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ORIGINAL PAPER

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COST OF FEBRILE NEUTROPENIA TREATMENT IN BOSNIA AND HERZEGOVINA

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Febrile neutropenia is common chemotherapy complication significantly impacting patient's outcomes, quality of life and costs, too. Febrile neutropenia (FN) often leads to hospitalization, the need for intravenous antibiotics and use of granulocyte colony-stimulating factors (GCSF) in order to avoid its complications. Cost of febrile neutropenia is well described in literature, but no study has been performed in Bosnia and Herzegovina. We have conducted observational cohort study with aim to describe and present costs of FN treatment from payers' (provider's) perspective. Only direct medical costs from one middle-sized oncology Clinic in Bosnia and Herzegovina database have been included and presented. We found that overall cost in five months period (January-May 2015) were almost 30.000 euros, or 1.0035 euro per episode/patient in average. The highest cost are allocated to hospitalization (40%), followed by GCSF (36%), while rest of costs are generated by laboratory tests performed and drug application. Proportion of costs is in line with other published studies even with huge differences in absolute values, mainly to low prices of services in Bosnia and Herzegovina. This was the first study on costs of chemotherapy induced FN in Bosnia and Herzegovina suggesting that significant costs are inquired by this conditions and that further research should be performed including larger patient population and other clinical oncology data, including pharmacoeconomic analysis.

Key words: febrile neutropenia, cost of treatment, pharmacoeconomic, GCSF, oncology, health policy.**1. INTRODUCTION**

Chemotherapy-induced neutropenia is characterized by a marked decrease in the peripheral blood neutrophil count. Since neutrophils are an integral part of the innate immune system, this may result in severe complications such as life-threatening infections (1, 2). As a result, neutropenia is considered to be the most serious chemotherapy-related hematological adverse event, frequently leading to dose delays or reductions which may compromise treatment outcomes (3). Neutropenia dampens most of the signs and symptoms of infection, and patients typically present with only fever, which is why this neutropenia-associated complication is referred to as febrile neutropenia (FN) (4). Depending on the number of comorbidities, chemotherapy-induced FN is thought to be responsible for the deaths of up to 50% of affected patients (5). Therefore, prevention and treatment of FN is considered a primary goal of supportive care in cancer patients at high risk undergoing cytotoxic chemotherapy (6). Febrile neutropenia often leads to hospitalization, the need for intravenous (iv.) antibiotics, additional interventional care like use of granulocyte colony-stimulating factor (GCSF) and further treatment in the outpatient setting (7).

This may result in chemotherapy dose delays or dose reductions, and interferes with delivery of optimal treatment, adversely affecting patient outcomes, including survival.

Beside medical consequences of FN, there is a significant economic impact of this condition in terms of its treatment. One of the main drivers of costs related to antineoplastic chemotherapy is hospitalization which often includes other direct and indirect medical costs such as antibacterial treatment and inability to work (8, 9). In the United States (US), the direct cost of neutropenia reported in the literature ranged from \$US 2.893 to \$US 38.583 (2006 values \$US 4.842-\$US 49.917) per episode for inpatients (10). For outpatients, the cost was \$US 1893 (2006 value \$US 2632) per episode. Outside of the US, the cost per episode ranged from \$US 300 (2006 value) for non-febrile cases to \$US 32.395 for elderly breast cancer patients with neutropenic complications. In general, the cost of neutropenia appeared to be lower in other countries compared with the US, with most estimates being <\$US 7.000 (2006 value) per episode. Hospitalization was the largest driver of the cost of neutropenia, comprising as much as 82% of the total direct medical costs for neutropenia (11). Major components of the hospital costs included

the room (36-38% of hospital costs), pharmacy (27-33%), supplies (4-17%) and blood bank (3-14%) (12). Other key cost drivers included outpatient drug costs and diagnostic tests (13). Indirect costs for neutropenia, such as costs associated with patient work loss, caregiver work loss, paid caregiver and/or non-revenue-generating support centers, were estimated to be \$US 3.834-\$US 5.738 per episode (2006 values \$US 4.741-\$US 8.781), thus representing approximately 34-44% of the total cost of managing neutropenia (12). Study published in 2009 reported that one of the most common reasons for cancer patient hospitalization was FN resulting in average hospitalization of 12,9 days and incurring significant costs (14).

Treatment of FN is mainly based on different GCSFs (15), and antibiotics in order to prevent or treat serious infections since this patients are immune compromised (16).

As authors' best knowledge, there is no any publication describing this issue in Bosnia and Herzegovina. In this observational, retrospective cohort study, data from a database that included costs from one hospital/oncology department were used to calculate the hospitalization costs and overall treatment costs associated with neutropenic complications. The aim of this study was to analyze cost of FN treatment from one hospital/oncology department in Bosnia and Herzegovina.

