



Resource Use and Costs Related to Hematological Complications of Chemotherapy: Cost of Illness Study Based on Data from Balkan Country with Recent History of Socioeconomic Transition

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Abstract

Background: The administration of chemotherapy positively correlates with diverse adverse drug reactions, including the significant impact of hematological hazards such as anemia, leukopenia-neutropenia, thrombocytopenia, and pancytopenia. This pilot pharmacoeconomic study aimed to estimate the total direct costs of treating hematological toxicity induced by chemotherapy and its main determinants.

Methods: The study was conducted as a retrospective cost of illness study using the "from bottom to the top" approach from the perspective of the Republic Health Insurance Fund. This study included 88 patients treated due to developing at least one episode of one of the types of hematological complications of cytostatics in 2018 at the Oncology Clinic of the University Clinical Center Kragujevac, Kragujevac, the Republic of Serbia.

Results: Among cancer patients who developed haematological toxicity, treating pancytopenia was most demanding in a pharmacoeconomic manner compared to neutropenia and thrombocytopenia, with an estimated value of direct costs of 264,14, 178,19 and 157,76 euros per patient per year respectively. Regarding total direct costs, the main determinants were the costs of drugs, their parenteral administration, and costs due to hospitalization.

Conclusion: Due to the rising cancer incidence and obligatory hospital treatment of hematological toxicity induced by chemotherapy, the identification of the pharmacoeconomic aspects of the treatment of these complications is needed. Future research should focus on the development of new modalities of treatment regarding patient characteristics anticipating high costs.

Keywords: Hematological complications; Chemotherapy; Cost of illness; Direct costs; Pharmacoeconomics



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Introduction

Therapeutic strategies for cancer are complex and encompass a multimodal approach. The magnitude of adverse drug reactions in patients treated with chemotherapy is immense. Administration of chemotherapy positively correlates with diverse adverse drug reactions, including the significant impact of hematological hazards such as anemia, leukopenia-neutropenia, thrombocytopenia, and pancytopenia. Pancytopenia encompasses the diminishing of all three types of blood cells, while anemia, leukopenia-neutropenia, and thrombocytopenia include decreasing the number of red blood cells, white blood cells, and platelets, respectively (1,2).

Hematological toxicity induced by chemotherapy contributes to the occurrence of negative therapeutic outcomes and favors an increase in mortality and morbidity in patients with chemotherapy. Medical consequences of hematological toxicity induced by chemotherapy are diverse. Anemia leads to fatigue, which is one of the most frequent adverse drug reactions in these patients. Neutropenia represents one of the most serious adverse effects induced by chemotherapy contributing to a higher susceptibility of these patients to potentially life-threatening infections. The development of febrile neutropenia, characterized by fever and low absolute neutrophil count, often leads to urgent hospitalizations and requires the administration of intensive pharmacological treatment due to the risks of death from diverse infections. The occurrence of thrombocytopenia in these patients induces a higher risk of bleeding, which can develop into severe form in less than 10% of patients with solid tumors (3-8). Hematological toxicity induced by chemotherapy influence the course of treatment of these patients negatively, contributing to physicians' decisions about the further course of treatment, either to reduce the dose of chemotherapeutic agents or to limit further administration of the drug. Finally, these medical consequences diminish the treatment success of chemotherapy. He-

matological adverse reactions lead not only to serious medical consequences but also to an additional increase in the use of medical services such as hospitalizations, administration of drugs, and health care services, which finally may have implications regarding costs for not only treating these adverse effects but also treating cancer. Estimating and understanding resource use and costs of hematological toxicity of chemotherapy is important not only for health providers but also for health professionals and patients, especially in the pharmacoeconomic milieu of countries with a recent history of socioeconomic transition (1,2,9).

The aim of this pilot pharmacoeconomic study was to estimate the total direct costs of treating hematological toxicity induced by chemotherapy and its main determinants.

Materials and Methods

Study settings and perspective

In order to evaluate the pharmacoeconomic aspects of treating hematological complications of chemotherapy, we conducted a retrospective cost of illness study with the "bottom to the top" approach from the perspective of the Republic Health Insurance Fund.

