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Frequency of Chemotherapy Induced Febrile Neutropenia: A Tertiary Care Hospital Study

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Abstract: Febrile neutropenia (FN) is a serious complication of cancer chemotherapy that can lead to treatment delay as well as reducing chemotherapy dose, compromising treatment efficacy. This study determines the frequency of chemotherapy-induced febrile neutropenia. A cross-sectional study was conducted at the oncology unit of Hayatabad Medical Complex, Peshawar from July, 11 -2020 to December-11-2020. A total of 202 patients with solid organ or hematological malignancy were included in the study and assessed for chemotherapy-induced neutropenia. The patient's average age was 22.4 + 11.3 years. Males comprise 67.3 percent of the study population, while females were 32.7 percent respectively. The average number of follow-up visits was 7.3 + 2.6. The majority of the patients (51%) were given a treatment regimen with a moderate risk of neutropenia. Hematological malignancies affected 76.2 percent of the patients. In 33.7 percent of patients, febrile neutropenia was found. Febrile neutropenia is a common problem in our local population with subjected to chemotherapy for solid organ or hematological malignancy and is significantly common in patients with a high risk of a chemotherapy regime.

Keywords: Absolute neutrophil count, Chemotherapy, Febrile neutropenia, hematological malignancy.

INTRODUCTION

Febrile neutropenia (FN) is a significant side effect of cancer chemotherapy that can cause treatment delays and require dose reductions, compromising treatment efficacy (Klastersky *et al.,* 2016). Approximately 1% of cancer patients receiving chemotherapy develop FN, which increases morbidity and mortality and places a significant burden on healthcare resources for the treatment of this population (Freifeld *et al.,* 2011).

Neutropenia is defined as a reduction in neutrophil counts below normal levels that occurs within 7 to 12 days after cancer chemotherapy (Llamas *et al.,* 2019). A blood test diagnose it by an absolute neutrophil count (ANC) of less than 500 cells per microliter following cytotoxic treatment, or an ANC likely to fall below 500 cells per microliter within 48 hours (Mehta *et al.,* 2015). Patients with neutropenia may have a diminished ability to fight infections due to low neutrophil numbers in the blood (Zecha *et al.,* 2019). As a result, even a mild infection in neutropenic patients might turn deadly. It's critical to keep an eye on patients for signs and symptoms of infection, such as fever, chills, or sweating (Callen & Kessler, 2019).

Neutropenia is sometimes accompanied by a fever caused by an illness. In patients with chemotherapy-induced neutropenia, fever may be the only sign of an underlying infection; other signs and symptoms of inflammation may be missing (Goldsmith *et al.,* 2018). As a result, patients with neutropenia must be evaluated for the risk of serious infection as soon as they come with a fever. An oral temperature more than 101ºF in a single reading, or an oral temperature of at least 100.4ºF sustained over a 1-hour period, or reported from two consecutive readings in a two-hour period, is considered FN (Wang & Chan, 2017).

The severity of neutropenia (which directly influences the incidence of FN) and the degree of chemotherapy have a strong association. Currently, the various regimens are characterized as having a high risk of FN (> 20%), an intermediate risk (10% -20%), or a low risk (10%) of FN (Rasmy *et al.,* 2017). Chemotherapy-induced neutropenia was found in 147 (50.5%) of patients during 378 (23.4%) chemotherapy rounds in one research. Over the course of 25 (1.5%) cycles, febrile neutropenia occurred in 20 (6.9%) patients (Hashiguchi *et al.,* 2015). Another study found that FN episodes were more common in patients with solid tumors (57 percent) than in those with hematological malignancies, and that they were more closely linked to Gram-negative bacteria infections (56.25 %). However, there was no substantial difference in morality between the two categories of patients (14% vs. 12.5%) (Rasmy *et al.,* 2016).

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The present study is designed to determine the frequency of chemotherapy induced FN in patients receiving cancer chemotherapy at this part of world. The idea behind doing this study came into our mind by doing through literature search and observing the FN being the most common and most neglected problem in cancer chemotherapy patients. Moreover, the exact burden of FN is not known in our population due to lack of local evidence and if not treated in time, it has adverse consequences in addition to other effects of chemotherapy itself. This study quantifies local magnitude of the problem and provides direction for future research and policy recommendations for the control of FN with chemotherapy.

