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Full length Research Paper

Prevalence of Neutropenia among Patients with Solid Tumors undergoing Chemotherapy at Moi Teaching and Referral Hospital, Kenya

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Abstract
Chemotherapy-induced neutropenia (CIN) is among the most common serious adverse effects of chemotherapy. At times it can be complicated by febrile neutropenia. The risk of neutropenic infections may be threat and challenge to cancer patients undergoing chemotherapy as they have also to cope with the cancer as a disease too. Neutropenia is life threatening and should be addressed as medical emergency. The cancer patients with chemotherapy-induced neutropenia often suffer from Fever and infection. Moi Teaching Referral Hospital (MTRH) serves great number of cancer patients from North Rift, South Rift, Western and Nyanza. The patients with solid tumors are managed on chemotherapy and neutropenia is a major side effect occurring to these patients .Effects of neutronenia leads to change in chemotherapy management causing poor patient outcome. The objective of the study was to examine the prevalence of neutropenia among patients with solid tumors undergoing chemotherapy at MTRH. The study was carried out at MTRH in Eldoret. This was a retrospective study. The total numbers of patient with solid tumors on chemotherapy treatment between the periods of January 2014 to December 2015 were approximately 1100. Purposive sampling was used to select the target population and systematic random sampling was used to select the sample size of 314 files. Subjects included patients of age 18 years and above with a confirmed diagnosis of solid tumors and underwent chemotherapy at the facility. Data was collected from patients' records. SPSS version 20 statistical tool was used to enter the data. Data was analyzed using descriptive statistics. The prevalence of neutropenia was 10.5%. 2.1% of the patients developed neutropenic fever. The study concluded that the prevalence of neutropenia can be reduced further by developing guidelines on how to identify the high risk patients and administration of granulocyte colony stimulating factor as a prophylactic measure..

Keywords: *chemotherapy, solid tumors, neutropenia*

Introduction

According to literature neutrophils belong to the group of cells in phagocyte system and represent the first cellular components of the inflammatory response. They form a key component of innate immunity (Poele *et al* 2009). Reduced neutrophils level below the normal ranges is termed as neutropenia. The Common Toxicity Criteria of the National Cancer Institute established a scale of four grades for neutropenia. Grade 1 is mild while grade 4 is most severe. Grade 1, Absolute neutrophils count (ANC) $\geq$1.5 to <2x10^3/l; grade 2, ANC $\geq$1.0 to <1.5x10^3/l; grade 3, ANC $\geq$0.5 to <1x10^3/l; grade 4, ANC <0.5x10^3/l (Bhavik *et al* 2012)It has been noted that, chemotherapy-induced neutropenia (CIN) is among the most common serious adverse effects of chemotherapy and can be complicated by febrile neutropenia (Moreau 2009). Aapro*et al*, 2010 states that febrile neutropenia (FN) is associated with decreased quality-of-life and increased treatment expenses which may result in delay or reduction of chemotherapy doses hence interfering with the cure rates. A study done in Germany came with a conclusion that granulocyte colony stimulating factor (G-CSF) was safe and effective when administered for the prevention of chemotherapy induced neutropenia (Kurbacher*et al* 2015). More importantly, use of G-CSFs in patients undergoing chemotherapy can reduce the need for clinicians to postpone chemotherapy cycles or reduce the doses. The updates from European organization for research and treatment of cancer (EORTC) guidelines on the use of G-CSF in chemotherapy patients support the recommendations of the American Society of Clinical Oncology (ASCO) that prophylactic use of G-CSF should be reserved for high-risk patients (Aapro *et al*, 2011) At Moi teaching and referral hospital (MTRH) majority of the patients undergo chemotherapy with various regimen depending on the type of cancer. The likely side effect they face is neutropenia

which may lead to febrile neutropenia. This is life threatening condition requiring emergency oncology attention (Szwajer*et al*., 2011). Neutropenia can be managed or prevented by use of G-CSFs as a treatment or prophylaxis preventive measure (Bosly*et al*, 2007).

