Article published online: 2021-06-03

Original Article

Assessment of Chemotherapy-Induced Febrile Neutropenia in Cancer Patients

Malona Lilly Philip, Neethu Saj, Antony Mathew Sebastian, Uday Venkat Mateti, Vijith Shetty[1]

Department of Pharmacy Practice, NGSM Institute of Pharmaceutical Sciences, Nitte (Deemed to be University), [1]Department of Medical Oncology, K. S. Hegde Medical Academy, Justice K. S. Hegde Charitable Hospital, Mangalore, Karnataka, India

Abstract

Purpose: Chemotherapy-induced febrile neutropenia (CIFN) is an adverse drug reaction which needs medical attention. The treatment options for the CIFN are mandatory to improve treatment outcomes and quality of life. **Methods:** A prospective observational study was conducted in the in-patients and out-patients of oncology department who received chemotherapy from October 2016 to March 2017. The information such as demographics (age, gender, and comorbidities), complaints on admission, hematological investigations (neutrophil counts, platelet counts, hemoglobin levels, erythrocyte sedimentation rate, and white blood cells), type of tumor, stage of cancer, prophylaxis, cycle of antineoplastic chemotherapy that cause febrile neutropenia, treatment history, and outcome data were obtained from the patient's clinical record. The Multinational Association for Supportive Care in Cancer score and Absolute Neutrophil Count grading was used to predict the patient's risk of developing CIFN. **Results:** Out of 200 patients, 19 patients developed 22 episodes of CIFN. The overall occurrence of CIFN during the study was 9.5%. The higher incidence of CIFN has been observed among male gender (57.89%), stage III patients (42.10%), solid tumor (73.68%), and double chemotherapy regimen (59.1%). The higher incidence of CIFN was developed in I cycle (36.36%) followed by II cycle (22.72%) and VI cycle (18.18%). **Conclusions:** The incidence of CIFN during the study was 9.5%. In the 19 chemotherapy-induced FN patients, there has no significant effect of prophylaxis to prevent the febrile neutropenia.

Keywords: *Adverse drug reactions, cancer, chemotherapy, febrile neutropenia, incidence*

Introduction

Cancer is the second most common cause of morbidity and mortality in most countries. Chemotherapy is an important treatment option in most cancers. Chemotherapy regimens are associated with variable period of myelosuppression.[1] Chemotherapy suppresses the bone marrow. Thus, neutrophils, white blood cells (WBC), platelets, and red blood cells which are produced by the bone marrow decrease in count making the person more vulnerable to infections. Decrease in the count of neutrophils with fever can lead to a febrile neutropenic condition.[2] Febrile neutropenia (FN) is defined as a "single oral temperature of ≥38.5°C or sustained temperature of ≥38.0°C over a 1 h period with <500 neutrophils/mm or <1000 neutrophils/mm with a predicted decline to 500 cells/mm over 2 days". The incidence and severity are based on the neutrophil count.[3]

A survey of literature states that the incidence of chemotherapy-induced FN (CIFN) was reported in: paclitaxel and carboplatin (1%), docetaxel and carboplatin (2%), doxorubicin (3%), paclitaxel (6%), irinotecan and nedaplatin (7%), adriamycin and cisplatin (11%), docetaxel and gemcitabine (33%), irinotecan and mitomycin C (40%), etc.[4] The Higher risk of CIFN was observed in patients treated with prophylaxis chemotherapy regimen. The risk of CIFN can be obtained from the Multinational Association of Supportive Care in Cancer (MASCC) score and from absolute neutrophil count (ANC). MASCC score of >21 indicates low risk and <21 indicates high risk of FN.[5] FN is divided into Grades 1-4 based on the ANC counts (cells/mm^3).[6]

The duration of hospitalization is a predictive factor in evaluating the severity of CIFN. High-dose chemotherapeutic regimen, hematological malignancies, comorbidities, infections and can upsurge the duration of FN and consequently lead

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Philip ML, Saj N, Sebastian AM, Mateti UV, Shetty V. Assessment of chemotherapy-induced febrile neutropenia in cancer patients. Indian J Med Paediatr Oncol 2019;40:249-56.