MATERIAL AND METHODS

A cross sectional study was conducted at Oncology Department, Hayatabad Medical Complex, Peshawar from July, 11 -2020 to December-11-2020. Sample size was 202 keeping in view 6.9%10 proportion of chemotherapy induced FN, 95% confidence level and 3.5% absolute precision. All patients were selected using non probability consecutive sampling technique. Inclusion criteria was all newly diagnosed patients of any type of cancer scheduled for chemotherapy including both gender having Age group between 5 to 50 years. Patients presenting with sudden onset of fever of more than $99^{O}F$ were also included in the study. Those having chronic liver disease diagnosed by history and medical records or History of blood transfusions in the last three months and History of any type of bleeding of any amount in the last three months were excluded from the study.

The study was conducted after approval from hospitals ethical and research committee. All patients of cancer (any type, newly diagnosed and scheduled for chemotherapy) was included in the study through oncology Out Patient Department. The purpose and benefits of the study was explained to all patients and a written informed consent was obtained.

All patients was subjected to detailed history, followed by complete routine examination and baseline investigations was done which include complete blood picture. All patients were subjected to standard chemotherapy as prescribed by the consultant oncologist of the war. All patients were followed till 5th day of start of therapy. Patients representing with fever was checked for the ANC to confirm the presence or absence of FN. All the above mentioned information including name, age and gender was recorded in a pre-designed Proforma. Strictly exclusion criteria was followed to control confounders and bias in the study results.

The collected data was stored and analyzed in SPSS version 20 for windows. Mean $\pm$ SD was calculated for numerical variables like age, ANC count at follow up visit. Frequencies and percentages was calculated for categorical variables like gender, type of cancer (solid organ or hematological), chemotherapy regime and FN. FN be stratified among age, gender, type of cancer, and chemotherapy regime to see the effect modifications using chi square test keeping p value of ≤ 0.05 as significant. All results were presented in the form of tables and graphs.

RESULTS

The study was conducted on 202 patients subjected to chemotherapy for hematological or solid organ malignancies. The mean age of the sample was 22.4 + 11.3 years. We categorize the age in three different categories (Table1).

Table 1. Age-Wise Distribution and Frequency of Febrile Neutropenia Patients (n=202)

Age-wise distribution* Febrile Neutropenia		**Febrile Neutropenia**		**P value**
		Yes	**No**	
Age Groups	**5-19 years**	37	57	0.273
		39.4%	60.6%	
	> 19-32 years	16	38	
		29.6%	70.4%	
	> 32-44 years	15	39	
		27.8%	72.2%	
Total		68	134	
		33.7%	66.3%	

While distributing the patients with regards to gender, we observed that in our study 67.3% of the sample was male and 32.7% were female gender. (Table 2) We stratified febrile neutropenia with regards to age, gender, follow up visit, type of chemotherapy regime and type of tumor.

***Corresponding Author:** Shehryar Ahmad

Table 2. Gender -wise Distribution of Patients (n=202)

Gender	Frequency	Percent
Male	136	67.3
Female	66	32.7
Total	202	100.0

Table 3. Type of Malignancy

Type of Malignant Tumor	Frequency	Percent
Solid organ	48	23.8
Hematological	154	76.2
Total	202	100.0

Table 4. Febrile Neutropenia Cases * Type of Malignancy

Febrile Neutropenia Cases* Malignancy		Febrile Neutropenia		P value
		Yes	No	
Type of tumor	Solid organ	20	28	0.179
		41.7%	58.3%	
	Hematological	48	106	
		31.2%	68.8%	
Total			134	
			66.3%	

The mean follow up visit was 7.3 + 2.6. See table 5 for categories of follow up visit. Most of the patients 51% were subjected to intermediate risk of neutropenia regime of chemotherapy (Table 7). 76.2% of patients were having hematological malignancies (table 4). Febrile neutropenia was recorded in 33.7% of patients (table 4).

