Original Article

Factors Associated With Chemotherapy-Induced Neutropenia In Patients With Haematological Malignancies At Dr George Mukhari Academic Hospital, Pretoria, South Africa

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ABSTRACT

AIM Chemotherapy for haematological malignancies is often associated with occurrence of neutropenia and often times such an association is influenced by a number of factors. This study investigated various factors that could have been responsible for neutropenia among patients treated with chemotherapy for haematological malignancies.

METHODS A retrospective, cross-sectional, descriptive study of 245 patients, diagnosed with neutropenia while being treated with chemotherapy for haematological malignancies was conducted at Dr George Mukhari Academic Hospital, Pretoria, South Africa. Descriptive statistics was performed and Pearson's correlation coefficient analysis was used to evaluate the association of physical characteristics and laboratory variables of patients with chemotherapy-induced neutropenia (CIN). All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.0.

RERSULTS Patients' ages ranged between 18 and 87 years (median = 45 years), most of the patients (150; 61%) were older than 40 years and only 13 patients (5.3%) were ≤ 20 years. The cohort was made up of 52.7% males (n = 129) and 47.3% females (n = 116). Haematological malignancies treated at the time of the study were: Non-Hodgkin lymphoma (46.9%), Multiple-myeloma (15.9%), Hodgkin lymphoma (15.5%), Chronic lymphocytic leukaemia (6.9%), Chronic myeloid leukaemia (6.1%), Acute lymphoblastic leukaemia (3.7%), Acute myeloid leukaemia (2.0%) and Myelodysplastic syndrome (2.0%). The most significant co-morbid condition in association with CIN was HIV (n = 70; 28.6%). Advanced age (> 60 years) and BMI (> 20 kg/m²) were significantly correlated ($p < 0.05$) with CIN. However, gender of the patients, serum albumin, haemoglobin and body surface area were not directly related to CIN.

CONCLUSION The study emphasizes the need for healthcare professionals to adopt more stringent monitoring of patients with haematological malignancies while on chemotherapy, with particular emphasis for patients in their advanced age and those with co-morbidities (such as HIV infection and obesity).

Keywords: Chemotherapy; Neutropenia; Haematological malignancy; South Africa; Africa.

INTRODUCTION

Neutropenia is a condition of low absolute neutrophil count (ANC) below 1.5x10⁹/L, and it is categorized based on the severity of ANC reduction [1]. When it occurs, chemotherapy induced neutropenia (CIN) is a condition that warrants special medical attention and if not appropriately managed could result in

hospitalization and further compromise quality of life of the patient.

A previous report did indicate that CIN as well as febrile neutropenia (FN) occur frequently as complications in patients with cancer, undergoing chemotherapy [2]. FN refers to an ANC below $0.5x10^9$/L accompanied with 38°C or more by oral temperature for over one hour [3]. The blood neutrophil concentration itself is influenced by age, physical activity, genetic as well as environmental factors, and drugs. For instance, CIN is the most common side-effect associated with the administration of cancer drugs [4]. The severity of neutropenia does determine the prognosis and course of treatment outcomes, hence a grade 4 neutropenia characterized with ANC below $0.5x10^9$/L, moderate neutropenia with ANC in the range of $0.5x10^9$/L to $1.0x10^9$/L and mild neutropenia of $1.0x10^9$/L to $1.5x10^9$/L will present different medical challenges.

CIN incidence and prevalence vary widely. Studies have shown that the CIN prevalence among hospitalised patients ranges from 12% to 23% [5, 6]. These previous studies estimated that the condition accounts for overall mortality rates of about 5% among cases with solid tumours, 1% among low-risk patients and up to 11% in some cases with haematological malignancies. Individuals with neutropenia are more vulnerable to infectious organisms found on the skin, in the nasopharynx and those occurring in the intestinal flora. It was previously reported that the risk of infections varies inversely with the severity of neutropenia [5]. In a retrospective study involving 11,980 cancer patients on chemotherapy, CIN patients had a relatively high mortality risk of 15%. More especially, non-Hodgkin lymphoma (NHL) patients with CIN were reported to have significantly higher overall mortality rate than individuals who did not have CIN [6].

