Research plan for the article [protocol]:"

Stević, I., Janković, S., Petrović, N., Čanak-Baltić, N., Lakić, D.. (2024). Non-oncological drug-induced blood disorders: a cost of illness study using themicrocosting Methodology - study plan [protocol]

NON-ONCOLOGICAL DRUG-INDUCED BLOOD DISORDERS: A COST OF ILLNESS STUDY USING THE MICROCOSTING METHODOLOGY – STUDY PLAN

Stević I[1], Janković S[2, 3], Petrović N[2, 3], Čanak-Baltić N[2], Lakić D[1]
[1] University of Belgrade, Faculty of Pharmacy, Belgarde, Serbia
[2] University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia
[3] Department of Clinical Pharmacology - University Clinical Center of Kragujevac

INTRODUCTION

Drug-induced disorder „can result from unanticipated or anticipated drug effects“ (1). The prevalence of hematological adverse drug reactions (ADR) in chemotherapeutics is expected to be high; for non-chemotherapeutics, there is insufficient epidemiological data, although a spontaneous reporting system is mandatory in a drug's life cycle (2-6). ADR is considered to be the fifth cause of death, with the hospitalization rate caused by ADR estimated to be between 0.9-7.9% (7-8), while one study suggests that about „10 to 20% of hospitalized patients will experience ADRs during their stay“ (9). Frequency data on hospital admissions due to hematological ADR vary between studies, e.g., 9% (7) up to 26.5% (10).

The study by Abu et al. categorized major ADR types based on system disorders, where hematologic ADR encountered 9.9-15.2% of ADRs (9). The same study estimated costs per ADR from 65.00 to 12,129.90 USD, whereas costs were generally lower when the micro-costing approach was used (9).

A cost-of-illness (COI) study should be performed to precisely determine the costs generated by ADR. COI studies measure the economic burden of an illness on society, health insurance funds, or patients. Jefferson et al. (2000) defined “the aim of COI studies is descriptive: to itemize, value, and sum the costs of a particular problem with the aim of giving an idea of its economic burden“ (11). There are different methods of conducting this type of study, such as prevalence-based, incidence-based, or econometric approaches, with again different approaches (e.g., prospective, retrospective; top-down, bottom-up…) or with different perspectives of COI studies (such as societal, health care system, third-party payer) (11). However, micro-costing studies represent the gold standard for conducting COI studies (12).

Only a few cost drivers of HADR have been proven to date, e.g., prolonged in-hospital stay, costs of using drugs, and transfusion costs (13-14).

AIM OF THE STUDY

The aim of the study is two-fold: (1) to make healthcare utilization and cost analysis of non-cytotoxic drug-induced blood disorders, including anemia, leucopenia, and thrombocytopenia based on real-world evidence; and (2) to analyze main drivers of both utilization and cost outcomes.

HYPOTHESES

1. The healthcare utilization and costs of treating non-cytotoxic drug-induced blood disorders pose a significant burden on the healthcare system.
2. The severity of ADR is the primary driver of the healthcare utilization and costs of treating non-cytotoxic drug-induced blood disorders.

TYPE OF THE STUDY

The study was designed as a cost-of-illness study using the microcosting, bottom-up approach. Data will be collected in the real world at the Department of Clinical Pharmacology—University Clinical Center of Kragujevac, with the approval of the Ethics Committee of the University Clinical Center of Kragujevac.

This study will be conducted using the retrospective data from document collection. Data will be extracted from the archive of patient files (paper-based clinical pharmacologist consultations) at the Department of Clinical Pharmacology—University Clinical Center of Kragujevac. The data collection period will be for three years (1 Jan 2020 – 31 Dec 2022). This retrospective cost-of-illness study will be conducted from the perspective of the Serbian Health Insurance Fund.

RESEARCH POPULATION

The following inclusion and exclusion criteria characterize the study population:

Inclusion criteria: patients hospitalized in a tertiary health care hospital, having anemia, leucopenia, or thrombocytopenia mentioned in any part of the clinical pharmacologist's report, having laboratory findings indicating these disorders, or having a diagnosis code corresponding to these disorders attached to the patient file, and have rated the causal relationship between drug(s) and the blood disorders categorized by WHO-UMC system at least as „probable" (15).

