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A Study to Assess the Management of Febrile Neutropenia in Oncology Patients in a Tertiary Care Hospital

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Abstract

Background: The cytotoxic chemotherapy is the mainstay treatment of cancer and it is usually complicated with infections. Appropriate antibiotics and other supportive medications must be started immediately as bacterial infections may progress with the absence of granulocytes. Improved outcomes can be seen with empirical administration of broad-spectrum antibiotics and they remain as the standard of care. Patients with intermediate-risk for Febrile Nuetropenia (FN) (10%-20%) need to be evaluated for additional patient risk factors, after assessment, patients who present with at least one of the risk factors for FN is recommended for treatment with a G-CSF. ***Methodology:*** Our study was a retrospective cohort single centered observational study carried out randomly in 104 patients in the oncology department of Lourdes hospital, Cochin Data of the patients were collected from Mediware system, medical records and Statistical software SPSS were used for analysis of the data. ***Results:*** In our study febrile neutropenia was managed using antimicrobials, of which antibiotics and antifungals prescribed were 12.09% and 1.97% respectively and with granulocyte-colony stimulating factors (G-CSFs) (6.15%). Principally used empirical monotherapy was meropenem sulbactum / meropenem (n = 48) which was followed by piperacillin tazobactum (n=18) and cefoperazone sulbactum (n=15) This study had a leading prescription of Cyclophosphamide containing chemotherapy regimens which led to neutropenia. Breast cancer patients accounts the majority of febrile neutropenic episodes despite of receiving GCSF prophylaxis. The most common type of cancer patients who are suffering from neutropenia were breast cancer. The compliance with National Comprehensive Cancer Network (NCCN) guidelines were analyzed in that we can see 84.6% patients had partial compliance and 14.4% patients had full compliance. ***Conclusion:*** A total of 66 patients received both antibiotics and G-CSF treatment however 13 patients and 25 patients were managed only with G-CSF and antibiotic therapy respectively. This study had a leading prescription of Cyclophosphamide containing chemotherapy regimens which led to neutropenia. These regimens were used mainly in breast cancer patients. Breast cancer patients accounts the majority of febrile neutropenic episodes despite of receiving GCSF prophylaxis. The most common type of cancer patients who are suffering from neutropenia were breast cancer. The NCCN guidelines, majority of patients showed partial compliance(86.6%) and about (14.4%) showed full compliance.

Keywords: Febrile neutropenia, National comprehensive cancer network**,** chemotherapy induced nausea and vomiting, granulocyte colony stimulating factor, absolute neutrophil count, multi drug resistant bacteria.

INTRODUCTION

Febrile neutropenia is one of the most common complications of chemotherapy regimens. Neutropenia is defined as an absolute neutrophil count (ANC) of less than 500 or 1000 cells /mm^3 reducing to less than 500 cells /mm^3 in a period of 48 hrs. If neutropenic patient develops fever (>=38.3^oC or >38^oC for at least 1 hr), then it is termed as febrile neutropenia (FN). The cytotoxic chemotherapy mediated febrile neutropenia is a serious obstacle for the treatment of cancer patients with a high risk of morbidity and mortality [1, 2]. It is an emergency that leads to an extended hospital stay and high medical cost or even results in the dose reductions or holdback of chemotherapy [3-5]. Neutrophils have an inevitable role in the immune system to eliminate the pathogen directly by releasing cytokines and attacking bacteria or fungal hyphae at the site of infection [6]. In patients with neutropenia, sepsis is a common complication. Among them, gram-negative and gram-positive infections are about 50% case. Mortality is increased in febrile neutropenia especially with bacteraemia [7]. Due to deteriorated immune response fever is the first and foremost sign of infection. It should be identified and managed timely to prevent the progression to severe sepsis and death [8].

The risk factors for the development of febrile neutropenia depends on several factors such as duration of chemotherapy, degree of chemotherapy-induced

neutropenia, age, comorbidity, and serum albumin levels [9]. Myelosuppressive chemotherapy affects the neutrophils which is an important component in the immune system thereby rendering the patient immunocompromised. Thus, the neutropenic patients remain susceptible to infections from all varieties of microbes comprising bacteria, fungi, and virus [9, 8, 1]. Most promptly, the patients enduring myelosuppression/ immunosuppressive therapy such as haematology and hematopoietic stem cell transplant (HSCT) are at high risk of febrile neutropenia. In this 13-60% of patient who receives HSCT grew bloodstream infections [10]. Patients should be evaluated as, low to high-risk patients according to the chemotherapeutic regimen which he/she receives [11]. Secondary to the manufacture of recent pharmaceuticals and with the use of systemic chemotherapy, chemotherapy services for both solid and liquid malignancies have drastically expanded. This has improved patient remission and cure rates. Long term and increasing use of chemotherapeutic agents are the reason for the incidence of chemotherapy-induced adverse drug reactions [12].