Complications and/or side effects of chemotherapy treatment for haematological malignancies may have a negative bearing on clinical outcomes and quality of life (QOL) of a patient. According to Lyman and Kuderer [7], chemotherapy may adversely affect patient's QOL socially, physically and global functionality. For instance, patients with febrile neutropenia are frequently hospitalized and treated with antibiotics in order to prevent the threat to life posed by sepsis [8, 9]. CIN according to Caggiano et al [10] is associated with neutropenia hospitalization incidence of about 7.83 cases in every 1000 cancer patients. The effect of hospitalization and isolation alone may adversely affect the quality of life, apart from the possibility of clinical consequences of febrile neutropenia.

Patients with bacteraemia are characterised with the worst prognosis of which those with gram-negative and gram-positive bacteraemia have mortality rates of 18% and 5% respectively. The prognostic index showed mortality rates in the range of 3% for Multinational Association for Supportive Care in Cancer (MASCC) score of ≥ 21 to high 36% for the MASCC score of < 15 [11].

Therefore, this study was guided by the following objectives: to establish the association between CIN with age, gender, BMI, serum albumin levels as well as blood haemoglobin among patients undergoing chemotherapy for haematological malignancies. The study also provided an opportunity to evaluate any possible association between co-morbidities with prevalence of CIN among these patients.

METHODS

Study design and sample size The study used a retrospective, cross-sectional, descriptive design to describe CIN associated factors among 245 patients with haematological malignancies who were undergoing chemotherapy treatment at Dr George Mukhari Academic Hospital (DGMAH). The health facility responsible for the treatment of these patients is a "quaternary" level institution located at approximately 30 km to the north of the city of Pretoria, South Africa. All participants were confirmed cases of haematological malignancy using relevant laboratory methods: biopsy, cytogenetics and other laboratory parameters as determined by the malignant type. Medical records of patients treated between 1st January 2010 and 31st December 2012 were included in the study. The sample size of 278 patients was calculated based on previous reported CIN prevalence range of 12% and 23% among hospitalized patients [6, 10], 90% power of the study and an alpha error limit of 0.05. The number was later scaled down to 245, corresponding to 88.1% retrieval of records because 26 (11.9%) attrition cases were excluded as a result of illegible

entries and/or insufficient information as well as inappropriate diagnosis.

Eligibility criteria For this study, medical records of all patients who received treatment at the haematology clinic, based on the eligibility criteria including: those who started new chemotherapies, those with proven cancers using recommended laboratory methods and parameters, those above 18 years of age and cases with no previous chemotherapy and/or radiotherapy for any other malignancy. Patients would have had absolute neutrophil count below 2.0 x 10^9/l; patients had been treated with appropriate as well as standard chemotherapy regimen. Cases excluded were records of patients with non-haematological cancers, cases with past chemotherapy or radiotherapy treatment or absolute neutrophil count greater than 2.0 x 10^9/l and records of patients on non-standardized treatment including salvage regimens.

Data collection methods and research instrument Data collection was done using pre-determined patient data collection form containing variables relevant for the study objectives. Cases with neutropenia and its severity were graded based on European Society for Medical Oncology (ESMO) as well as Common Toxicity Criteria of the National Cancer Institute [12]. Notably, those parameters that were missing in the patients records were considered as an omission rather than a negative finding. The data collection form was pre-tested for completeness of the desired information and to ensure that there was no ambiguity in the research variables using five patients' files which were selected based on study criteria. The pilot was followed with correction of the data collection form to ensure necessary wording and contents. The files that were used in the pilot study to clarify any potential data collection errors were excluded from the final study analysis. The data collected were age, gender, weight, height, body surface area (BSA), body mass index (BMI), types of haematological malignancy, FBC and serum albumin concentration and patients' co-morbidities. The study was approved by the institutional ethics committee of Sefako Makgatho Health Sciences University (Cert. No: SMUREC/M/251/2013: PG).

