies by Lal et al. [20] and Kuse et al. [25] demonstrated a connection between the degree of comorbidity and treatment costs. The impact of patient's age on the cost of cancer was significant in a number of studies, but differed in scale and type of impact [20–22,24,25]. Some research described an impact of tumor site on total costs of the diseases [21,22,24]. Yabroff et al. [23] showed that cost for the treatment of localized diseases is lower, a conclusion supported by Lai et al. [20] who noted that the highest costs were for hematological malignancies among other types of cancer.

A limited number of economic analyses that describe factors influencing the cost of CLL treatment specifically were found. These studies showed a positive correlation between age and cost of drug treatment [6,26]. Danese et al. [26] also concluded that male gender is associated with higher cost for CLL drug treatment.

Similar to Yabroff et al. [23], CLL phase-specific health care costs for the US-Medicare population were found to have a U-shaped pattern over lifetime [27]. A study in the United States by Lafeuille et al. [27] also reported significantly higher health care costs for a CLL population compared to matched controls, mainly because of the higher costs for physicians, caregivers, and inpatient care. Besides inpatient hospital stay, pharmaceuticals were the main cost drivers of CLL in a study in Germany [28], where the cost of treatment per case is about twice as high as the cost per case for highly prevalent diseases, such as chronic obstructive pulmonary disease or diabetes. This study also revealed that the average annual cost for patients with CLL from

Table 2 – Drug utilization related to patients' population characteristics.

Drugs*	Patients using the drug (%)	Average age (SD) of patients using this item (y)	n (%)		Mean volume per patient (mg)
			Men among ones who are using this drug	Prescriptions during the first year of treatment	
Alemtuzumab (inj.)	10.3	57.90 ± 9.25	9 (60.00)	0 (0.00)	87.14
Chlorambucil (po)	7.6	74.45 ± 4.61	5 (45.50)	6 (54.5)	4.76
Cyclophosphamide (Adriablastine inj.)	4.8	64.29 ± 5.85	6 (85.70)	4 (57.10)	7.24
Cyclophosphamide (all brand names)	66.2	62.95 ± 9.13	59 (61.50)	29 (30.20)	2900.34
Dexamethasone (inj.)	10.0	60.07 ± 8.71	19 (65.50)	7 (24.10)	22.70
Dexamethasone (po)	5.4	59.20 ± 6.50	3 (60.00)	1 (20.00)	4.41
Fludarabine (Fludara inj.)	44.4	60.56 ± 8.82	36 (57.10)	13 (20.60)	377.87
Fludarabine (po)	3.4	59.80 ± 8.35	3 (60.00)	0 (0.00)	30.48
Fludarabine inj. (all brand names)	47.6	60.65 ± 8.82	40 (58.00)	13 (18.80)	411.79
Methylprednisolone (po)	4.8	56.29 ± 10.42	4 (57.1)	1 (14.3)	22.59
Mitoxantrone (inj.)	5.5	58.12 ± 6.31	7 (87.50)	0 (0.00)	4.35
Prednisolone (inj.)	5.5	60.63 ± 10.64	5 (62.50)	2 (25.00)	224.63
Prednisolone (po)	26.2	66.63 ± 8.07	26 (68.40)	14 (36.80)	179.37
Rituximab (inj.)	12.4	59.28 ± 6.72	13 (72.20)	5 (27.80)	258.62
Vincristine (inj.)	31.0	64.51 ±9.57	34 (75.60)	17 (37.80)	1.66

inj., injection; po, *per os* (by mouth).
* Trade name is indicated if a product was prescribed not by generic but by a trade name with a high frequency (for cyclophosphamide and fludarabine).

the sickness fund perspective decreased with increasing age until 60 to 65 years, and thereafter increased.

Results of these US and German studies [27,28] differed from the results of our analysis conducted in Ukraine, where the cost of medical care is relatively low and the major expenses are drug related. Similar to our results, a literature review conducted by Stephens et al. [16] concluded that the cost of drug therapy is the main driver for CLL treatment costs, significantly exceeding hospitalization costs.

Previous research has suggested that the major factors influencing the cost of cancer conditions are stage at diagnosis and stage at treatment, degree of comorbidity, age and gender, tumor site, and type of therapy received. Our study on a Ukrainian sample from two specialized institutions, however, showed that only hospital choice had a significant impact on the cost of drug treatment. Possible explanations may be risk-patient selection or difference in treatment practice within the hospitals. High usage of injectable forms of drugs such as fludarabine and dexamethasone also was observed in this study. Because no health technology assessment agency currently exists, there are no recommendations comparing injectable and oral forms developed in Ukraine. Nevertheless, the National Institute for Health and Clinical Excellence [29] recommends giving preference to the oral form of fludarabine because of its higher efficiency. Rationality of the use of the injectable form of fludarabine in CLL treatment practice may be a potential topic for further research in Ukraine.

Ukraine is a country with a post-Semashko model of the health care system, and currently there is no state reimbursement system. Limited reimbursement for in-hospital treatment, however, is provided under governmental programs for such diseases as AIDS, tuberculosis, diabetes, cardiovascular diseases, and cancer, among other diseases. These in-hospital state purchases cover from 7% to 40% of oncologic patients' needs depending on the region and hospital type [30,31]. Major expenses on drugs are covered by patients' out-of-pocket payments. Thus, the high treatment cost of chronic conditions such as CLL may be a significant economic burden, especially for patients with low income.

The average annual cost of drug treatment for patients with CLL is 2047 EUR, with the majority of costs paid out of pocket. From December 1, 2011, the minimum annual subsistence level in Ukraine is equal to 1155 EUR for people of working age and 920 EUR for those who are retired. These figures are lower than annual costs of drug treatment for patients with CLL in Ukraine, according to current clinical practice in specialized hospitals. This may impose a significant economic impact of the disease on vulnerable populations (e.g., elderly poor), taking into account only limited governmental subsidy. With high costs for the treatment of hematologic malignancies [15,26], and insufficient reimbursement level for drug treatment in Ukraine [9], the treatment of CLL in specialized hospitals may be financially difficult for economically unprotected patients because of high therapy costs.

Implications

Our analysis indicates that there is likely to be a significant difference in the practice of treating CLL within different hospitals of Ukraine, resulting in a significant deviation in drug expenditures. Therefore, it is not clear whether treatment standards are being followed within the hospitals and whether the schemes used are evidence based and rational. These issues should be explored further in future studies.

Limitations

Retrospective analysis allowed us to make an estimation of treatment cost for CLL in specialized medical institutions of Ukraine and to explore its correlation with patient characteristics. Our research, however, suffered from several limitations.

First, our research does not allow us to assess the economic burden of CLL in Ukraine. It is expected that costs of treatment in the current study may be higher than in the regional oncology dispensaries because of larger state subsidiaries and patients' expenditures on drugs.

Moreover, data on stage of the patient's disease and health state on Eastern Cooperative Oncology Group (ECOG) criterion were missing and thus excluded from the factor list. It is possible, however, that these factors may have an impact on CLL costs.

We conducted a linear regression analysis on logarithmic-transformed costs data while excluding six outliers on the basis of Cook's distance. Disregarding these six observations may have increased the significance of the statistical analysis and the strength of the relation between the independent variable (hospital choice) and the dependent variable (health care costs).

Conclusions

Drug treatment comprises the largest portion of total costs, which presumably may be a high economic burden for a patient with CLL who is the major payer of treatment expenses in Ukraine. Costs of drug treatment significantly depend on the type of hospital selected.

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