Neutropenia related infections are the commonest cause of death for cancer patients. Thus, Cancer patients with neutropenic fever must receive broad-spectrum antibiotics to prevent life-threatening complications [13]. The administration of IV empirical antibiotic remains the cornerstone in the initial management of febrile neutropenia. It improves patient survival and prevents death due to infection [14]. The timely commencement of empirical antibiotic is of utmost importance in the initiation of therapy [14, 8]. The monotherapy with broad-spectrum antibiotics is usually followed. The use of granulocyte colony stimulating factors (G-CSF) provides better outcomes in the prevention of neutropenia. This reduces the risk of neutropenic infections and thereby prevent patients from getting nosocomial infections due to intermittent hospital admissions, thus avoiding allied medical costs [15, 4].

Although some guidelines exist for the management of febrile neutropenia, the adherence to it is usually less. The main reason for this non-adherence is the fluctuating patterns of infections, causative agents and the anti-microbial resistance developed by them. Thus, the clinicians rely on the individualised treatment to provide optimal patient care. A variety of multi-drug resistant bacteria (MDR) is emerging nowadays. As a result, the likely pathogens and resistance patterns predominant in the institutions must be studied before initiating empirical antibiotic therapy [16, 8, 5]. The NCCN (National Comprehensive Cancer Network) guidelines recommend the quick initiation of empirical antibiotics after taking the blood cultures within 60 minutes of presentation of fever from neutropenia. The broad-spectrum iv antibiotics like Cefepime, Imipenem, Meropenem or Piperacillin Tazobactam can be used as empirical monotherapy as per the guideline. The empirical Vancomycin therapy is advocated if the gram-positive bacteria is suspected in conditions like iv catheter-related infections and soft tissue infections etc. The complete blood count (CBC) with differential analysis, liver function tests, renal function tests (BUN, Sr. Cr) and electrolytes must be monitored [17, 2].

The only recommendations for neutropenic cancer patients with, 100 neutrophils/µL for 7days are antimicrobials and antifungals. colony-stimulating factors (CSF's) can be recommended as primary prophylaxis for febrile neutropenia in oncology patients. The use of empirical antibiotic therapy and prevention by CSF's has reduced the risk and complications of febrile neutropenia [18]. The granulocyte colony stimulating factors (G-CSF) prophylaxis provides hematopoietic recovery preventing chemotherapy-induced neutropenia. This is achieved using granulocyte colony stimulating factors (G-CSF) for the proper duration of days depending on the undergoing chemotherapy [19]. The NCCN guidelines necessitate the use of granulocyte colony stimulating factors (G-CSF) prophylaxis for the patients receiving > 20% FN risk chemotherapy regimens. They do not recommend granulocyte colony stimulating factors (G-CSF) prophylaxis for chemotherapy regimens with < 20% neutropenia risk unless accompanied by any risk factors like elderly, poor performance status, compromised renal or hepatic function, previous therapy for cancer or any presenting infections or neutropenia [20, 3, 4, 15]. However, non-adherence to these guidelines were observed in some studies [20, 19]. The objective of this study is to analyse the prescription patterns of antimicrobials used and to check whether the treatment shows compliance with the NCCN guidelines for the management of febrile neutropenia. This study also evaluates the percentage of neutropenia with the chemotherapies provided and assess the type of cancer more prone to neutropenia.

METHODS

A retrospective single-centre observational study was conducted for a period of 6 months in the oncology department of Lourdes hospital, Cochin. It is a tertiary care multispeciality hospital with 500 beds. Patients were selected randomly from Lourdes Mediware system and medical records from 2016 January to 2020 January. Patients of all age groups on chemotherapy and diagnosed with Febrile neutropenia were included and those who are discharged against medical advice and with incomplete data were excluded from the study. A total of 104 patients were included in the study by calculating sample size. The data were collected using specially designed data collection form. Pertinent laboratory, as well as treatment details were extracted from Lourdes Mediware system and medical record. Statistical analysis was done using SPSS software, graphs and tabulation using Microsoft excel.

RESULTS

Demographic Details

Among cancer patients hospitalised with Febrile Neutropenia between 2016 January and 2020 January at Lourdes hospital Ernakulam, 104 cases were randomly selected and conducted a retrospective observational study. The mean age of patients was 55.84 years (SD ±10.53years) with 65 (62.5%) female and 39 (37.5%) males. Figure 1 depicts the distribution of female and male patients in the sample population according to their age category. The mean duration of hospital stay was 6.2days. The mean body temperature was 38.09°C range.