Address for correspondence:
Dr. Vijith Shetty, Department of Medical Oncology, K. S. Hegde Medical Academy, Justice K. S. Hegde Charitable Hospital, Deralakatte, Mangalore - 575 018, Karnataka, India.
E-mail: drvijithshetty@gmail.com

Access this article online

Website: www.ijmpo.org

DOI: 10.4103/ijmpo.ijmpo_31_18

Quick Response Code:

hospitalization.[7] Based on the risk of FN, prophylactic treatment such as granulocyte monocyte colony-stimulating factors (CSF) or granulocyte CSF (G-CSF) is endorsed as a standard in the chemotherapy regimen. Antibiotics are also considered as prophylactic agents due to increased vulnerability to infection and as a treatment option for CIFN.[8] Treatment options for the management of CIFN depend on age, gender, comorbidities, primary or secondary prophylaxis, the severity of the neutropenia, appropriate prophylactic use, antibiotics used and the response of the patient to the therapy.[5]

Methods

Study design

A prospective observational study was conducted for a period of 6 months (October 2016–March 2017). This study was conducted in patients admitted to and visiting the outpatient setting in the Oncology Department of Justice K. S. Hegde Charitable Hospital, Dakshina Kannada, Deralakatte, Mangaluru.

Ethical approval

The study was approved by the Institutional Ethics Committee (REF: INST. EC/EC/97/2016–2017) at K. S. Hegde Medical Academy, Mangalore.

Study criteria

The inclusion criteria consisted of patients of all age groups of either gender, all cancerous patients receiving chemotherapy and who have given the written informed consent form. Acquired or congenital neutropenic patients, radiation-induced neutropenia and patients not willing to participate in the study were excluded from the study.

Data collection

Information such as demographics (age, gender, and comorbidities), complaints on admission, hematological investigations (neutrophil counts, platelet counts, hemoglobin levels, erythrocyte sedimentation rate [ESR], WBC), type of tumor, cycles and antineoplastic chemotherapy that cause FN, treatment history, option and outcome data were obtained from the patients' clinical records. Details necessary for evaluation regarding concomitant medications, comorbidities, tumor type, stage of cancer, prophylaxis, and dose modification for causality assessment and management that helps to assess the incidence of CIFN and their expected outcomes.

All the prescriptions of the study population were screened for CIFN. The details regarding temperature, length of hospitalization, and laboratory reports were obtained from the patient's clinical record. Demographics of the patients were studied to find out the pattern of adverse drug reactions (ADRs).

Identification of chemotherapy-induced febrile neutropenia

All the patients receiving chemotherapy were classified according to MASCC 2013 as patients at risk for serious complications of FN into high and low risk patients and CIFN was graded according to ANC.[6,9] Patients who met the inclusion criteria were assessed for the incidence, causality assessment, severity assessment, preventable measures, evaluation of risk factors, and treatment outcome of CIFN.

Identification of CIFN was done based on regular follow-up of the patients by analyzing the subjective findings. Consultant oncologist assessed suspected ADRs and relevant data were filled in the case record form. The details of laboratory manifestations, medications used were recorded in the case record form and ADR form.

Data of the reported ADRs were evaluated to understand the pattern of the ADRs with respect to patient demographics, the severity of the reaction, characteristics of the drug involved, the outcome of the reaction and the management of FN.

Analysis of chemotherapy-induced febrile neutropenia

To assess the likelihood that a drug has caused the reaction, causality assessment was done using Naranjo scale (1991) which classifies CIFN as certain, probable, possible and unlikely and the WHO probability scale as certain probable, possible, unlikely, unclassified and conditional to be drug-induced depending on the level of association.[10,11] Depending on the severity, CIFN was classified into mild, moderate, and severe reactions using the criteria developed by Hartwig *et al*. and ANC for severity assessment.[9,12] CIFN was categorized into definitely preventable, probably preventable and not preventable using the criteria of Schumock and Thornton modified.[13]

Predisposing factors

Factors that could have predisposed to the occurrence of CIFN in the individual reports were evaluated. Predisposing factors were generally classified for the study into age, gender, multiple disease state, and polypharmacy.

Management of chemotherapy induced febrile neutropenia

Management of CIFN was categorized as drug withdrawal, dose reduction, additional treatment for further complications, and no change in regimen with any additional treatment. Spontaneous reporting of suspected ADRs by the physician, pharmacist, and nurse can facilitate prevention of CIFN.