2. METHODS

Retrospective cohort studies of patients treated at Oncology department of Cantonal hospital Zenica have been analyzed. Only patients who were admitted and treated for chemotherapy induced febrile neutropenia have been considered. Patients treated in period January-May 2015 have been included in analysis. Data on age, cancer type, FN grade, chemotherapy protocol and duration of hospitalization as well as medical treatment have been extracted and taken into the consideration. Only direct medical cost of drugs, laboratory tests, hospitalization and drug administration have been included. Data on cost and prices have been taken from the official price list applied in this hospital. No discount rate on cost has been applied due to short time frame of the study.

All results have been summarized and analyzed in MS Excel, and presented in form of tables and figures.

3. RESULTS

In total we have included 27 patients with different cancer types diagnosed and treatment protocols applied. All patients have had Grade IV of FN occurred at different stage of therapy/cycle. Detail overview of patient sample is presented in Table 1. Therapeutic regimens (protocols) used in treatment of different cancer types are presented in Figure 1. Febrile neutropenia episode has occurred at different stages of treatment or cycle and detail overview is given in Table 2. Majority of FN episodes appeared after second and third cycle (22% and 26% respectively). Five patients have been treated in outpatient conditions, one has combined treatment (hospitalization and outpatient care) while majority of them have been hospitalized (81%). Total hospital days consumed was 180, and on average patients have been hospitalized for 6.7 days. For all patients routine

Patient characteristics	Number of patients (n=27) (%)
Age in years	Number of patients (n=27) (%)
Mean (SD)	52,7 (15,73)
18-40	6 (22%)
41-60	13 (48%)
61-80	8 (30%)
Gender	
Male	11 (41%)
Female	16 (59%)
Cancer Type	
Anal	1 (4%)
Breast	7 (26%)
Cervical	1 (4%)
Esophageal	1 (4%)
Laryngeal	1 (4%)
Osteosarcoma	1 (4%)
Ovarian	3 (11%)
Pancreatic	1 (4%)
Prostate	1 (4%)
Stomach	3 (11%)
Testicular	5 (19%)
Uterine	1 (4%)
Vesicle	1 (4%)

Table 1. Clinical and demographic characteristics of the subjects

Cycle	Occurrence/Cases of FN (%)
Cycle 1	5 (19%)
Cycle 2	6 (22%)
Cycle 3	7 (26%)
Cycle 4	5 (19%)
Cycle 5	3 (11%)
Cycle 6	1 (4%)

Table 2. Occurrence of FN at different stage of treatment

Service/Treatment provided	Number of services/units provided	Unit cost (EUR)	Total cost (EUR)
Hospitalization (days)	180	61,36	11.044,80
Outpatient visits (number)	18	15,34	276,12
Laboratory tests			
Complete blood count (CBC)	135	3,58	483,30
Differential Blood Count (DBC)	135	2,56	345,60
Creatinine	54	2,05	110,70
The blood urea nitrogen (BUN) test	71	2,05	145,55
Blood glucosis	63	1,53	96,39
Chest X-ray	6	10,23	61,38
Preparation of iv/sc medicine	577	2,56	1.477,12
SC application	577	2,56	1.477,12
Drug costs			0,00
GCSF	191	52,48	10.023,68
Meopenem 1g	70	4,32	302,40
Imipenem/cilastatin 500 mg/500 mg	316	6,65	2.101,40
Total cost in period January_May 2015		27.945,56	

Table 3. Overview of resources utilized and costs for treating FN laboratory tests have been performed meaning complete blood count (CBC) and differential blood count (DBC), and for some of them, depending on health status and diagnosis

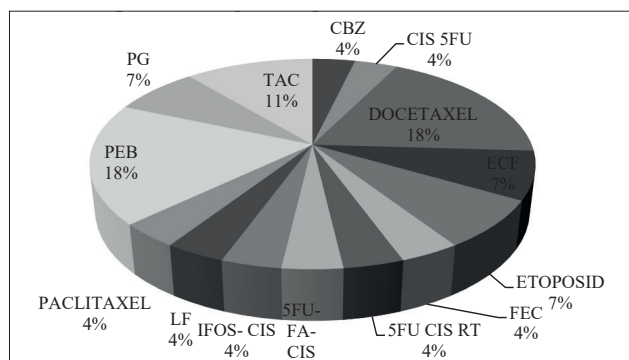


Figure 1. Therapeutic regimens used in treatment

additional test like chest X-ray (4 patients; 15%), creatinine, the blood glucose and blood urea nitrogen test-BUN (5 patients; 19%). All patients have been treated with granulocyte colony-stimulating factor (GCSF) and majority of patients required introduction of antibiotic therapy (59%). Filgrastim or lenograstime as GCSFs were applied one vial per dose, and meropenem and imipenem/cilastatin intravenous in doses 1 g every 8 hours and 500 mg/500 mg every 6 hours, respectively, were antibiotics of choice. Totally 191 vials of GCSFs have been consumed, and on average antibiotics treatment duration was 3,5 days or 96 days in total. Detailed overview of services provided and unit doses used with unit and total cost in euro are presented in Table 3. In total costs, cost of hospitalization is the highest and amount in 11.044,80 EUR (40%) followed by cost of GCSF amount in 10.023,68 EUR (36%). Cost of antibiotic treatment participate 9% in total costs, or 2.101,40 EUR. Significant part in cost structure is allocated to preparation and application drugs and amount 2.954,24 EUR or 11%. Total cost of treating febrile neutropenia induced by chemotherapy in five months period is 27.945,56 EUR, or 1.035,02 EUR per patient or episode per average.