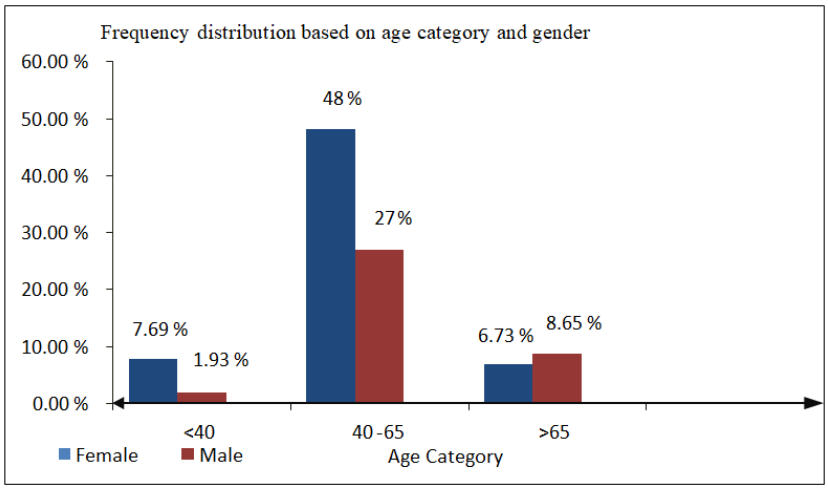

Figure 1: Distribution of subjects based on Age Category and Gender

Febrile neutropenia is most common in Solid tumours, among them Breast cancers is more 28 (26.9%) followed by ovarian cancer 10(9.6%). Non-Hodgkin lymphoma about 15 (14.4%) in Haematological Malignancies are also common in our study.

Table 1 and Figure 2 indicates the distribution of types of cancer among the febrile neutropenic patients in oncology taken in our study. Five (3female and 2 male) patients were expired during the hospital stay. The Absolute Nuetrophil count of three of them were below 50. Two patients having breast cancer and one each with ovarian cancer, lung cancer, and pancreatic cancer.

Table 1: Distribution of subjects based on types of cancer

Solid Tumors (83.65%)	**N= 87**	**Hematological Malignancies (16.35%)**	**N= 17**
Breast Cancer (32.3%)	28	Non Hodgkins	15
Ovarian Cancer (11.6%)	10	Lymphoma (88.3%)	
Colon Cancer (10.4%)	9	Myelodysplastic	1
Rectum Cancer (6.9%)	6	Syndrome (5.8%)	
Lung Cancer (6.9%)	6	Multiple Myeloid	1
Esophageal Cancer (4.6%)	4	Leukemia (5.8%)	
Endometrium Cancer (4.6%)	4		
Pancreas Cancer (4.6%)	4		
Hypopharynx Cancer (4.6%)	4		
Liver Cancer (2.3%)	2		
Prostrate Cancer (2.3%)	2		
Stomach Cancer (2.3%)	2		
Squamous Cell Cancer (1.1%)	1		
Atypical Extraskeletal Erwigs Sarcoma (1.1%)	1		
Malignant Round Cell Neoplasm (1.1%)	1		
Ampullary Tumor (1.1%)	1		
Disseminated Carcinoma Appendix (1.1%)	1		
Multiple Germ Cell Tumor (1.1%)	1		