Statistical analysis

Frequency and percentage were used to summarize the categorical variables. Descriptive statistics such as mean,

standard deviation, and median were calculated for continuous variables. Chi-square test or Fisher's exact test was applied to test the association between categorical variables. Correlation between the continuous variables were tested by using Spearman's correlation and tested for its significance by using independent sample *t*-test with value $P < 0.05$ considered as statistically significant. Statistical software was used to analyze the data. The statistical analysis was performed by using SPSS version 16 (IBM Corp., Armonk, NY, United States of America).

Results

During the study, a total of 200 patients with different types of cancers receiving chemotherapy regimen were recruited. Out of 200 patients, 19 patients developed 22 episodes of CIFN. The overall occurrence of CIFN during the study was 9.5%. In the study, age group of 45–60 years (52.63%) exhibited a higher incidence of CIFN compared to other age groups. The mean age of the patients with and without CIFN was 55.26 ± 9.42 and 53.61 ± 12.69

Table 1: Characteristics of patients with and without chemotherapy induced febrile neutropenia

Category	Patients with CIFN (*n*=19), *n* (%)	Patients without CIFN (*n*=181), *n* (%)	*P*	Total number of patients (*n*=200), *n* (%)
Age group				
<30	-	8 (4.41)	0.689	8 (4)
30-45	3 (15.78)	38 (20.99)		41 (20.5)
45-60	10 (52.63)	82 (45.30)		92 (46)
60-75	6 (31.57)	46 (25.41)		52 (26)
<75	-	7 (3.86)		7 (3.5)
Gender				
Male	11 (57.89)	95 (52.5)	0.58	106 (53)
Female	8 (42.10)	86 (47.5)		94 (47)
Social habits				
Smoking	3 (15.78)	22 (12.15)	-	25 (1.25)
Alcohol	2 (10.52)	223 (12.70)		25 (1.25)
Substance use	1 (5.26)	4 (2.20)		5 (2.5)
Smoking and alcohol		13 (7.18)		13 (6.5)
Smoking, alcohol and substance use	1 (5.26)	1 (0.55)		2 (1)
No social habits	15 (78.94)	144 (79.55)		159 (79.5)
Comorbidities				
HTN	2 (10.52)	29 (16.02)	0.40	31 (15.5)
DM	3 (15.78)	18 (9.94)	0.40	21 (10.5)
Asthma	2 (10.52)	8 (4.41)	0.07	10 (5)
CLD	-	1 (1.81)	0.94	1 (0.5)
IHD	-	2 (1.1)	0.89	2 (1)
CKD	-	1 (1.81)	0.94	1 (0.5)
Tumor type				
Solid	14 (73.68)	165 (91.13)	-	179 (89.5)
Hematological	5 (26.31)	16 (8.83)		21 (10.5)
Stages of cancer				
Stage I	3 (15.78)	6 (3.31)	-	9 (4.5)
Stage II	3 (15.78)	48 (26.51)		51 (25.5)
Stage III	8 (42.10)	82 (45.30)		88 (44)
Stage IV	5 (26.31)	45 (24.86)		50 (25)
Length of hospital stay				
1-5	8 (42.10)	181 (100)	0.00	189 (94.5)
5-10	7 (36.84)	-		7 (3.5)
10-15	1 (5.26)	-		1 (0.5)
15-20	2 (10.52)	-		2 (1)
20-25	1 (5.26)	-		1 (0.5)
Prophylaxis				
No prophylaxis	2 (10.52)	43 (23.7)	0.001	45 (22.5)
Filgrastim	13 (68.42)	118 (65.19)		131 (65.5)
Peg - filgrastim	4 (21.05)	20 (11.04)		24 (12)

DM - Diabetes mellitus; HTN - Hypertension; CKD - Chronic kidney diseases; CLD - Chronic liver disease; IHD - Ischaemic heart disease; CIFN - Chemotherapy induced febrile neutropenia

years, respectively, (P = 0.689). Occurrence of CIFN was predominantly higher in males (57.89%) than in females (42.10%). CIFN patients exhibited significantly less social habits such as smoking, alcohol use, and substance abuse. Most of the patients who developed CIFN had diabetes mellitus (15.78%), followed by hypertension (10.52%) and other comorbidities.