This study was approved by the Ethics Committee of Clinical Centre Kragujevac (Authorization N° 01/ 18-843). It was performed in accordance with CHEERS criteria (10).

Study population

This study included all patients of both sexes and all ages who were treated due to developing at least one episode of one of the types of haematological complications of cytostatics during one year (between January 1 and December 31, 2018) at the Clinic for Oncology and Radiology of the University Clinical Centre Kragujevac. The sample size was calculated based on the formula: $n=(1.96)2x4*SD2/d2$, where SD

represents the standard deviation of the calculated costs, and d is the desired confidence interval width, regarding retrospective data study by Mayordomo et al. (11,12). The study population size was calculated on 52 patients, and we included 88 patients for the research.

Demographic and Clinical Data

Demographic (sex, age), clinical (primary diagnosis - a type of cancer, type and severity of treated haematological complications of chemotherapy, number of hospitalizations in the monitored period), and data related to direct costs of treatment (length of hospitalization, number, and type of medical examinations, administration of pharmacological agents and blood derivatives, health care services, laboratory analysis, blood derivatives, drugs, sanitary materials) were gathered from medical documentation of patients.

Costs

Medical and clinical data related to direct costs of treatment have been converted into specific monetary values using electronic publications of the current Price List of Medicines and Medical Services available on the website of the Republic Health Insurance Fund (13) and in the current Tariff Book (14).

The collected data were analyzed using the program IBM SPSS Statistics v21 (15), descriptively processed with the determination of central tendency (mean, median) and variability (SD - standard deviation and range), depending on whether the data follow a normal distribution, as determined by the Kolmogorov-Smirnov test. Determination of a statistically significant difference in the total costs among different populations was performed using non-parametric tests - Mann-Whitney Test U (two categories) and Kruskal-Wallis (three or more categories), or parametric T-test of independent samples (two categories) and One way (Analysis of variance) - ANOVA test (three or more categories). Multiple regression analysis was used to determine the main determinant of the total cost of treatment of hematological complications.

Results

In total, 88 patients with hematological toxicities induced by chemotherapy, used in the treatment of primary disease - cancer, of any type and stage, were included in the study. Among them, 65.91% were female patients, and 34.09% male patients. The median age of all subjects was 63.5 years (28-82), where 52.30% of patients were 65 and older, and 47.70% were younger than 65 years.

According to the type of hematological adverse drug reaction induced by chemotherapy, 53.40% of patients developed pancytopenia, while leucopenia (regardless of the type of leukocyte deficiency) and thrombocytopenia were presented in 42.05%, and 4.55% patients, respectively. Isolated anemia was not detected in examined population, and it was only presented as part of pancytopenia. The average number of hospitalizations due to hematological complications caused by chemotherapy for the monitored period of one year was 1 (1 hospitalization - 6 hospitalizations), while the median length of hospital stay per patient was four days (1 day - 38 days). Hematological complications due to chemotherapy were observed more in patients treated with single-agent chemotherapy (60%) than in patients treated with the combination of chemotherapy (40%). Vinorelbine, paclitaxel, docetaxel, and cisplatin as single agent chemotherapy were mostly related to hematological complications in 19.2%, 15%, 11.5%, and 11.5%, respectively, of the study population.

Total direct costs of treating hematological chemotherapy complications were estimated at 32,869.01 euros. Total direct costs of treating pancytopenia represented 74.17% of these costs with a value of 24,378.95 euros, while treating leucopenia and thrombocytopenia was presented with 23.67% and 2.16% with a value of total direct costs of 7,787.82 euros and 710 euros, respectively. Considering the importance of cost evaluations in the health care system, the following cost structure was observed: costs of administered drugs (32.33%), costs of parenteral drug

administration services (22.94%), hospitalization (17.64%), laboratory analyses (11.72%), blood products and their transfusion (7.31%), sanitary materials (5.72%) and medical examinations and health care (2.34%). Concerning the costs related to the application of therapy, 73.22% (€7,617.10) was used for the treatment of pancytopenia, 24.31% (€2,528.37) for the treatment of isolated leukopenia and 2.47% (€257.41) for therapy-isolated thrombocytopenia. Among the total population, the pharmaco-economically most important determinants were costs related to the

application of granulocyte colony-stimulating factor - G-CSF (26.78%) and crystalloid solutions (25.19%).