Data management The data collected was assessed, reviewed for completeness and accuracy and entered into a Statistical Programme for Social Sciences programme (SPSS; Version 21.0) for analysis. Descriptive statistics was used for analysis of means (± standard deviation), proportions, standard deviation as well as significant differences across the grade levels of neutropenia. Percentages were used to describe risk factors associated with CIN in patients with haematological malignancies. Comparisons were done between patient groups with their chemotherapy regimens. Pearson's correlation coefficient was calculated to evaluate association of variables to the occurrence of CIN. The study was tested at 95% confidence level and at significant level ≤ 0.05.

RESULTS

Demographic and physical characteristics of the patients The study evaluated 245 medical records for patients with CIN (i.e. ANC < 2 x 10^9/l). The patients' age ranged from 18 to 87 years with a median of 45 years. The majority (n = 150; 61%) of the patients were above 40 years compared to the least group of 13 (5.1%) patients below the age of 20 years. Out of a total of 245 CIN patients, 52.7% (n= 129) were males and 47.3% (n= 116) were females.

The patients' body surface area (BSA) and body mass index (BMI) as derived from their weights and heights show that the patients' weight distribution ranged from 27.0 to 95.0 kg with a mean (± standard deviation; SD) of 61.0 kg (± 13.1) and the heights ranged from 1.2 to 1.9 metres (m) with an average of 1.62 m (± 0.11 SD). The mean BMI (± SD) and BSA (± SD) for the group were 23.5 kg/m^2 (± 6.0) and 1.65m^2 (± 0.22) respectively (Table 1).

Patients' baseline haematological indices White blood cells (WBC) ranged from 0.2 - 11.2 (x 10^9/l) with a mean of 3.75 ± SD (1.67), haemoglobin was 5.1-19.7 g/l ± SD (2.33), haematocrit was 0.02 - 0.72, a mean of 0.33 ± SD (0.08), platelets; 3 – 1061 (x 10^9/l), mean of 250 ± SD (139), neutrophils; 0.02 - 7.22 x 10^9/l, mean of 1.59 ± SD (0.94), lymphocytes, 0.03 - 5.94 x 10^9/l; mean (1.44) ± SD (1.01) and eosinophils were 0.01-3.39 (x 10^9/l), mean of 0.15 44 ± SD (0.07), (Table 2).

Types of haematological malignancies treated About half of the patients, 115 (46.9%) had Non-

Table 1. Demographic and physical characteristics of the patients

Variables		Range	Median	Mean	Standard deviation
Age (yrs)		18 - 87	45	-	-
Gender:	Males	(n = 128)	(52.7%)	-	-
	Females	(n = 117)	(47.3%)	-	-
Weight (kg)		27.0 – 95.0	-	61.0	13.1
Height (m)		1.2 – 1.9	-	1.62	0.11
BMI (kg/m^2)		10.0 – 51.4	-	23.5	6.0
BSA (m^2)		1.08 – 2.74	-	1.65	0.22

Key: BMI = Body Mass Index; BSA = Body Surface Area

Table 2. Baseline haematological indices

Index	Range	Mean	Standard deviation	Normal value
WBC (x 10^9/L)	0.2 – 11.2	3.75	1.67	4 – 10
Haemoglobin (g/L)	5.1 – 19.7	11.1	2.33	Males: 13 -18; Females: 11 – 16.5
Haematocrit	0.02 – 0.72	0.33	0.08	Males: 0.4 – 0.54; Females: 0.37 - 0.47
Platelets	3.0 – 1061	250	169	150 - 400
Neutrophils (x 10^9/L)	0.02 – 7.22	1.59	0.94	2 – 7.5
Lymphocytes (x 10^9/L)	0.03 – 5.94	1.44	1.01	1.5 – 4.0
Eosinophils (x 10^9/L)	0.01 – 3.39	0.15	0.07	0.04 – 0.4

Hodgkin Lymphoma (NHL), 39 (15.9%) had Multiple-Myeloma (MM), 38 (15.5%) Hodgkin Lymphoma, 17 (6.9%) Chronic Lymphocytic Leukaemia (CLL), 15 (6.1%) Chronic Myeloid Leukaemia (CML), 9 (3.7%) Acute Lymphoblastic Leukaemia (ALL). Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndrome (MDS) had 5 (2%) each; and 2 (0.8%) had Myeloproliferative Neoplasm (MPN)/Polycythemia Rubra Vera (PRV), (Figure 1).