Exclusion criteria: history of surgery, COVID-19, having any form of malignant disease, or any other disease that in its course has the potential of hematological disorder (renal failure, lupus, hepatitis C, myelodysplastic syndrome, liver cirrhosis, etc.), and incomplete medical record.

SAMPLING

The sampling process will go through 2 phases: screening and causality assessment. In the first phase, two independent researchers (IS, NČB) will review all paper-based clinical pharmacologists' reports (1 Jan 2020 – 31 Dec 2022), screening for drug-induced blood disorders focusing on anemia, leucopenia, and thrombocytopenia. Screening for these disorders will be conducted manually by reading patient history, physician findings, laboratory, and diagnosis codes. In the second phase, an experienced clinical pharmacologist (JS) will review all cases selected in phase 1 (screening) and determine where there is enough evidence that hematological disorder is a consequence of the drug administered to the patient (causal relationship between drug(s) and blood disorders rated as at least „probable").

VARIABLES MEASURED IN THE STUDY

Dependent variables that will be extracted from the patient flies are utilization figures. The costs will be calculated using utilization data and unit prices:

Service Costs = "number of services provided" x "price of the service"

Drug Costs = "number of drug packs used" x "price of the drug."

The levels of anemia, leucopenia, and thrombocytopenia (grade 1-5) are expressed based on laboratory values using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (16). Table 1 provides this study's independent variables and confounders (*) of interest.

Table 1. Independent variables and confounders of interest

Variable type	**Variable name**
Demographic*	Gender
	Age
Patient status	Live / Died
Laboratory and diagnostic services	BLOOD COUNT • Anemia (HgB value, number of RBC; anemia level) • Leucopenia (number of WBC; leucopenia level) • Thrombocytopenia (PLT number; thrombocytopenia level)
	Number of biochemical analysis
	Number of microbiological analysis
	MORPHOLOGICAL DIAGNOSTIC SERVICES: • Number of CT • Number of X-ray images • Number of MRI • Number of ECG
Therapeutic services	Number of hospital days
	Number of HCP consultations
	Number of hematology consultations
Medication	PATIENT THERAPY • Drug brand name number • Drug INN name number • Number of drugs (INN) having blood disordes as ADR in SmPC
	TRANSFUSION • Number of PLT units • Number of RBC units • Number of plasma units • Number of blood derivates units • Number of Full Blood units • Coagulation factors units

HgB – hemoglobin, RBC – red blood cell, WBC – white blood cell, PLT - platelet; CT – computed tomography; HCP- healthcare professional; MRI- magnetic resonance imaging; ECG - electrocardiogram

STUDY POWER AND SAMPLE SIZE

The confidence interval for our study will be 95%.
The sample size (N) for each blood disorder of interest (anemia, leucopenia, thrombocytopenia) is calculated based on the formula (17):

$$N = \left(\frac{2 * 1{,}96}{GP} * SD\right)^2$$

SD (standard deviation) is based on data from the cost of illness study of Hematological Complications of Chemotherapy (13).
For our study, the minimum number of patients is presented in Table 2.

Table 2. Minimum number of patients per disorder

Disorder type	Minimum patient number
Leucopenia	31
Anemia	33
Thrombocytopenia	51

STATISTICAL DATA PROCESSING

For all variables (dependent, independent, cofounders), data will be analyzed first using descriptive statistics (mean, standard deviation, range, median) using rates and percentages.

Afterward, a generalized linear model will be used for multivariate analysis (because it does not require a normal distribution of data) to determine whether variables from Table 1 are associated with study outcomes—costs. The model will be built using gamma distribution and log link function. The goodness of fit will be estimated based on calculated deviance, Chi-square statistics, and Akaike information criteria. The Omnibus test will be used to estimate the validity of the model.

The results will be considered statistically significant if the probability of the null hypothesis is 0.05 or less. IBM SPSS v.29 will be used for the statistical analysis (18).