The total costs of each detected hematological complication of chemotherapy concerning type and severity are listed in Table 1. In the study population, a milder form of pancytopenia was more common (62.5%), while a more severe form was observed in 37.5% of subjects. Total costs per patient regarding age with its main determinants are presented in Table 2.

Table 1: Total costs per patient regarding severity and type of hematological complication as part of cytopenia

<i>Variable</i>	<i>Severity of clinical manifestation</i>		
	Mild	Moderate	Severe
Complication (as part of cytopenia)			
Anemia	317.80±251.15	611.22±156.29	1184.21
Neutropenia	223.50±140.66	268.10±243.39	212.61±111.54
Febrile neutropenia	-	439.91±171.85	530.35±358.25
Lymphopenia	314.62±222.09	909.44±2132.75	450.44±383.67
Thrombocytopenia	647.73±181.74	403.89±324.35	612.09±388.38

Table 2: Total costs per patient regarding age with its main determinants (EUR)

<i>Medical services/Treatment provided</i>	<i><65 years</i>	<i>≥65 years</i>
Parenteral drug administration (Mean ±SD)	106.42 ± 300.27	59.35 ± 60.68
Sanitary materials (Mean ±SD)	28.18 ± 101.57	12.98 ± 25.70
Inpatient visits and care Median, (Range)	0 (0 - 476.32)	0 (0 - 54.94)
Hospitalization	52.57 (10.52 - 543.12)	52.57 (10.51 - 433.66)
Blood transfusion	0 (0 - 177.7)	0 (0-81.64)
Laboratory tests	15.28 (2.45 - 700.10)	13.19 (0 - 185.09)
Drug costs*	67.62 (2.25 - 4029.11)	45.29 (0.94 - 208.05)
Total costs of treatment per patient per year	226.23 (34.16 - 8569.22)	184.73 (33.96 - 923.99)

*Statistically significant according to Mann-Whitney U test ($P \leq 0.05$)

Total costs per patient regarding the number of used cytostatics with its main determinants are presented in Table 3. Total costs per patient re-

garding the type of hematological adverse reaction with its main determinants are presented in Table 4.

Table 3: Total costs per patient regarding the number of used cytostatics with its main determinants (EUR)

<i>Medical services/Treatment provided</i>	<i>Single-agent chemotherapy</i>	<i>Combination of chemotherapy</i>
Parenteral drug administration (Mean \pm SD)	32.99 \pm 48.47	96.63 \pm 59.92
Sanitary materials (Mean \pm SD)	8.47 \pm 12.17	8.51 \pm 5.30
Inpatient visits and care Median, (Range)	0 (0 - 54.95)	0 (0 - 16.02)
Hospitalization*	42.06 (10.52 - 433.70)	72.30 (31.55 - 147.22)
Blood transfusion	0 (0 - 36.43)	0 (0 - 37.08)
Laboratory tests	12.87 (2.45 - 361.13)	15.28 (2.45 - 67.09)
Drug costs*	47.05 (14.37 - 275.32)	107.80 (21.54 - 229.65)
Total costs of treatment per patient per year*	143.52 (56.15 - 739.83)	293.24 (125.23 - 698.98)

*Statistically significant according to Mann-Whitney U test ($P \leq 0.05$)

Table 4: Total costs per patient regarding the type of hematological adverse reaction) (EUR)

<i>Medical services/Treatment provided</i>	<i>Leukopenia</i>	<i>Thrombocytopenia</i>	<i>Pancytopenia</i>
Parenteral drug administration (Mean \pm SD)	48.45 \pm 58	60.54 \pm 51.13	114.02 \pm 296.39
Sanitary materials (Mean \pm SD)	6.37 \pm 6.82	5.47 \pm 5.81	33.73 \pm 102.01
Inpatient visits and care Median, (Range)	0 (0 - 55)	0 (0 - 20.88)	0 (0-144.13)
Hospitalization*	42.08 (10.52 - 434.03)	26.30 (10.52 - 52.61)	52.61 (476.56 - 543.39)
Blood transfusion*	0 (0 - 46.84)	0 (0 - 0)	28.38 (0-144.13)
Laboratory tests*	9.8 (0 - 103.2)	13.86 (2.45 - 40.34)	25.79 (2.45-700.41)
Drug costs	47.51 (14.38 - 210.79)	58.29 (18.37 - 122.8)	61.50 (0.91 - 4,031.10)
Total costs of treatment per patient per year*	157,76 (34.17 - 606)	178,19 (56.19 - 293.19)	246,14 (34 - 8,573.45)