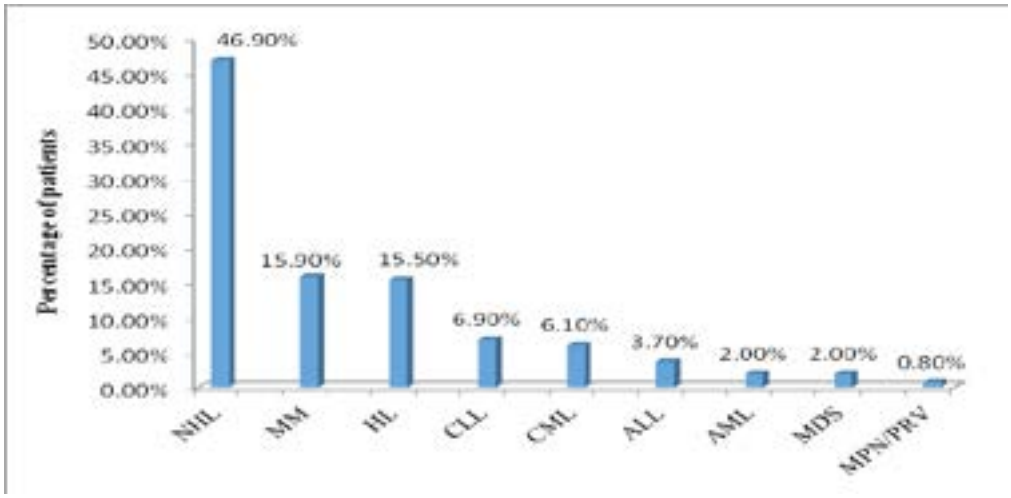
Types of chemotherapy regimens used The study patients received systemic anti-cancer therapy with either palliative or curative intent. Chemotherapeutic regimens administered were (Table 3): CHOP (82; 33.5%), Hyper-CVAD (36; 14.7%), ABVD-P (35; 14.3%), CVAD (19; 7.8%), MP (14; 5.7%), CODOX/IVAC (7; 2.9%), Glivec (6; 4.1%), Chlorambucil and Allopurinol 4 (1.6%), CALGB 8811 regimen 3 (1.2%), 7 + 3 regimen (2; 0.8%) and others (33; 13.5%). For all patients who received conventional cytotoxic chemotherapy, the dose was based on their weight, height and body surface area (Table 3).

Types of co-morbidities among patients There were 32.2% (n = 79) of cancer patients with co-morbidities. The most common co-morbidity was human immunodeficiency virus infection (HIV) found in 28.6% (n=70) as against 3 patients (1.2%) with sepsis, 3 patients (1.2%) diagnosed with tuberculosis, 2 patients (0.8%) had hypertension and only one patient (0.4%) with diabetes mellitus (Table 4).

Association of gender with CIN Patients on CHOP (being the most used chemotherapy regimen) were evaluated for association of CIN with gender. The result showed male to female ratio of between 1.5:1.0 for severe neutropenia; 1.8:1.0 for moderate neutropenia and 1.01:1.0 for mild neutropenia. There were 34.1% (n = 28) male patients with severe neutropenia versus 29.2% (n = 19) females. Male and female patients who had moderate neutropenia were 24.4% (n = 20) and 16.9% (n = 11) respectively. There was virtually no difference in the number of males (34, 41.5%) versus females (35, 53.8%) who had mild neutropenia. Gender differences in the occurrence of neutropenia were not statistically significant across all three severity levels of neutropenia (Table 5).