Cancer is subdivided into solid and hematological tumors. Solid tumors (73.68%) were prominent than hematological (26.31%) in patients who developed CIFN. Most of the patients in this study were diagnosed with stage III of cancer (44%), and among the 19 CIFN cases, patients diagnosed at stage III showed a higher incidence of CIFN (42.10%) than the other stages. Out of 200 patients, 9.5% of the patients developed a fever along with neutropenia. All these 9.5% of the patients were CIFN (n = 19). The median length of hospital stay for CIFN patients (n = 19) was 6 days and the interquartile (Q3–Q1) ranged from 15 to 10 days. Prophylaxis is commonly administered along with chemotherapy regimens to prevent CIFN. Out of 200 patients, 155 received G-CSF as prophylaxis and 45 were not. Levofloxacin was the only antibiotic given as prophylaxis in 3 patients who were at high risk. Among the 19 CIFN cases reported, 17 patients showed the incidence of CIFN even though they received G-CSF as prophylaxis. The details regarding the characteristics of CIFN are summarized in Table 1. Among the 19 CIFN patients, 10.52% were in low risk and 89.47% were in high-risk category based on MASCC. In the ANC analysis, higher incidence of CIFN was exhibited in Grade 1: Cycle 4 (78.94%), Grade 2: Cycle 1 and 2 (10.52%), Grade 3: Cycle 3 (15.78%), and Grade 4: Cycle 6 (42.10%). The details regarding the predictors of risk assessment are depicted in Table 2. Out of 200 patients, majority of the patients received double regimen chemotherapy. Out of 22 episodes of CIFN, double regimen patients developed higher incidence of CIFN (59.1%). Out of 19 patients, the first (36.36%) and second (22.72%) cycles of chemotherapy exhibited higher incidence of CIFN cases compared to other chemotherapy cycles. The details regarding the chemotherapy regimens and cycle are summarized in Table 3.

Table 2: Predictors for risk assessment in patients with and without chemotherapy induced febrile neutropenia

Category	Patients with CIFN (n=19), n (%)	Patients without CIFN (n=181), n (%)
MASCC score		
Low risk	2 (10.52)	99 (54.69)
High risk	17 (89.47)	82 (45.30)
ANC		
Grade 1		
Cycle 1	10 (52.63)	180 (99.44)
Cycle 2	13 (68.42)	180 (99.44)
Cycle 3	13 (68.42)	179 (98.89)
Cycle 4	15 (78.94)	179 (98.89)
Cycle 5	12 (63.17)	155 (85.63)
Cycle 6	9 (47.36)	150 (82.87)
Grade 2		
Cycle 1	2 (10.52)	-
Cycle 2	2 (10.52)	-
Cycle 3	-	2 (1.10)
Cycle 4	-	2 (1.10)
Cycle 5	-	-
Cycle 6	1 (5.26)	1 (0.55)
Grade 3		
Cycle 1	-	1 (0.55)
Cycle 2	-	-
Cycle 3	3 (15.78)	-
Cycle 4	1 (5.26)	-
Cycle 5	1 (5.26)	1 (0.55)
Cycle 6	1 (5.26)	-
Grade 4		
Cycle 1	7 (36.84)	-
Cycle 2	4 (21.05)	1 (0.55)
Cycle 3	3 (15.78)	-
Cycle 4	3 (15.78)	-
Cycle 5	6 (31.57)	25 (13.81)
Cycle 6	8 (42.10)	30 (16.57)

MASCC - Multinational association for supportive care in cancer; ANC - Absolute neutrophil count; CIFN - Chemotherapy induced febrile neutropenia

Causality, severity, preventability, and predictability of chemotherapy-induced febrile neutropenia

The WHO probability scale was used to analyze the suspected CIFN and the scale showed that 81.81% of CIFN reactions were probably followed by certain (13.63%) and possible (4.54%). To assess the causality of the suspected CIFN, Naranjo's causality assessment scale was used. The scales showed that 77.27% of CIFN were probable followed by 13.63% were certain and 9.09% were possible. Severity assessment scale was used to classify the intensity of CIFN cases. Mortality rate due to CIFN among the 19 patients were 2 (%). Majority of the CIFN cases had moderate (level 4a) scale of severity (36.36%). Preventability assessment for CIFN was done using Schumock and Thornton scale. The scale showed that 27.27% of CIFN were not preventable and 72.72% were probably preventable. All the 22 episodes of CIFN reported were predictable. Among 19 CIFN patients, 40.90% of drugs were withdrawn, 4.5% of doses were altered, and 54.54% had no change. Majority of the CIFN cases were treated specifically (86.36%) and few were treated symptomatically (13.63%), Outcome of the patients depends on the intensity of the reaction. Majority of the CIFN patients were recovered 59.09% and the others ceasing the drug that has caused the reaction can confirm the causative agent. In this study, out of 22 CIFN reactions, 12 (54.53%) were dechallenged. Reintroducing the drug can identify the causative drug that has caused CIFN. Out of 22 CIFN reactions, 6 (27.26%) were rechallenged. The details regarding the assessment of CIFN are depicted in Table 4. Majority of the patients had breast