Table 5. Follow Up visit and Frequency of Febrile Neutropenia

Follow up visit* Febrile Neutropenia		Febrile Neutropenia		P value
		Yes	No	
Follow up visit	3-6th	29	50	0.534
		36.7%	63.3%	
	> 6-9th	20	50	
		28.6%	71.4%	
	> 9-12th	19	34	
		35.8%	64.2%	
Total		68	134	
		33.7%	66.3%	

Table 6. Age Group Wise Stratification of Neutropenia

Stratification of Neutropenia with Age		Febrile Neutropenia		P value
		Yes	No	
Age Groups	5-19 years	37	57	0.273
		39.4%	60.6%	
	> 19-32 years	16	38	
		29.6%	70.4%	
	> 32-44 years	15	39	
		27.8%	72.2%	
Total		68	134	
		33.7%	66.3%	

***Corresponding Author:** Shehryar Ahmad

Table 7. Febrile Neutropenia* Chemotherapy regime

Chemotherapy regime wise stratification of Neutropenia		**Febrile Neutropenia**		**P value**
		Yes	No	
Chemotherapy regime	**High risk**	35	26	< 0.001
		57.4%	42.6%	
	Intermediate risk	28	75	
		27.2%	72.8%	
	Low risk	5	33	
		13.2%	86.8%	
Total		68	134	
		33.7%	66.3%	

DISCUSSION

As outpatient chemotherapy becomes more common, chemotherapy-induced neutropenia may become a bigger issue in the safe administration of chemotherapy. Neutropenia caused by chemotherapy is a well-known source of anxiety for both doctors and patients. Neutropenia caused by febrile neutropenia is a major clinical condition. (Lyman *et al.,* 1998; & Crawford *et al.,* 2011). G-CSFs are frequently given to cancer patients to prevent such complications. The ASCO recommendations update 2006, the EORTC guideline 2010, and the NCCN guideline update 2011 are all international guidelines for the usage of G-CSF (Smith *et al.,* 2006; & Crawford *et al.,* 2011). Although the clinical benefits of G-CSF treatment are evident in particular chemotherapy, with a threshold rate of febrile neutropenia of 20%, the clinical benefits of G-CSF use are evident in specific chemotherapy, with a threshold rate of febrile neutropenia of 20%. The identification of febrile neutropenia risk factors may be critical for the safe management of chemotherapy-induced neutropenia without the use of G-CSFs.

Chemotherapy-induced neutropenia was seen in 33.7 percent of the individuals in our research. Chemotherapy-induced neutropenia has a wide range of reported incidences. Chemotherapy-induced neutropenia was observed in 6–50% of patients by Lyman *et al.* (1998), depending on the cancer type, illness stage, patient functional state, and chemotherapy treatment. Treatment-induced neutropenia was found in 43 percent of women with ovarian cancer after first chemotherapy, according to Laskey *et al.* (2011)

Shama *et al.* (2006) found febrile neutropenia in 12% of epithelial ovarian cancer patients receiving first-line adjuvant treatment, indicating that the rate of febrile neutropenia was higher than previously reported. During initial treatment, febrile neutropenia was described in 7% of patients with ovarian cancer by Laskey *et al.* (2011). Feverish neutropenia was reported often in early cycles, especially after cycle 1.

Several studies found that increasing age was an independent predictor of febrile neutropenia development (Lyman *et al.,* 1998; & Crawford *et al.,* 2004). In patients with solid tumors, 50 percent of all cases of febrile neutropenia occurred at or near the start of chemotherapy sessions (cycles 1 and 2), as reported by Okera *et al.* (2011). According to Shama *et al.* (2006), 60 percent of febrile neutropenia occurrences in patients undergoing first-line adjuvant treatment for epithelial ovarian cancer occurred after cycle 1. Poor performance status was not clearly mentioned as a risk factor for febrile neutropenia in G-CSF guidelines such as the ASCO recommendations update 2006, the EORTC guideline 2010, and the NCCN guideline update 2011 (Lyman *et al.,* 1998; & Okera *et al.,* 2011).

Patients' demographics (age, gender, and comorbidities), cancer kinds, stages, and chemotherapy regimen characteristics significantly influence the development of myelosuppression during chemotherapy. Chemotherapy-induced febrile neutropenia (CIFN) was shown to be more common in people over the age of 32. In a study by Catic *et al.* (2016) the age range 41–60 years was found to have a greater incidence of CIFN (48 percent) among 27 CIFN patients. The findings of this study are consistent with those of Catic *et al.* (2016), who found a greater incidence of CIFN in adults.