Association of CIN with patients' physical and laboratory variables The table shows that BMI < 20

Figure 1. Types of malignancies diagnosed



KEY: NHL (Non-Hodgkin lymphoma); MM (Multiple Myeloma); HL (Hodgkin lymphoma); CLL (Chronic Lymphocytic Leukemia); CML (Chronic Myeloid Leukemia); ALL (Acute Lymphoblastic Leukemia); AML (Acute Myeloid Leukemia); MDS (Myelodysplastic syndrome); MPN/PRV (Myeloproliferative neoplasm/Polycythaemia Rubra Vera)

Table 3. Chemotherapy regimens and number of patients treated in the study

Regimen	Number of patients (n = 245)	Percentage
CHOP	82	33.5
Hyper-CVAD	36	14.7
ABVD-P	35	14.3
CVAD	19	7.8
MP	14	5.7
GLIVEC	10	4.1
CODOX/IVAC	7	2.9
CAB	4	1.6
CALGB 8811 regimen	3	1.2
7 + 3 regimen	2	0.8
Others	33	13.5
TOTAL	245	100

KEY: CHOP = Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; CVAD= Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone; Hyper-CVAD= Cycle A (Cyclophosphamide, Vincristine, Adriamycin, Dexamethasone) plus Cycle B (Methotrexate, Leucovorin, Cytarabine); ABVD-P= Adriamycin, Bleomycin, Vincristine, Dacarbazine, Prednisone; CODOX/IVAC= Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide, Cytarabine; MP= Melphalan and Prednisone; 7 + 3 regimen = Cytarabine and Daunorubicin; CAB = Chlorambucil, CALGB 8811= Cyclophosphamide, Daunorubicin, Vincristine and Prednisone plus Methotrexate and Cytarabine

Table 4. Types of co-morbidities among patients

Type of co-morbidity	Number of patients (n = 245)	Percentage
HIV	70	28.6
Sepsis	3	1.2
TB	3	1.2
Hypertension	2	0.8
DM	1	0.4
No co-morbidity	166	67.8

KEY: HIV = Human immunodeficiency virus, TB = Tuberculosis, DM = Diabetes mellitus

Table 5. Association of gender with CIN

	Severity of Neutropenia		
Gender	Severe (%)	Moderate (%)	Mild (%)
Males (n = 128)	44 (34.1)	31 (24.4)	53 (41.5)
Females (n = 117)	34 (29.2)	20 (17.1)	63 (53.8)
p-value	*0.9461*	*0.7854*	*0.1346*

kg/m^2 is significantly associated ($p < 0.05$) with CIN and this is closely related to the weight (<70 kg, $p = 0.0003$) and height (<1.65 metres, $p < 0.0001$) of the patients. Similarly, age of patients older than 60 years was significantly associated with CIN with $p < 0.05$. However, serum albumin, haemoglobin as well as body surface area were not significantly associated with CIN (Table 6).

Hospital admission patterns among the patients revealed that 109 patients (44.5%) did not require hospital admission for neutropenia, 93 (38.0%) had 1 - 2 admissions, 13 (5.3%) required 3 - 4 admissions and 4 patients (1.6%) in the series were admitted for more than five times.

Table 6. Association of CIN with patients' physical and laboratory variables

	CHOP		Hyper-CVAD		ABVAD		CVAD	
Variables	*R*	*P*	*R*	*P*	*R*	*P*	*R*	*P*
Weight (kg); > 70 vs < 70	0.6852	0.0003	0.1836	0.0394	0.1152	0.2021	0.0314	0.9997
Height (m); > 1.65 vs < 1.65	0.7328	<0.0001	0.0308	0.9996	0.7681	<0.0001	0.7825	<0.0001
BMI (kg/m^2); > 20 vs < 20	0.7421	<0.0001	0.6708	<0.001	0.4428	<0.001	0.0642	0.6939
BSA (m^2); > 1.5 vs < 1.5	0.1195	0.1167	0.6154	0.0023	0.1828	0.0219	0.0217	0.9996
Age (yrs); > 60 vs < 60	0.4286	<0.0001	NTF		NTF		NTF	
Albumin; > 3.5 vs < 3.5	0.1741	0.0249	0.0762	0.5187	0.0629	0.5997	0.0485	0.7663
Haemoglobin (g/l); > 12.0 vs < 12.0	0.1188	0.1274	0.1684	0.1515	0.0291	0.8083	0.0352	0.8293

KEY: *R* = Correlation Coefficient of association; Probability (*P)* of an association between a study variable: p-value < 0.05 represents significant association; BMI = Body Mass Index;BSA = Body Surface Area; Hb = Haemoglobin; NTF = Number too Few.