Table 3: Chemotherapy regimen and cycle in chemotherapy induced febrile neutropenia patients

Category	Frequency (*n*=22), *n* (%)
Chemotherapy regimens	
Single regimen	7 (31.8)
Azacitidine	4 (57.14)
Paclitaxel	1 (14.28)
Bendamustine	1 (14.28)
Decitabine	1 (14.28)
Double regimen	13 (59.1)
Irinotecan + capecitabine	1 (7.69)
Etoposide + carboplatin	3 (23.07)
Doxorubicin + capecitabine	1 (7.69)
Gemcitabine + docetaxel	1 (7.69)
Gemcitabine + carboplatin	1 (7.69)
Epirubicin + oxaliplatin	1 (7.69)
Paclitaxel + carboplatin	3 (23.07)
Docetaxel + carboplatin	2 (15.38)
Triple regimen	1 (4.5)
Vincristine + doxorubicin + cyclophosphamide	1 (4.5)
Quadruple regimen	1 (4.5)
Adriamycin + bleomycin + vinblastine+dacarbazine	1 (4.5)
Chemotherapy cycles	
Cycle 1	8 (36.36)
Cycle 2	5 (22.72)
Cycle 3	3 (13.63)
Cycle 4	1 (4.54)
Cycle 5	1 (4.54)
Cycle 6	4 (18.18)

cancer (18.5%), but FN was mostly observed in patients diagnosed with stomach cancer (15.7%). Out of the 19 CIFN patients, 16 experienced FN once whereas 3 of them experienced FN twice. The regimen that caused FN twice were Carboplatin-Etoposide, Carboplatin-Placlitaxel and Adriamycin + Bleomycin + Vincristine + Dacarbazine regimen. The detailed description of cancer with chemotherapy regimen in patients with and without FN is depicted in Table 5.

Discussion

The development of myelosuppression during chemotherapy is influenced by the demographics of the patients (age, gender, and comorbidities), cancer types, stages, and characteristics of the chemotherapy regimen used.

Higher incidence of CIFN was exhibited in the age group between 45 and 60 years (52.63%) among 19 CIFN patients compared to other groups. In a study conducted by Catic *et al*., higher incidence of CIFN was observed in the age group of 41–60 years (48%) among 27 CIFN patients.[14] The present study is in concurrence with the Catic *et al*., study, where the results showed a higher incidence of CIFN in the age group of 40–60 years.[14]

Table 4: Causality, severity, preventability and predictability of chemotherapy induced febrile neutropenia

WHO scale, *n* (%)	
Certain	3 (13.63)
Probable	18 (81.81)
Possible	1 (4.54)
Unlikely	-
Unclassified	-
Conditional	-
Naranjo's scale, *n* (%)	
Certain	3 (13.63)
Probable	17 (77.27)
Possible	2 (9.09)
Unlikely	-
Hartwig's severity scale, *n* (%)	
Level 1	2 (9.09)
Level 2	1 (4.54)
Level 3	3 (13.63)
Level 4a	8 (36.36)
Level 4b	5 (22.72)
Level 5	1 (4.54)
Level 6	-
Level 7	2 (9.09)
Preventability scale, *n* (%)	
Definitely preventable	-
Probably preventable	16 (72.72)
Not preventable	6 (27.27)
Predictability scale, *n* (%)	
Predicatble	22 (100)
Not predictable	-
Management of CIFN, *n* (%)	
Drug withdrawan	9 (40.90)
Dose altered	1 (4.54)
No change	12 (54.54)
Treatment of CIFN, *n* (%)	
Specific	19 (86.36)
Symptomatic	3 (13.63)
Nil	-
Outcome of CIFN, *n* (%)	
Fatal	2 (9.09)
Recovery	13 (59.1)
Continuing	7 (31.8)
Dechallenge (*n*=12), *n* (%)	
Definite improvement	3 (25)
No improvement	5 (41.6)
Unknown	4 (33.3)
Rechallenge (*n*=6), *n* (%)	
Recurrence of symptoms	-
No occurrence of symptoms	3 (50)
Unknown	3 (50)