Sammut & Mazhar (2012) evaluated 32 CIFN patients, 62.5 percent of which were female and 37.5 percent of which were male. The current investigation was comparable to the previous one. Solid tumours had a greater incidence of CIFN than hematological cancers in this investigation. Solid tumours accounted for 71.5 percent of 396 CIFN events in a research by Ahn *et al.* (2011), whereas hematological malignancies accounted for 28.5 percent. As a result, this research backs up a recent study that found solid tumours to have a greater rate of CIFN events.

In a research by Hashiguchi *et al.* (2015) the most prevalent treatment among 291 patients was paclitaxel and carboplatin (double regimen), which was used in 50.5 percent of CIFN cases (Hashiguchi *et al.,* 2015). The median length of stay for patients with CIFN was 8.14 days, according to a research conducted by Weycker *et al.* (2015). Culakova *et al.* found 9.7% of CIFN in cycle 1, then 5.7 percent and 3.8 percent in cycles 2 and 3, respectively (Culakova *et al.,* 2015).

***Corresponding Author:** Shehryar Ahmad

According to the chemotherapeutic index score for CIFN risk among the patients (n = 202), 30.2 percent were at high risk, 51 percent were at intermediate risk, and 18.8 percent were at low risk. 57.4 percent of high-risk patients developed CIFN, while 13.2 percent of low-risk patients developed CIFN (p 0.001), indicating a clear link between the risk of developing CIFN and the risk of developing CIFN. Ahn *et al.* (2011) found that 90 percent of low-risk patients and 72 percent of high-risk patients used the MASCC risk index score, with 18.9% of high-risk patients dying.

As a result, this study agrees with a recent study in which the MASCC score was used to predict low and high-risk patients. The incidence of CIFN was 33.7 percent in the study, and Shiota *et al.* (2014) conducted a study on 37 patients with a CIFN incidence of 10.8 percent. Talwar *et al.* (2017) conducted a study in which the majority of patients with CIFN were in stages 3 (33.2%) and 4 (16.6%) of cancer.

The severity of neutropenia (which directly influences the incidence of FN) and the degree of chemotherapy have a clear link. Currently, the various regimens are characterised as having a high risk of FN (>20%), an intermediate risk (10% -20%), or a low risk (less than 10%) of FN. Bacteria, fungi, and viruses are among the causal organisms. Gram-positive (now dominant) and Gram-negative (dominant in the 1970s) bacteria are the most common pathogens that cause FN and complex illnesses. Although the morbidity and death rates of FN have decreased over time as a result of adequate antibiotic treatment, preventive measures, and the implementation of a standard risk management plan in accordance with guidelines, it remains an oncological emergency FN is associated with significant morbidity, as 20 percent to 30 percent of patients have complications that necessitate in-hospital treatment, with a total in-hospital mortality rate of 10% (Rasmy *et al.*, 2016).

Total leukocyte count 6.90x109/mm3 (3.8-19.5x109/ mm3) and absolute neutrophil count 4.3 x109/mm3 (1.6-17.0 x109/ mm3) pre-treatment were found to be at higher risk of developing febrile neutropenia in a study (Jenkins *et al.*, 2012). Prior chemotherapy, poor liver and renal function, and low leukocyte count were shown to be the most important independent risk factors in multi variate analysis after controlling for age and cancer type (Lyman *et al.*, 2011; & Lyman *et al.*, 2014).

Another study Reardon *et al.* (2007) found that advanced age, the first round of chemotherapy, and an absolute neutrophil count of less than 2.0x109/mm3 were all risk factors for developing febrile neutropenia. Female gender is more likely to develop febrile neutropenia or be admitted to the hospital for febrile neutropenia care, according to studies done on non-Hodgkin lymphoma and small cell lung cancer patients (Lyman *et al.*, 2011; & Crawford *et al.*, 2005). The risk factors for febrile neutropenia in patients following chemotherapy showed no significant difference (p - value=0.931) between the two genders in a research (Ahmad *et al.*, 2017). In our study, febrile neutropenia was detected in 30.9 percent of males and 39.4 percent of females, which was not statistically significant (p-value=0.230).

CONCLUSION

Febrile neutropenia is a common problem in our local population with subjected to chemotherapy for solid organ or hematological malignancy, and significantly common in patients with high risk of chemotherapy regime. More studies are required to develop association of its risk factors which lead to febrile neutropenia, its control and its effect on efficacy of chemotherapy.

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