DISCUSSION

This study investigated the various factors associated with occurrence of neutropenia in patients on chemotherapy for treatment of haematological malignancies at DGMAH. The results found that although the patients' age ranged from 18 to 87 years, majority of the patients were over the age of 40 years. This is consistent with the findings by Hasan et al [13] who had reported that the incidence of neutropenia was higher among patients who were 50 – 59 years. The present study also found that there were more male patients (52.7%; n = 128) as compared with females (47.3%; n = 117). The gender differences in incidence of CIN were also reflected in the pattern of severity, in which male patients were more prone to have severe neutropenia. However, this finding is inconsistent with a previous report by Lyman and Delgado [14] which had shown that female gender was at higher risk of hospitalization for CIN than the male gender. The gender effect was again emphasized in the study by Lyman and Wilmot [15] who reported that female gender is a risk factor that plays a role in the development or occurrence of neutropenia and febrile neutropenia (FN). However, their study did not show significant association between female gender and severity of neutropenia an observation which was attributed to the small sample size of that particular study.

In a different study by Nakagawa et al [16], the investigators reported that the risk of febrile neutropenia remained significantly associated with a number of risk factors: age ≥ 65 years, (Hazard Ratio = 1.65; 95% CI: 1.18 – 2.32), renal disease (HR =

1.91; 95% CI: 1.10 – 3.30), cardiovascular disease (HR = 1.54, 95% CI: 1.02 – 2.33) and baseline haemoglobin < 12 g/dl. (HR = 1.44, 95% CI: 1.04 – 2.0) [15]. It is in the face of such evidence that the authors advocated the need for frequent monitoring of patients with haematological malignancies and co-morbidities when undergoing chemotherapy.

The most common haematological malignancy found in the present study was non-Hodgkin lymphoma which was reported in 115 patients (46.9%), followed by Multiple-Myeloma (39 patients; 15.9%), Hodgkin lymphoma (38 patients; 15.5%), chronic lymphocytic leukaemia (17 patients; 6.9%) and chronic myeloid leukaemia (6.1%). In addition, the finding in this study of human immunodeficiency virus (HIV) being the most common co-morbid infection is not surprising, considering the state of the HIV pandemic in Southern Africa. Nevertheless, the predominant nature of HIV co-morbidity is at variance with the work of Lyman and Delgado [14] who in their study found a strong association between hepatic disease and increased risk of hospitalization for febrile neutropenia.

The patients' weight distribution ranged between 27.0 to 95.0 kg while the height ranged from 1.2 – 1.9 metres. The mean body mass index (BMI) and body surface area (BSA) for the group were 23.5 kg/m² and 1.65 m² respectively. All the chemotherapy regimens used (CHOP, Hyper-CVAD and ABVD-P), except one (CVAD) were significantly associated with BMI in terms of comparison between > 20 kg/m² and < 20 kg/m² ($p < 0.001$). This suggests that BMI < 20 kg/m² is significantly associated with occurrence of neutropenia when patients were on chemotherapy for haematological malignancy. This finding is in agreement with previous reports that low BMI or low BSA increases the risk of CIN or CIN-related hospitalization [15, 16]. Although Pettengell et al [17] reported that bigger weight was protective against developing CIN in the first cycle of chemotherapy. This phenomenon is most likely reflected as reductions in the delivered dose intensity associated with dose capping or the use of idealized body weight in dose calculations.

CONCLUSION

The occurrence of neutropenia among patients treated with chemotherapy for haematological malignancies is influenced by various factors, including age, weight, co-morbid conditions such as HIV and TB as well as the level of haemoglobin. Although haematological malignancies can be managed by the use of chemotherapy, this study found that some agents are associated with higher incidence of neutropenia, as in the case of CHOP and Hyper-CVAD. This highlights the need for close monitoring of patients with haematological malignancies and co-morbidities while on treatment with chemotherapy. However, this study was limited by inadequate number of patients who were treated with a variety of other chemotherapy regimens and the degree of their effects in association with CIN.

FOOTNOTES

Conflict of interest: The authors declare no competing conflicts of interest.

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