*Statistically significant difference $P \leq 0.05$ based on Kruskal-Wallis Test

Multiple regression analysis resulted in the model that explained 75.5% of the total treatment cost variance ($F(5, 12)=11.478, P=0,000$). The main contributors to the total costs of treating hematological complications of chemotherapy were: age ($B= -346.973, 95\% \text{ CI } (-478.520 - -215.427), P=0.000$), isolated neutropenia ($B= -9,758.758,$

$95\% \text{ CI } (-18,157.259 - -1,360.256), P=0.026$), isolated monocytopenia ($B= -13,291.994, 95\% \text{ CI } (-21,106.187 - -5,477.801), P=0.003$), isolated thrombocytopenia ($B= -7,675.209, 95\% \text{ CI } (-11,968.211 - -3,382.208), P=0.002$) and isolated anemia ($B=7,292.598, 95\% \text{ CI } (2,710.304-11,874.891), P=0.005$).

Discussion

Economic analysis of treating cancer can contribute to key stakeholders in the Balkans in their future decision-making, especially in circumstances of limited healthcare budgets and a rising cancer incidence. Results from this study pointed out that treating pancytopenia induced by chemotherapy is the most demanding in a pharmacoeconomic manner compared to other types of hematological toxicities, as well as that the most significant determinants of total costs are costs related to the use of the drug (among which are the most demanding G-CSFs), their parenteral administration and costs due to hospitalization. Results from our study indicate that the median cost of treatment of hematological complications of chemotherapy in the entire study population was € 202.77, while the average treatment of isolated leukopenia (median) per patient was estimated at € 157.09, which is significantly lower compared to countries as in the Balkan region, e.g., in Bosnia and Herzegovina (€ 1,035.02) (16) as well as in Western Europe, e.g., Spain (€ 3,841.00) (12) and in the world: USA (€ 21,769.53) (17) and Singapore (€ 2,494.36) (18). Similar results of the latest published systematic review, which analyzed the costs of treatment of chemotherapy-induced neutropenia, indicate that the treatment of these complications in Serbia was lower than in all studied countries, which were Canada (€ 5,208.08), Australia (€ 3,176.64), United Kingdom (€ 2,450.01), Germany (€ 2,388), Italy (€ 2,357), France (€ 2,000), Spain (€ 1,529) and the Netherlands (€ 877) (19). Such discrepancies in the total generated costs are expected, taking into account the differences in the organization of the functioning and financing of health systems in comparable countries where the prices of drugs are similar and prices of health services are significantly higher than in the socio-economic milieu of the Republic of Serbia. For similar reasons, the difference in the cost of treating one episode of isolated thrombocytopenia resulting from hematological toxicity of chemotherapy, whose median in the study was € 178.19

per patient, can be explained. This value is significantly lower than in comparable countries such as the USA, where a cost of € 6,026.48 per patient was recorded (20).

In this study, the most significant determinant of total costs came from the drugs (detected isolated leukopenias and thrombocytopenias), with a share of about 30% of the total treatment costs. Drugs were also the most significant determinant of total expenses of chemotherapy-induced neutropenia in Bosnia and Herzegovina (16), accounting for 45% of the total. Drugs are the second determinant of the total costs of these complications in Spain, with a share of 17% (12) in total costs, and in the United States, with a share of 27% (2). Such results were expected, given that the main treatment of these complications consists of drugs intended for hospital use, contributing to a significantly large share in the total cost of treatment of hematological complications of chemotherapy (21).