REFERENCES:

1. Cynthia Reilly. Chapter 1 - Drug Safety and Drug-Induced Diseases: the Regulatory, Legal, and practice Environments. In: Tisdale JE, Miller DA, editors, Drug-Induced Diseases: Prevention, Detection, and Management. 3rd Edition. Bethesda, MD; American Society of Health-Systems Pharmacists, Inc. 2018..
2. Meulenhoff, J. S. Adverse-effects of drugs on the blood. Pharmaceutisch Weekblad-Scientific Edition. 6(1), 39 - 47 (1984).
3. Knight, K., Wade, S. & Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. Am J Med. 116 Suppl 7A, 11S-26S (2004) https://doi.org/10.1016/j.amjmed.2003.12.008
4. Aapro M, Österborg A, Gascón P, Ludwig H, Beguin Y. Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron. Ann Oncol. 2012 Aug;23(8):1954-1962. doi: 10.1093/annonc/mds112. Epub 2012 May 9. PMID: 22575608.
5. Saint, A. et al. Iron deficiency during first-line chemotherapy in metastatic cancers: a prospective epidemiological study. Support Care Cancer. 28(4), 1639-1647 (2020).
6. Wassie, M., Aemro, A. & Fentie, B. Prevalence and associated factors of baseline anemia among cervical cancer patients in Tikur Anbesa Specialized Hospital, Ethiopia. BMC Women's Health. 21(1), 36 (2021) https://doi.org/10.1186/s12905-021-01185-9
7. Olivier, P. et al. Assessing the feasibility of using an adverse drug reaction preventability scale in clinical practice: a study in a French emergency department. Drug Saf. 25(14), 1035-44. (2002) doi: 10.2165/00002018-200225140-00005
8. MEMO/08/782, Brussels, 10 December 2008. Strengthening pharmacovigilance to reduce adverse effects of medicine. European Commission http://europa.eu/rapid/press-release_MEMO-08-782_en.htm?locale=en. Accessed 8 July 2023
9. Abu, S.F.; Shafie, A.A.; Chandriah, H. Cost Estimations of Managing Adverse Drug Reactions in Hospitalized Patients: A Systematic Review of Study Methods and Their Influences. *Pharmacoepidemiology* **2023**,*2*,120–139. https://doi.org/10.3390/pharma2020012
10. Giardina, C. et al. Adverse Drug Reactions in Hospitalized Patients: Results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study. Front Pharmacol. 9, 350 (2018) doi: 10.3389/fphar.2018.00350
11. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014 Dec;20(4):327-37. doi: 10.3350/cmh.2014.20.4.327. Epub 2014 Dec 24. PMID: 25548737; PMCID: PMC4278062.
12. Tan SS, Rutten FF, van Ineveld BM, Redekop WK, Hakkaart-van Roijen L. Comparing methodologies for the cost estimation of hospital services. Eur J Health Econ. 2009 Feb;10(1):39-45. doi: 10.1007/s10198-008-0101-x. Epub 2008 Mar 14. PMID: 18340472.
13. Kostić M, Janković S, Desnica J, Lukić S, Mijailović S, Anđelković M, Pirković MS, Milovanović O, Spasić M, Vojinović T, Zečević DR. 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. Iran J Public Health. 2022 Nov;51(11):2573-2581
14. Elting LS, Cantor SB, Martin CG, Hamblin L, Kurtin D, Rivera E, Vadhan-Raj S, Benjamin RS. Cost of chemotherapy-induced thrombocytopenia among patients with

lymphoma or solid tumors. Cancer. 2003 Mar 15;97(6):1541-50. doi: 10.1002/cncr.11195.
15. The use of the WHO-UMC system for standardised case causality assessment. Available from: https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf. Last accessed: 14 December 2022
16. Common Terminology Criteria for Adverse Events (CTCAE). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed: 10 September 2022
17. Janković M. Slobodan. Dizajn istraživanja. Fakultet medicinskih nauka, Univerzitet u Kragujevcu, 2023
18. IBM Corp. (2023). IBM SPSS Statistics for Mac (Version 29.0) [Computer software]. IBM Corp.