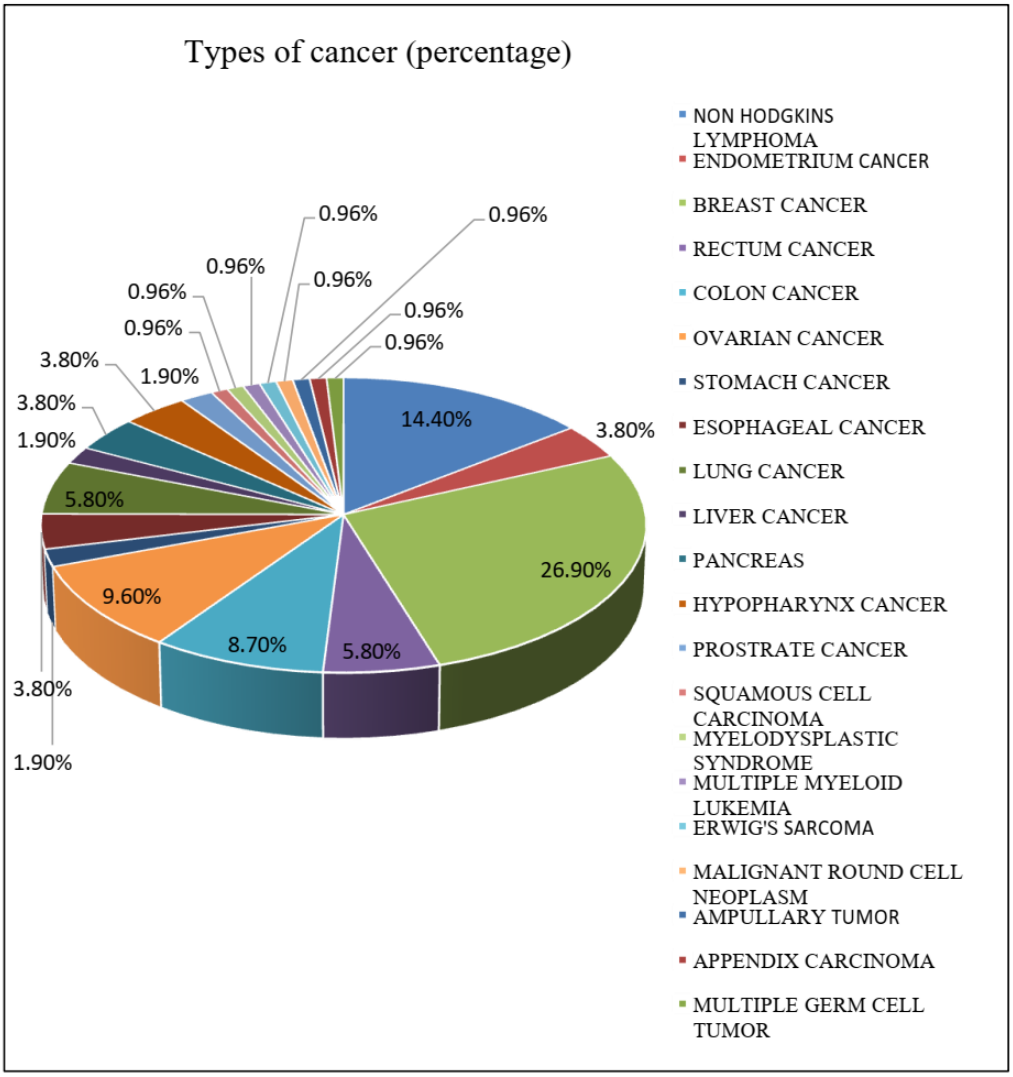

Figure 2: Distribution of patients based on types of cancer

The mean ANC was 279.88cells/ mm^3. About 19(18.3%) patients has ANC less than 100cells/ mm^3, 36(34.6%) patients had ANC ranging from 100-300 cells/ mm^3 and 49(47.1%) patients ranging from 300-500 cells/mm^3. Table 2 depicts the distribution of sample population according to their Absolute Neutrophil Count and age category (ANC).

Table 2: Distribution of subjects based on absolute neutrophil count (ANC)

Age Category	ANC Category			Total N
	<100	100-300	300-500	
<40	2	2	6	10
40-65	13	29	36	78
>65	4	5	7	16
TOTAL	19	36	49	104

Prescribing Pattern of Drugs used in febrile neutropenia Management and all other drugs used

The results were tabulated using Microsoft Excel and Microsoft Word. A total 1364 drugs were prescribed in these patients including those prescribed during hospital stay and discharge. The prescription patterns of all drugs were differentiated and tabulated based on the frequency of their distribution in males and females as given in Figure 3.

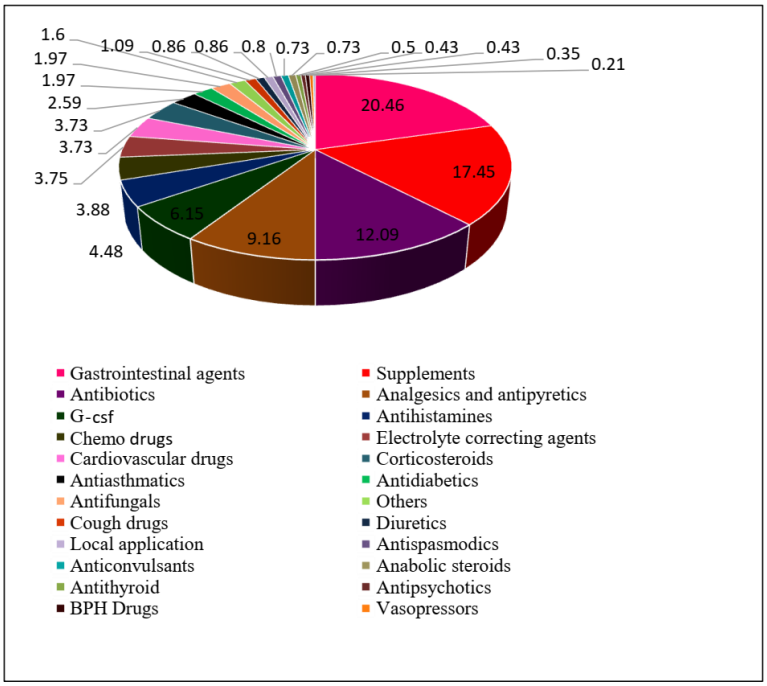

Figure 3: Distribution of all drugs prescribed in the febrile neutropenic patients

In our study febrile neutropenia was managed using antimicrobials, of which antibiotics and antifungals prescribed were 12.09% and 1.97% respectively and with granulocyte-colony stimulating factors (G-CSFs) (6.15%). Table 3 indicates the drugs used in our department for the management of febrile neutropenia.