The second most significant treatment costs in our study, in the cumulative costs and costs of treatment of isolated leukopenia and thrombocytopenia, were the costs associated with parenteral administration of drugs, while in the case of pancytopenia, they represented the most significant cost determinant. The reason for that lies in the fact that all drugs, regardless of the type of hematological complication and patient characteristics, are administered parenterally, usually intravenously, then subcutaneously and intramuscularly, so the value of these costs is expected to be high. No works by other authors have been found that present these costs as individual determinants. The assumption is that these costs are classified together with drug costs or within hospital costs, which are certainly the most significant determinants of total costs in most research. Pancytopenias are more complicated to treat than other isolated complications, so the number of drugs used is higher (22).

We also found that the most pharmacoeconomically demanding drugs in this study were stimulating growth G-CSFs, i.e., filgrastim. The use of filgrastim accounted for 26.06% of the total cost of pharmacological therapy, which is similar to

the results of a study (12). The use of G-CSFs accounted for 82.67% of the costs intended for the use of drugs in the treatment of neutropenia in Bosnia and Herzegovina (16). The cost of filgrastim per patient during hospitalization was estimated at € 371.25 in Bosnia and Herzegovina (16), € 184.00 in Spain (12), and in € 177.62 per day in the USA (17), which is significantly higher than in pharmacoeconomic conditions of the Republic of Serbia (detected median for the entire length of hospitalization in this study was € 21.21). Considering that in the mentioned studies, as special determinants, the costs of preparation and application of drugs were not singled out, we can assume that they are included in the presented values and that this is one of the reasons for the differences. The decision regarding the administration of G-CSF in patient therapy in a therapeutic manner should be based on careful consideration of the goals of the chemotherapy cycle, the probability of prolonging patient life, and eliminating symptoms, as on the quality of patient's life and the pharmacoeconomic aspects of this medical procedure (23).

Our results pointed out that length of hospitalization is a significant determinant of the total costs of treating hematological complications induced by chemotherapy. The median length of hospitalization of patients with isolated leukopenia in our study was 4.0 hospital days, which is shorter than the data related to treatment in the United States, Bosnia and Herzegovina, Singapore, and Spain in which the average length of hospitalization due to chemotherapy-induced neutropenia was 9.6, 6.7, 5.9, and 7.0 days respectively. (12, 16, 17, 18). Length of hospitalization substantially affects the total direct costs of treating hematological complications induced by chemotherapy in the pharmacoeconomic sphere of the Balkan country with the recent history of socioeconomic transition, despite the fact that these costs are significantly lower than in other regions due to differences in health policies and financing health services within comparative health systems. For example, the cost of one day in the hospital setting in the Republic of Serbia is € 13.10, which is significantly lower than in regions such as Bosnia

and Herzegovina, where the price of a hospital day is € 61.36 (13, 16).

Overall, our study indicates that treating hematological complications induced by chemotherapy in younger patients and the presence of isolated neutropenia and isolated thrombocytopenia per se was associated with lower total direct costs, while the presence of isolated anemia generated more costs in total direct costs of treating this medical condition. Treating hematological toxicity induced by chemotherapy in older adults generates the costs of treating this medical condition for many reasons. In older adults with cancer, we can expect an increased risk of chemotherapy-induced hematological complications, which can be explained by the presence of multiple comorbidities, poor socioeconomic status, presence of polypharmacy, and decreased functional status of organs at this age, not only the liver, kidneys but also of hematopoietic organs (24). In our study, we did not have patients with isolated anemia, but this condition was "captured" as part of cytopenia and, per se, significantly affects the increasing total costs. These findings are expected due to the increasing use of inpatient-related services among patients with anemia induced by chemotherapy (25).

Our study had a few limitations since we included the calculated sample size and did not estimate indirect costs. However, these facts can be explained by the lack of a comprehensive patient register.

Conclusion

Measuring the economic burden of hematological adverse drug reactions induced by chemotherapy using an institutional perspective is important within health systems of higher-middle-income countries with the recent history of social and economic transition not only for payers but also for caregivers, patients, and society in general. Furthermore, this kind of study is a useful technique for pharmacists and other health professionals to provide future policy decisions regarding the selection of optimal treatments for pa-

tients with cancer, especially those with haematological malignancies taking into account not only the medical consequences of this condition but also socioeconomic too which can provide for better allocation and prioritization of health care budget.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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