Studies show that severe neutropenia and febrile neutropenic events are major causes of adjustment in chemotherapy regimen or even postponement of the therapy. These changes in the therapy influence the outcome of the patient survival. (Pettengell*et al*., 2008). In a study done by Derek *et al (*2015) febrile neutropenia remains a common event among patients receiving myelosuppressive chemotherapy regimen. This result in admissions of affected patients in the hospitals and some of the patients even die. To add on neutropenia, and more so febrile neutropenia, lead to deterioration in quality of life hence causing increase in morbidity and mortality (Hughes *et al.* 2002). Lyman *et al. (*2003) also added that, in days to come, chemotherapy-induced neutropenia will become a bigger burden because of the increase in number of the elderly populations especially in the developed countries. These will lead to a higher prevalence of solid tumors and other types of cancer and hence an increase in the age-related risk of chemotherapy-induced neutropenia. The reported incidence and prevalence of neutropenia differ widely. According to Caggiano*et al.*(2005) one of the most reliable estimates documented in the literature suggests an incidence of 7.83% of cancer patients' hospitalized with neutropenia. A study done in Spain on patients with breast cancer and lymphoma showed that, the incidence of chemotherapy induced neutropenia grade 3 and 4 was 11%. Among these 11 %, 4.3 % developed febrile neutropenia (Jolis*et al* 2013). However, neutropenia has been observed in 6–50% of patients, depending on the type of cancer, the stage of the cancer, patient functional status and the type of chemotherapy regimen (Smith *et al.* 2006). Another study done in the USA, reported that inpatient that died of grades 3 and 4 neutropenia ranged from 3.4% to 10.5%, with an overall mortality ranging from 6.8% to 9.5% (Kuderer*et al.* 2006).

According to Lyman *et al*., (2010), when patients develop febrile neutropenia, they are likely to face serious negative outcomes which may lead to them being hospitalized. Febrile neutropenia, as well as severe or prolonged neutropenia, also can interfere with the planned delivery of treatment and adversely affect important patient outcomes and survival.

In a study done of 2131 patients, 401 experienced a total of 458 febrile neutropenia episodes. Risk of febrile neutropenia during the chemotherapy regimen course was 16.8%. In cycle 1 alone, risk of febrile neutropenia was 8.1%. The study also found out that, 25% of patients treated with chemotherapy are likely to develop febrile neutropenic events. This percentage could increase up to 96% in some particular type of tumors (Bhavik*et al* 2012). In another prospective study done in Iran by Gharhramanfard *et al*(2013), it showed that 3.6 % of the patients had severe neutropenia of grade three and four following chemotherapy administration. A study by Hashiguchi *et al* 2015 revealed that, chemotherapy-induced neutropenia occurred in 50.5% of patients over 23.4% of chemotherapy cycles. This is an indication that, reported incidence of chemotherapy-induced neutropenia differ widely. The current study aimed at identifying the prevalence of chemotherapy induced neutropenia at MTRH, a knowledge information gap which the current study endeavored to fill.

Materials and Methods

Study site

Haemato- Oncology centre at Moi Teaching and Referral Hospital (MTRH) Eldoret which islocated along Nandi road in Eldoret town 310 km Northwest of Nairobi city, UasinGishu County, in the North rift region of western Kenya

Study design

This was a retrospective study. Data was obtained from files of patients with solid tumors and have undergone chemotherapy at the site for the past two years.

Study population

Patients of age 18 years and above with a confirmed diagnosis of solid tumors, clients who presented with normal neutrophils count before commencement of chemotherapy and had undergone chemotherapy at the site. These patients underwent chemotherapy between the periods of January 2014 to December 2015.

Inclusion and Exclusion criteria

Inclusion criteria

- Patients with histological confirmed diagnosis of solid tumor
- Adult participants (age 18 or older, without upper age limit) who had started chemotherapy
- Patients with neutrophils level above 1.0×10^3/l before commencement of chemotherapy

Exclusion Criteria

- Neutropenia before commencement of chemotherapy
- Active infection within 72 hour prior to start of chemotherapy
- Malignant conditions with myeloid characteristics
- Patients on combined treatment modalities (chemotherapy and radiation)

Sampling method

The sample size of 314 files was determined using Fisher's method 2003. All the files of patients with solid tumors, aged 18 years and above and underwent chemotherapy were identified using purposive sampling from the data base software at the oncology clinic.