Table 3: Prescribing pattern of drugs used in febrile neutropenia

Drugs Used	**Frequency**		**Total**
Antibiotics	**Female**	**Male**	
Cephalosporins	24	16	40
Cefoperazone Sulbactum	12	4	15
Cefepime Tazobactum	0	2	2
Cefpodoxime	1	0	1
Cefotaxime	1	1	2
Cefuroxime	3	4	7
Cefepime	2	1	3
Cefixime	5	4	9
Carbapenems	44	24	68
Meropenem Sulbactum	28	15	43
Meropenem	6	5	11
Imipenem	1	0	1
Faropenem	9	4	13
Aminoglycosides	2	2	4
Tobramycin	1	1	2
Amikacin	1	2	3
Fluroquinolones	7	6	13
Ciprofloxacin Tinidazole	2	2	4
Ciprofloxacin	3	0	3
Levofloxacin	0	1	1
Ofloxacin	2	3	5
Penicillins	17	10	27
Amoxicillin Clavulanate	4	2	6
Crystalline Penicillin	0	1	1
Piperacillin Tazobactum	13	7	20
Others	6	7	13
Metronidazole	0	2	2

Drugs Used	Frequency		Total
Antibiotics	**Female**	**Male**	
Vancomycin	0	1	1
Colistin	2	0	2
Nitrofurantoin	1	1	2
Sulfamethoxazole/Trimethoprim	1	1	2
Rifamycin	0	1	1
Tinidazole	1	0	1
Linezolid	1	1	2
Antifungals	19	8	27
Fluconazole	18	8	26
Clotrimazole	1	0	1
G-CSF	57	27	84
Filgrastim	56	27	83
Pegfilgrastim	1	0	1

The antibiotic classes often prescribed in our study population follows the order of Carbapenems (41.20%), Cephalosporins (24.24%), Penicillins (16.36%), Fluroquinolones (7.89%), Aminoglycosides (3.03%) and others (7.9%) which includes metronidazole, vancomycin, colistin, nitrofurantoin, sulfamethoxazole/trimethoprim, rifamycin, tinidazole and linezolid as plotted in Figure 4.

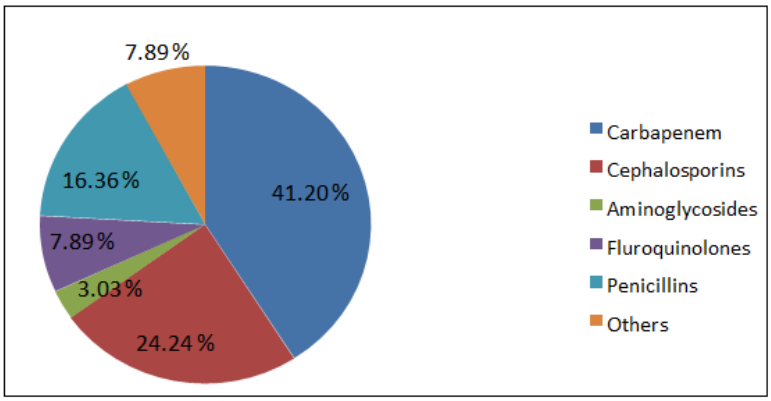

Figure 4: Distribution pattern of antibiotics

Antibiotics such as linezolid, metronidazole, nitrofurantoin and SMX-TMP were included in group others. Various antibiotic regimens used were mentioned in Table 4.

Table 4: Empirically used antibiotic regimens

Empirical Antibiotic Regimen	Number of Patients
Meropenem Sulbactum / Meropenem	48
Piperacillin Tazobactum	18
Cefoperazone Sulbactum	15
Cefepime Tazobactum	2
Amoxicillin Clavulanate	2
Cefixime	3
Cefuroxime + Meropenem Sulbactum	1
Meropenem + Vancomycin	1
Piperacillin Tazobactum + Amikacin	4
Piperacillin Tazobactum + Smx/Tmp	1
Cefotaxime + Metronidazole + Tobramycin	1
Meropenem/Imipenem + Ciprofloxacin + Tinidazole	2
Cefoperazone+ Meropenem	3

Principally used empirical monotherapy was Carbapenem, meropenem sulbactum/ meropenem (n = 48) which was followed by piperacillin tazobactum (n=18) and cefoperazone sulbactum (n=15) and the rest was stated in table 4. Empirical dual (n=5) as well as triple therapy (n=8) was also observed. All the empirical antimicrobial therapy were initiated in intravenous route. A total of 66 patients received both

antibiotics and G-CSF treatment however 13 patients and 25 patients were managed only with G-CSF and antibiotic therapy respectively. Table 5 shows the pattern of use of G-CSF and antibiotic prophylaxis among patients based on their ANC values. Empirical antibiotics were used alone in patients mostly (n=13) falling in an ANC category of 300-500 cells/mm3 as is observed with G-CSF monotherapy (n=8). Inj.Filgrastim 300mcg was the G-CSF of choice in our department and one patient was treated with Inj.Pegfilgrastim. Antifungal prophylaxis with Inj.Fluconazole was observed in 26 patients. Only one female patient was prescribed with Tab.Itraconazole.