CIFN - Chemotherapy induced febrile neutropenia

Out of 19 CIFN patients, 57.89% of patients were male and 42.10% were female. A study conducted by Sammut and Mazhar *et al.,* analyzed 32 CIFN cases in which

Table 5: Types of cancer and chemotherapy regimen administered in patients with and without chemotherapy induced febrile neutropenia

Cancer types	Chemotherapy regimen	Patients with FN (*n*=19), *n* (%)	Patients without FN (*n*=181), *n* (%)
Solid			
Breast	Doxorubicin + cyclophosphamide	-	27 (14)
	Paclitaxel	1 (5.2)	9 (4.9)
Stomach	Oxaliplatin	-	5 (2.7)
	Epirubicin + oxaliplatin	1 (5.2)	6 (3.3)
	Docetaxel + capecitabine	-	4 (2.2)
	Docetaxel + carboplatin	2 (10.5)	2 (1.1)
	Epirubicin + oxaliplatin + capecitabine	-	5 (2.7)
	Epirubicin + 5-flurouracil + cisplatin	-	2 (1.1)
Lung	Carboplatin + etoposide	2 (10.5)	8 (4.4)
	Pemetrexed + carboplatin	-	6 (3.3)
	Gemcitabine + carboplatin	-	4 (2.2)
Ovary	Bevacizumab	-	2 (1.1)
	Liposomal Doxorubicin + carboplatin	-	6 (3.3)
	Gemcitabine + carboplatin	1 (5.2)	4 (2.2)
	Carboplatin + paclitaxel	1 (5.2)	6 (3.3)
Rectum	Oxaliplatin + capecitabine	-	12 (6.6)
Oropharynx	Carboplatin + paclitaxel	-	15 (8.2)
Colon	Oxaliplatin	-	3 (1.6)
	Oxaliplatin + capecitabine	-	5 (2.7)
	Irinotecan + capecitabine	1 (5.2)	2 (1.1)
Gall bladder	Gemcitabine + carboplatin	-	7 (3.8)
Neuroendocrine	Oxaliplatin + capecitabine	1 (5.2)	3 (1.6)
Esophageal	Carboplatin + paclitaxel	1 (5.2)	3 (1.6)
Bladder	Cisplatin + gemcitabine	-	2 (1.1)
	Gemcitabine + carboplatin	-	2 (1.1)
Pancreas	Gemcitabine + oxaliplatin	-	3 (1.6)
Larynx	Cisplatin	-	3 (1.6)
Soft tissue sarcoma	Gemcitabine + docetaxel	1 (5.2)	2 (1.1)
Postate	Docetaxel	-	2 (1.1)
Gliblastoma multiforme	Bevacizumab	-	2 (1.1)
Ewings sarcoma	Etoposide + ifosfamide	-	2 (1.1)
Cervix	Cisplatin	-	1 (0.55)
	Paclitaxel + carboplatin	1 (5.2)	-
Haematological			
AML	Azacitidine*	3 (15.7)	1 (0.55)
MDS	Decitabine*	1 (5.2)	-
Follicular lymphoma	Bendamustine + rituximab	-	2 (1.1)
NHL	Rituximab + doxorubicin + vincristine +cyclophosphamide + prednisolone	-	3 (1.6)
	Doxorubicin + vincristine + cyclophosphamide + prednisolone	1 (5.2)	1 (0.55)
Ann arbor	Adriamycin + bleomycin + vincristine + dacarbazine	1 (5.2)	2 (1.1)
Multiple myeloma	Bendamustine	1 (5.2)	1 (0.55)
	Bortezomib + cyclophosphamide	-	2 (1.1)
Hodgkin lymphoma	Adriamycin + bleomycin + vincristine + dacarbazine	-	2 (1.1)
DLBL	Rituximab + doxorubicin + vincristine + cyclophosphamide + prednisolone	-	2 (1.1)

*Most commonly reported in the literature and observed in the study. AML - Acute myeloid leukemia; MDS - Myelodysplastic syndrome; NHL - Non-Hodgkin lymphoma; DLBL - Diffuse large B-cell lymphoma; FN - Febrile neutropenia

62.5% were female and 37.5% were male.[15] The present study was contradictory to the reference study. In the present study, solid tumors exhibited higher incidence of CIFN (73.68%) than hematological tumors (26.31%). In a study conducted by Ahn *et al*., out of 396 episodes of CIFN, solid tumors (71.5%) were predominantly more than

hematological (28.5%).[9] Hence, this study is in agreement with the previous study were solid tumors shows higher CIFN events.