From the selected files systematic sampling was applied to obtain the sample size of 314 files from the target population by selecting every n^{th} file. The target population for the 2 years was approximately 1100. The n^{th} value was every third file which was obtained by dividing the target population by the sample population.

Data collection

A self-formulated transcription form with variables was used to obtain the required information. Variables included demographic data, types of solid tumors, chemotherapy regimen, laboratory results and granulocyte colony stimulating factor. Key informant interview guide was used to obtain information from the heads of department. One research assistant was trained on data collection procedure using the transcription form with variables. A list of patients above 18 years and had solid tumors from the period of January 2014 to December 2015 was extracted from the data base software using purposive sampling. Systematic sampling was used to get the 314 files from the extracted files by picking every n^{th} file. Using a self-formulated transcription form with variables, the required information was retrieved from the patients' files. All study files had a unique identification number that was recorded on the transcription form.

Data management and analysis

Collected data from the study was thoroughly checked and validated for accuracy and completeness. The data was stored in electronic formats and hard copies. Data collecting tools were kept in lockable cabinets that had authorized access. It was only directly accessible only to the investigators.Data from the tool was coded, cleaned and entered into a computer software; Statistical Package for Social Science (SPSS) version 20. Descriptive statistics was used to determine the prevalence of neutropenia,

Ethical consideration

The study was conducted after academic approval by the school of graduates, institutional Research and Ethics committee of MasindeMuliro University of Science and Technology and Moi University. Permission to carry out the study was obtained from the hospital and at the Oncology centre before data collection process began.. Patients' files were handled safely and with confidentiality throughout the study. Only the authorized personnel were allowed to handle the files to be used in the study. Results obtained from this study were kept safely and handled with confidentiality.

Results

The study sought to determine the prevalence of neutropenia among cancer patients with solid tumors undergoing chemotherapy at the clinic; the study results were as follows;

Absolute neutrophil count at First and Second Cycle

The study results on the levels of ANC in the first cycle revealed that 2.8% had between 0.0-0.3; 1.1% had between 0.31-70; 2.5% had between 0.71-1.0 while 90.2% had greater than 1.0. The study results on the levels of ANC in the second cycle revealed that 0.7% had between 0.0-0.3; 3.5% had between 0.31-70; 3.9% had between 0.71-1.0 while 74.7% had greater than 1. (table 1 below)

Table 1. Absolute neutrophil count at First and Second Cycle

First cycle	Frequency	Percent
0.0-0.3	7	2.8
0.31-0.7	2	1.1
0.71-1.0	6	2.5
Greater than 1	285	90.2
Missing	11	3.5
Total	**314**	**100**
Second cycle	**Frequency**	**Percent**
0.0-0.3	1	0.7
0.31-0.7	9	3.5
0.71-1.0	8	3.9
Greater than 1	242	74.7
Missing	54	17.2
Total	**314**	**100**

State of Neutropenia among patients with solid tumors undergoing chemotherapy

The study results revealed that 3.8% had mild neutropenia 0.6% had moderate neutropenia and 6.1% had severe neutropenia. The total number of patients who developed neutropenia was 10.5%. (Table 2 below)

Table 2. State of Neutropenia among patients with solid tumors undergoing chemotherapy

Mild Neutropenia	**Frequency**	**Percent**
Yes	12	3.8
No	302	96.2
Total	**314**	**100**
Moderate Neutropenia	**Frequency**	**Percent**
Yes	2	0.6
No	312	99.4
Total	**314**	**100**
Severe Neutropenia	**Frequency**	**Percent**
Yes	19	6.1
No	295	94.9
Total	**314**	**100**

Prevalence of Neutropenia among Patients with solid tumors undergoing chemotherapy

The study results on the neutropenia indicated that 10.5% of the patients had neutropenia while 89.5% had no neutropenia. This shows that most of the patients had no neutropenia. As regards the view of the key informants, all of them (4 of 4) agreed that patients with solid tumors undergoing chemotherapy at oncology center in MTRH develop neutropenia. Most of them agreed that neutropenia among patients with solid tumors undergoing chemotherapy at the oncology centre is a common problem. (Table 3 below)