Table 5: Management of FN among patients

Treatment of FN	ANC Category			
	<100	100-300	300-500	TOTAL(n)
G-CSF	1	4	8	13
Empirical Antibiotic	1	11	13	25
G-CSF + Empirical Antibiotic	17	28	21	66

Percentage of neutropenia with each drug

The previous chemotherapy regimens administered to the patients that resulted in this febrile neutropenic episodes were tabulated in table 4.3.1.In our study Cyclophosphamide was found commonly (34.6%) in most of the chemotherapy regimens, which patients were treated before this febrile neutropenia episode, followed by Doxorubicin (29.8%), Carboplatin (20.19%), Capecitabine (13.46%), Docetaxel (13.46%), 5Flurouracil and Vincristine (12.5%) and other chemotherapy drugs as depicted in Table 6.

Table 6: Percentage of febrile neutropenia with each chemotherapy drug

Chemotherapy Agent	Number of patients (104)	Percentage (%)	Chemotherapy Agent	Number Of patients	Percentage (%)
Cyclophosphamide	36	34.61	Gemcitabine	7	6.73
Doxorubicin	31	29.80	Cisplatin	7	6.73
Carboplatin	21	20.19	Irinotecan	7	6.73
Capecitabine	14	13.46	Paclitaxel	5	4.80
Docetaxel	14	13.46	Prednisone	4	3.84
5FU	13	12.5	Cetuximab	3	2.88
Vincristine	13	12.5	Bendamustine	2	1.92
Calcium Leucovorin	12	11.53	Eribulin	2	1.92
Oxaliplatin	10	9.61	Trastuzumab	2	1.92
Rituximab	10	9.61	Mitoxanthrone	2	1.92
Etoposide	9	8.65	Others	12	0.96
Bevacizumab	8	7.69			

Thus, we assume that Cyclophosphamide had contributed largely to febrile neutropenia occurrence. Cyclophosphamide with Doxorubicin were prescribed in 11 breast cancer patients which was followed by Cyclophosphamide and Docetaxel combination among 10 breast cancer patients. The next leading Cyclophosphamide containing regimen was found in Non Hodgkins Lymphoma treatment (n=6). The cytotoxic chemotherapy regimens that are observed chiefly in our sample population was given in Table 7 with their corresponding ANC values.

Table 7: Distribution of chemotherapy regimen of most commonly administered regimens with anc category

Chemotherapy Regimen	<100	100-300	300-500	Total	Type Of Cancer
1.Inj.Cyclophosphamide, Inj.Doxorubicin	2	3	6	11	Breast
2.Inj.Cyclophosphamide, Inj.Docetaxel	1	5	4	10	BREAST
3.Inj.ETOPOSIDE, Inj.CARBOPLATIN	2	3	2	7	Lung, Pancrea S, Prostrate, Breast
4.Inj.Rituximab, Inj.Cyclophosphamide, Inj.Vincristine, Inj.Doxorubicin	2	3	1	6	NHL
5.Inj.Paclitaxel, Inj.Carboplatin	0	1	3	4	Breast, Ovary, Esophagus

The most common type of cancer patients who are suffering from neutropenia were breast cancer (n=28).

Patient compliance with NCCN guidelines

Table 8: NCCN guideline compliance

Guideline standard	n %
1.Full compliance with guideline	14.4%
2.Partial compliance with guideline	84.6%
3.Empirical antibiotics given within 1hour	80(77%)
4.Other antibiotics given other than empirical antibiotics(Acc. to NCCN guideline)	19(18%)
5.Culture done	19(18%)
6.Patients with positive culture	11(10.5%)
7.G-CSF drug given	78 (75%)
8.Patients with Complete Blood Count done	102(98%)
9.Patients with Complete Metabolic Panel done	78 (75%)

In this we can see 84.6% patients had partial compliance and 14.4% patients had full compliance with the NCCN guidelines from 104 patients analyzed in our study (Table 11). Empirical antibiotics were given to the patients admitted in the oncology department within 1 hour (n=80) about 77% patients and other antibiotics administered in patients which was recommended by NCCN guidelines were (n=19) 17.7% which helped the patients improve their disease state and health condition. G-csf drugs (n=78)75% were also given along with these antibiotics. Cultures were done in patients who had persisting infection and high ESR values (n=19)18.2% of patients, where patients with positive culture was n=11(10.5%).The lab parameters which included complete blood count (n=102)98% and complete metabolic panel (n=78)75% were also done in these patients.

Association of antibiotic alone and antibiotic and filgrastim combination with length of stay.

Table 9: t-test on Antibiotics and combination of Antibiotics and Filgrastim

	Treatment	N	Mean	Std. Deviation	Mean difference	Df	t value	P value
Length of hospital stay	Antibiotic only	23	6.6522	5.40714	0.07917	88	0.070	0.944
	Filgrastim+Anti biotics	67	6.7313	4.40586			0.063	

The mean length of stay of patients in our study was found to be 6.2308(SD±4.55) (Table 9). The t- test conducted showed no significant association between patients taking antibiotics and those taking combination of antibiotics and filgrastim with their length of stay with p value of 0.944 ($p \leq 0.5$).