Out of 200 patients, majority of the patients received double regimen chemotherapy (59.1%) and showed higher incidence of CIFN. In a study conducted by Hashiguchi *et al.,* among 291 patients, the most common chemotherapy was paclitaxel and carboplatin (double regimen) which exhibited 50.5% of CIFN cases.[4] Hence, the present study resembles the previous study that double regimen shows higher incidence of CIFN. The median length of stay for patients who developed CIFN was 6 days. The *P* value was 0.00, which showed strong association between length of hospitalization and the development of CIFN. The study conducted by Weycker *et al.,* reported that the median length of stay was 8.14 days for patients with CIFN.[16] The incidence of CIFN in each cycles varied, 36.63% were encountered in cycle 1 followed by 22.72% and 18.18% in cycle 2 and cycle 6, respectively. Culakova *et al.,* reported 9.7% of CIFN in cycle 1 followed by 5.7% and 3.8% in cycle 2 and 3, respectively.[17] The present study is in correspondence with the previous study that incidence is more in cycle 1 and 2, but varied in the following cycles.

The MASCC risk index score was used to predict the risk of CIFN among the patients (n = 200), 50.5% of them were in low risk and 49.5% of them were in high-risk category of patients. Of the high-risk patients, 89.47% developed CIFN and 10.52% developed CIFN in low-risk patients. The *P* value for MASCC score was 0.001, which showed strong association with the risk of developing CIFN. A study conducted by Ahn *et al.,* showed 90% of low-risk patients and 72% of high risk patients using MASCC risk index score, where 18.9% of high risk died.[9] Hence, this study is in correspondence with the previous study that MASCC score is used to predict low and high-risk patients. The incidence of CIFN in the study was 9.5%, similarly Shiota *et al.,* conducted a study on 37 patients and the incidence of CIFN was 10.8%.[18]

The higher incidence of CIFN was shown in Stage 3 of cancer (42.10%), similarly Talwar *et al.,* conducted a study, where most of the patients with CIFN presented in stage 3 (33.2%) and in Stage 4 (41.6%) of cancer.[19] To the best of our knowledge, this is the premier study to analyze the CIFN reactions by using causality, severity, preventability, and predictability scales. As per the WHO and Naranjo's scales, most of the CIFN reactions were classified as probably 81.82% and 77.2%, respectively. Out of 22 CIFN cases, 9.09% of mortality has been reported, and all the CIFN reactions were predictable. Preventability assessment scale showed that 27.27% of reactions are not preventable and 72.72% reactions are probably preventable. As management of CIFN among 19 patients, 40.90% of drugs were withdrawn, 4.5% of doses were altered, and 54.54% had no change. In addition, 86.36% were treated specifically whereas, 13.63% were treated symptomatically. Moreover, 50.09% of patients recovered, whereas 22.72% of patients continued in the same condition and 18.18% were fatal. The percentage of patients underwent dechallenge were 54.53% and rechallenge were 27.26%.

Conclusions

In this study, the incidence of CIFN was 9.5%. The age group of 45–60 years (52.63%) showed higher incidence of CIFN compared to another age group. In gender-wise distribution, the occurrence of CIFN was predominantly higher in males (57.89%) than in females (42.10%). The patients diagnosed at stage 3 showed greater incidence of CIFN (42.10%) than the other stages. The solid tumors (73.68%) were prominent than hematological tumor (26.31%). The length of hospitalization had prolonged for all patients who developed CIFN with a median of 6 days. The patients who received double chemotherapy regimen (59.1%) showed a higher incidence of CIFN than the other chemotherapy regimens. The incidence of CIFN was higher in I and II cycles of chemotherapy showed 36.36% and 22.72%, respectively.