Table 3. Prevalence of Neutropenia

Neutropenia	**Frequency**	**Percent**
Yes	33	10.5
No	281	89.5
Total	314	100

A total of 2.1% of the patients developed neutropenic fever. These were among the 10.5% of the patients who developed neutropenia. This indicates that 2.1% of the patients with low absolute neutrophils count developed infection (Table 4 below)

Patients who developed neutropenic fever following low neutrophils count

Table 4. Patients who developed neutropenic fever

Neutropenic Fever	**Frequency**	**Percent**
Yes	7	2.1
No	307	97.9
Total	**314**	**100**

Discussion

From the study results the prevalence of neutropenia was10.5% .The current study compared well with another one done in Spain on patients with breast cancer and lymphoma, which indicated prevalence of 11% whereby 4.3% were found to develop febrile neutropenia. (Jolis *et al* 2013). From the current study findings, the patients who developed severe neutropenia were 6.1%, moderate were 0.6% and mild were 3.8%. 2.1% developed febrile neutropenia which was slightly low as compared to those who developed febrile neutropenia in the previous study by Jolis *et al* 2013. Another study done in Iran by Ghahramanfard *et al* (2013) reported a prevalence of severe neutropenia which was 3.6 %. This value was almost in line with the findings from the current study was 3.8% of the patients developed severe neutropenia. The study showed that most of the patients had no neutropenia. The study results further revealed that the (absolute neutrophil count) ANC levels both in the first and the second cycle were more than 1000cells/µl. This implies that, the prevalence of neutropenia was considered low. Neutropenia is defined as a decrease in the absolute neutrophil count (ANC) .This is supported by Lyman *et al. (*2003) previous studies which showed that neutropenia generally occurs in one out of three patients treated with chemotherapy. Study done in the USA, reported inpatient mortality rates associated with grades 3 and 4 neutropenia range from 3.4% to 10.5%, with an overall mortality ranging from 6.8% to 9.5% (Kuderer *et al.* 2006). This is also in line

with the current study were the prevalence is 10.5%.When patients with neutropenia develop fever, there are at high risk developing infection and serious consequences leading to hospitalization. Febrile neutropenia, as well as severe neutropenia, also can interfere with the planned delivery of treatment and adversely affect the expected patient outcomes (Lyman *et al*., 2010). In the current study 23.5% of the clients had their treatment delayed while 17.2% dropped the therapy .7% of the patients had their treatment regimen revised. This is in line with Layman *et al*(2010) who found out that neutropenia and febrile neutropenia interfere with chemotherapy administration and hence poor patient outcome. In a study done of 2131 patients, 401 experienced a total of 458 febrile neutropenia episodes. Risk of febrile neutropenia during the chemotherapy regimen course was 16.8%. The study also found out that, up to 25% of patients treated with chemotherapy are likely to develop a FN episode although this percentage could increase up to 96% in some particular type of tumors (Bhavik*et al* 2012). In the current study, the prevalence of febrile neutropenia was 2.1%. This is much less as compared to 8.1% in the above study by Bhavik.According to the key informants, on the rate of chemotherapy induced neutropenia at the centre, most of the key informants (3 of 4) noted that the rate of chemotherapy was low while 1 of 4 noted that the rate of chemotherapy was moderate. The study findings on the prevalence of chemotherapy induced neutropenia at Moi teaching and referral hospital (MTRH) is almost similar to most of the studies done on prevalence of neutropenia in other countries.

Conclusion and Recommendations

The prevalence of neutropenia from the current study was found to be 10.5% and this was similar to other studies by Jolis *et al 2013*. However, some of the earlier findings by other researchers like smith *et al* 2006 found prevalence of 6 to 50%. Therefore, in conclusion study established that prevalence of neutropenia at MTRH was low when compared to other study findings with prevalence of upto 50%. However the prevalence of neutropenia should be brought to a lower percentage of less than 10.5 % in the current practice. This can be achieved by developing guidelines and policies on ways to identify high risk patients, reducing the risks, and administration of granulocyte colony stimulating factor (GCSF) early on time as a prophylactic measure.

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