DISCUSSION

Our study is a retrospective observational study which aimed at analysing the prescription pattern of all drugs in particular those used in the management of febrile neutropenia and thus help in comparison for further studies. The study also determines the type of cancer and chemotherapy drug which largely contributed to low absolute neutrophil count (ANC) by taking into account the percentage of neutropenia with each chemotherapy agent. The prescription pattern studies similar to our study has not been done before because in our study we reviewed all the drugs prescribed in the prescriptions of 104 febrile neutropenic patients ,selected randomly.

Number of patients in the age category 40-65 were predominantly higher than the other age categories. As in our studies, this study also has highest number of patients with age group of 50 to 65 years [21].

Types of cancer:

The most common type of cancer seen in our sample populations were Solid tumors 87(83.65%).Among them breast cancer 28 (32.3%), and ovarian cancer 10(11.6%). Schelenz S et al conducted a similar study in 2012 where the most common patient groups were with Breast cancer in that study as well, Ovarian cancer was in third place which is analogous to our study followed by oesophageal cancer [22].

Patients taken in our study was categorised according to Absolute Neutrophil Count (ANC) and age category. Out of 104 sample populations, 19 patients have ANC value below 100 cells/ mm^3. Among them 2 patients were under the age group less than 40years, 13 patients were aged between 40-65years and 4 patients were having age above 50 years. 36 patients have ANC value between 100-300 cells/ mm^3 and ANC category between 300-400 cells/ mm^3 have 49 patients.

In our prescription patterns the gastrointestinal (GI) agents ranked high accounting for about 20.46% Antimicrobial prophylaxis and G-CSF prophylaxis remains mainstay in the management of FN. Either antibiotic therapy or G-CSF therapy was used alone in patients with ANC count above 300cells/mm3. Both

treatments were received together in 29 patients with ANC values 100 to 300cells/mm3 however 17 patients with profound neutropenia received more than one antibiotic therapy alongwith G-CSF therapy. The therapy may vary with patients performance status, severity of infection, comorbidities and stage of cancer. Febrile neutropenia was also managed with antifungal agents. Antiviral prescriptions were not observed. All the patients were initiated empirical antibiotics therapy intravenously. A greater number of patients were treated with empirical monotherapy with meropenem whereas in a study by K. A. Al. Balushi *et al.*, Empirical dual therapy with Piperacillin tazobactum and Gentamycin (n=82) were paramount followed by Meropenem/Imipenem monotherapy. Besides monotherapy and dual therapy, triple therapy was ordered less frequently [23]. In a similar UK survey study empirical dual therapy with Piperacillin tazobactum and Gentamycin was major (50.4% of oncology units) but only few patients in this setting were prescribed with this dual therapy [24]. Carbapenem monotherapy showed higher success rates which is also evident from metaanalytic study by Xiuge Tang *et al*., [25]. Most of the patients had their fever resolved – days after initiation of empirical monotherapy. Antifungal prophylaxis with Inj.Fluconazole was predominantly practiced in our centre. In other similar studies antifungal prophylaxis with Amphotericin B was observed [23, 24, 26].

G-CSF prophylaxis is necessary in patients undergoing chemotherapy to prevent neutropenia. Inj.Filgrastim was the one common in use. The use of G-CSF in treatment of neutropenia has now become a routine clinical practice even though NCCN guidelines recommend only its prophylactic use [27, 28].

Among 104 patients a total of 244 chemotherapy drugs were prescribed before the development of neutropenia symptoms. From this, we assumed that Cyclophosphamide (34.61%) is the drug that most causes febrile neutropenia. Other chemotherapeutic agents also contributed to the development of febrile neutropenia. We also assumed that the most common type of cancer patients suffering from febrile neutropenia was with breast cancer (n=28) followed by Non-Hodgkin lymphoma (n=15), Ovarian cancer (n=10).

In a similar study conducted by et al Yosunori et al on 2009-2011. Paclitaxel was their contributing chemotherapeutic regimen for the increase of febrile neutropenia followed by Docetaxel, Cyclophosphamide, Nedaplatin, Doxorubicin, and Carboplatin. Just like in our study the most common type of cancer suffering from neutropenia was breast cancer [29].

Cyclophosphamide and doxorubicin combination regimen had contributed to neutropenia producing ANC values in the range of 300-500 cells/mm3 prominently. Only few patients had profound neutropenia les than 100 cells/mm3.

Patients with temperature of $\geq 38^0$C and neutrophil count <500cells/mm^3 are considered as a patient with febrile neutropenia according to the NCCN (National cancer comprehensive network) guidelines. The patients were then checked for history of prior infections as some patients may acquire febrile neutropenia (FN) episodes more than once and also the time since last chemotherapy is checked for possible correlation with the episode of febrile neutropenia. Other factors such as exposure to other patients with tuberculosis, travelling, pets, Blood administration etc. are checked.