4. DISCUSSION

This observational cohort study have included just direct medical cost and showed relatively high average cost per patient or episode of FN. Other studies conducted in Western European countries and US showed significantly higher costs. A study by *Caggiano et al*, using 1999 data from a longitudinal hospital discharge database that contained data from across seven US states, reported average neutropenia hospitalization costs (SD) of \$13.400 (\$21.000) across 13 cancer types (17). A study by *Kuderer et al*, using a longitudinal hospital discharge database with data from 115 US academic medical centers collected over 6 years (1995 to 2000), reported average febrile neutropenia hospitalization costs of \$19.110 [18]. Study by *Weycker et al*, using 2001 to 2003 data, reported average neutropenia related hospitalization costs of \$7,813 (95% CI 6,537-9,379) (19). Regarding cost structure, one study from Singapore reported highest cost allocated to drugs (20), while most of the studies from western countries reports hospitalization as highest cost part. Even our findings showed similar portion among cost allocation between major cost types, we have noticed high difference in absolute value. This due to very low cost of hospital days and low prices for medical services overall, and due to different time frames when studies are conducted. It is reported

in previous studies that hospital costs in general differ from country to country (21). Time frame of this study included year 2015 when lot of generic drugs penetrated market, CGSFs and antibiotics, which impacted on relatively low cost of drugs in comparison to the results of studies published in Western countries. This is also interesting to take into the consideration by health care policy decision makers in terms of evaluating introduction of new medicines into the reimbursement system in regards to transferability of data from studies published abroad (22).

Recently, pharmacoeconomic criteria has been introduced into legislation as part of reimbursement submission dossier (23), but still not fully implemented, mainly because of lack of experts in this field employed in decision making institutions and lack of education in this field (24, 25).

Significant costs are incurred when FN develops in a patient treated with chemotherapy, as mentioned above. These costs include both direct medical costs and indirect costs that are borne by the patient and his or her family. Economic analyses estimated the different types of aggregate costs that are incurred in hospitalization for FN, and these can be weighed against the costs of the use of prophylactic GCSFs. Primary prophylaxis with GCSFs significantly reduces FN incidence in adults undergoing chemotherapy for solid tumors or lymphoma (26). An early cost-minimization analysis calculated that, when the risk of FN was about 40%, the cost of universal prophylactic GCSF was equaled by the reduction in the costs of hospitalization for FN (27). In Bosnia and Herzegovina, due to restricted budgets and in order to make savings (28), decision on prophylactic use of GCSF sometimes is not approved by the payer; even published evidences clearly show benefits of prophylactic use in terms of avoiding complications and cost savings (29). In general, health insurance fund (HIF) cover all costs for oncology patients and all drugs used in treatment are procured by central tender, meaning that medication prices are unified in all hospitals and clinical centers. In our study cost estimates include direct medical costs but not nonmedical costs that patients incur, such as time lost from work and transportation costs. Focusing on only part of the costs, such as the direct medical expenses, may lead to cost shifting and fails to consider the actual financial impact on all affected parties. Main limitation of our study is small sample of patients taken into analysis, and short time frame counting just first five months. Based on this, it is possible to estimate that cost of treating chemotherapy induced neutropenia on a national level is much higher especially taking into the consideration total number of treated patients at more than ten oncology clinics and departments of different sizes.

5. CONCLUSION

Our study showed that approximately cost of treating febrile neutropenia is significant and count 1.035,02 EUR per patient or episode. Results are based on analysis of small patient population and experiences from middle-sized oncology department. Proportion of costs of hospitalization, drugs and services are in line with other studies published but with significant differences in absolute values due to low prices for these services in Bosnia and Herzegovina and generic drugs. Proper treatment and prophylaxis, especially in

case of high risk patients and chemotherapy protocol, could result in significant cost savings and better resources allocation. It is also important to take into the consideration pharmacoeconomic analysis results at national level as useful tool for decision making and resource allocation, but also at micro level (hospital). In order to implement current legislation on reimbursement criteria, it is necessary to popularize and educate health care professionals and stakeholders in field of pharmacoeconomic. Further research on this issue is recommended through inclusion of other oncology clinics and departments in Bosnia and Herzegovina, and also taking into the account societal perspective in order to estimate total burden of FN treatment.

- Author's contribution: all authors contributed equally in the preparation of the manuscript.
- Conflict of Interest: the authors declare that they have no conflict of interest.

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