Acknowledgments

We are thankful to the authorities of Nitte (Deemed to be University), Mangaluru, India; Dr. Jayarama Shetty, Professor, Department of Oncology, Justice K. S. Hegde Charitable Hospital, Mangaluru; Dr. C. S. Shasty, Principal, NGSM Institute of Pharmaceutical Sciences, Mangaluru.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Rang HP, Ritter JM, Flower RJ, Henderson G. Drugs used for the treatment of infection and cancer. Rang and Dale's Pharmacology. Anticancer Drugs. 8th ed. London: Elsevier Churchill Livingstone; 2012. p. 676-90.
2. Morin PJ, Trent JM, Collins FS, Vogenstein B. Cancer Genetics. In: Kasper DC, Hauser SL, Jameson JL, Fauci AS, Longo DL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. Part 10. 19th ed., Vol. 3, Sec. 3. Ch. 101e. United States of America: McGraw-Hill Education; 2016. p. 1-10.
3. Rosa RG, Goldani LZ. Cohort study of the impact of time to antibiotic administration on mortality in patients with febrile neutropenia. Antimicrob Agents Chemother 2014;58:3799-803.
4. Hashiguchi Y, Kasai M, Fukuda T, Ichimura T, Yasui T, Sumi T, *et al.* Chemotherapy-induced neutropenia and febrile neutropenia in patients with gynecologic malignancy. Anticancer Drugs 2015;26:1054-60.
5. Garnica M, Nouér SA, Pellegrino FL, Moreira BM, Maiolino A, Nucci M, *et al.* Ciprofloxacin prophylaxis in high risk neutropenic patients: Effects on outcomes, antimicrobial therapy and resistance. BMC Infect Dis 2013;13:356.
6. Yu MG, Villalobos RE, Juan-Bartolome MJ, Berba RP. Predictors of outcome and severity in adult Filipino patients with febrile

neutropenia. Adv Hematol 2015;2015:920838.

7. Bengre ML, Venkatraya PM, Arun S, Prasad K, Gopalkrishna BK. Evaluation of the multinational association for supportive care in cancer (MASCC) score for identifying low risk febrile neutropaenic patients at a South Indian tertiary care centre. J Clin Diagnostic Res 2012;6:839-43.
8. Aapro M, Ludwig H, Bokemeyer C, Gascón P, Boccadoro M, Denhaerynck K, *et al.* Predictive modeling of the outcomes of chemotherapy-induced (febrile) neutropenia prophylaxis with biosimilar filgrastim (MONITOR-GCSF study). Ann Oncol 2016;27:2039-45.
9. Ahn S, Lee YS, Chun YH, Kwon IH, Kim W, Lim KS, *et al.* Predictive factors of poor prognosis in cancer patients with chemotherapy-induced febrile neutropenia. Support Care Cancer 2011;19:1151-8.
10. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
11. Mateti UV, Nekkanti H, Vilakkathala R, Rajakannan T, Mallayasamy S, Ramachandran P, *et al.* Pattern of angiotensin-converting enzyme inhibitors induced adverse drug reactions in South Indian teaching hospital. N Am J Med Sci 2012;4:185-9.
12. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49:2229-32.
13. Gholami K, Shalviri G. Factors associated with preventability, predictability, and severity of adverse drug reactions. Ann Pharmacother 1999;33:236-40.
14. Catic T, Mekic-Abazovic A, Sulejmanovic S. Cost of febrile neutropenia treatment in bosnia and herzegovina. Mater Sociomed 2016;28:112-5.
15. Sammut SJ, Mazhar D. Management of febrile neutropenia in an acute oncology service. QJM 2012;105:327-36.
16. Weycker D, Li X, Edelsberg J, Barron R, Kartashov A, Xu H, *et al.* Risk and consequences of chemotherapy-induced febrile neutropenia in patients with metastatic solid tumors. J Oncol Pract 2015;11:47-54.
17. Culakova E, Poniewierski MS, Wolff DA, Dale DC, Crawford J, Lyman GH, *et al.* The impact of chemotherapy dose intensity and supportive care on the risk of febrile neutropenia in patients with early stage breast cancer: A prospective cohort study. Springerplus 2015;4:396.
18. Shiota M, Yokomizo A, Takeuchi A, Kiyoshima K, Inokuchi J, Tatsugami K, *et al.* Risk factors for febrile neutropenia in patients receiving docetaxel chemotherapy for castration-resistant prostate cancer. Support Care Cancer 2014;22:3219-26.
19. Talwar V, Nirni SS, Mallavarapu KM, Ramkumar A, Sinha N. Safety and tolerability of peg-grafeel™, a pegfilgrastim, for the prophylactic treatment of chemotherapy-induced neutropenia and febrile neutropenia: A prospective, observational, postmarketing surveillance study in India. South Asian J Cancer 2017;6:20-4.