The complete blood count (CBC) was taken in 102 patients, showing how rationally the treatment was initiated after the count results. The ANC values were further calculated with an average mean of 279.88cells/ mm^3 which indicated for the use of antibiotics and in case of persisting fever antipyretics were provided, most prominently Paracetamol. The lab values were repeated the following days and in cases where respiratory symptoms continued bronchodilators and chest x-ray were done [30].

In our study 10% patients chest x-ray was done. In patients with ESR values elevated and persisting infection cultures were done. As the infection subsides the switch over therapy is initiated where the IV to oral therapy was given and thus lower risk medications were administered instead of broad spectrum of antibiotics along with other supportive care medications. After the antibiotic course of treatment in the hospital, the treatment is completed with the course of antibiotic during discharge upto 5-7 days. The appropriate completion of antibiotics is necessary to avoid resistance.

Initial monitoring of serum creatinine (75%), serum electrolytes (75%) and LFT's (comprehensive metabolic panel) reduced the risk in patients [30, 31]. The abnormalities had a negative impact on the patient outcome. Thus, they are immediately corrected by supplementation of electrolytes.

In patients with persistent fever and infection culture reports were required to rule out sepsis and sepsis related complications which are disseminated intravascular coagulation, multiple organ failure etc [31,32]. The positive culture reports were seen in 10.5% of patients. The cultures of the organisms isolated were Candida albicans (0.9%), E.Coli (1.9%), Enterococci (1.9%), Grampositive cocci (1.9%), Klebsiella pnuemoniae (1.9%) and MRSA (0.9%) which was further treated with culture sensitive antibiotics in aiming of eradicating the organism and providing the patient with clinical cure. The gram

positive organism to be treated with Vancomycin, Linezolid or Daptomycin as per the NCCN guidelines. Here 0.9% of patients each were treated with Vancomycin and Linezolid. In majority of the patients if culture sensitive and if the drug had coverage, Meropenem and Piperacillin Tazobactam were most preferred and other patients were given cephalosporins in for reducing the infection, increasing the ANC count and to eradicate the organism [31].

The patients with no culture (81%) was done were given empirical therapy accordingly to the NCCN guidelines which helped the patients recover completely from the disease state and further patient condition was improved following complete compliance to the treatment. Some patients had chemotherapy along with the febrile neutropenia treatment as the counts improved the chemotherapy was started while monitoring of lab parameters [32]. The delay in chemotherapy could lead to clash in due dates of the patients chemotherapy cycle. The clinicians make sure the patient's health condition is not compromised and appropriate supplementation is provided to maintain health of the patient.

The response of the therapy is daily evaluated through vital signs, lab parameters, signs and symptoms of the patient, cultures and X-ray done. The G-CSF (Granulocyte colony stimulating factor) were provided in (n=78) 75% of patients where the patients count could be increased [33]. The patients were rationally treated with compliance to the NCCN guidelines through which the procedures and treatment provided were exactly supporting to the patients therapeutic outcome.

Association of patients taking antibiotics and combination of antibiotics and filgrastim with their length of stay was not significant in our study according to the t-test analysis done. This shows that administering antibiotic alone or filgrastim and antibiotic combination did not affect their clinical outcome with length of stay. In a study by Regis et al the median of length of stay in their study was found to be 16 days [34]. 69% of patients were admitted for more than 10 days. There were patients admitted for 22 days with febrile neutropenia taking intensive therapy. Most patients had invasive fungal infections and blood stream infections which led to increased length of stay. Several factors may have contributed to this insignificant association such as patient's comorbidities, age, insurance claim and performance status.

CONCLUSION

Febrile Neutropenia is a commonly found in patients receiving certain chemo regimens. Our study concluded that prescription pattern of febrile neutropenia management includes antimicrobials accompanied by gastrointestinal agents to prevent stress ulcers, supplements to boost the immunity, GCF to accelerate recovery, antipyretics to treat fever. Cardiovascular agents, Antidiabetics, Antiasthmatics, Steroids, anticonvulsants etc. were prescribed in patients with comorbidities. This study had a leading prescription of Cyclophosphamide containing chemotherapy regimens which led to neutropenia. These regimens were used mainly in breast cancer patients. Breast cancer patients accounts the majority of febrile neutropenic episodes despite of receiving GCSF prophylaxis. However various risk factors like age, sex, comorbidities, stage of cancer and dose intensity can contribute to neutropenia. The NCCN guidelines are put forward to maintain an appropriate treatment pattern and accurate therapeutic outcome. The patients in our study was treated by the recommendations from NCCN guidelines, majority of patients showed partial compliance (86.6%) and about (14.4%) showed full compliance.

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Ethical Consideration

We had ethical clearance from Institutional ethics committee of Lourdes Hospital post graduate institute and research centre, Ernakulam.

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