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Research Article

ASSOCIATION OF FEBRILE NEUTROPENIA WITH CHEMOTHERAPEUTIC AGENTS IN MALIGNANCIES

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ABSTRACT

Introduction: Chemotherapy-induced febrile neutropenia (FN) is associated with substantial morbidity, mortality, and healthcare costs. The aim of this study was to evaluate episodes of FN in patients with malignancies, to find out the association of FN with various chemotherapeutic regimens, and to identify the microorganisms and the factors affecting the outcome.

Methods: All patients with FN were admitted and detailed history was taken with thorough clinical evaluation. Blood, urine, and throat swab cultures and cultures from any other clinically evident site of infection were sent to all the patients.

Results: Most common diagnosis was Ca breast and non-Hodgkin's lymphoma in 13 patients. The ECOG performance status of 2 was seen in 61% of patients. The FN episodes (11%) were associated with carboplatin plus paclitaxel, and in patients with Ca cervix, Ca esophagus, and Ca ovary. The chest was involved in 16% of patients followed by the GI tract in 10%. *Pseudomonas aeruginosa* organism growth was seen in a 50% sample of throat swabs. The mean number of days of chemotherapy, after which patients reported to have FN, was 3.6, and median (interquartile range [IQR]) days was 2. Granulocyte colony-stimulating factor was administered in all patients in this study. The mean number of days of recovery of the patients was 4.9 and median (IQR) days was 4.

Conclusion: The episodes of FN occurred mostly in patients with Ca breast, followed by non-Hodgkin's lymphoma. FN was more commonly seen with taxanes.

Keywords: Febrile neutropenia, Malignancy, Microbes, Chemotherapy, Colony-stimulating factors.

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INTRODUCTION

Febrile neutropenia (FN) is defined as a single oral temperature of >38.3°C (101°F) or 38°C or greater (100°F) for over 1 h in a patient with an absolute neutrophil count <500/mm^3 or <1000/mm^3, with predicted rapid decline [1,2]. The clinical use of cytotoxic chemotherapeutic agents has increased survival in cancer patients. However, treatment-associated bone marrow suppression and neutropenia often render patients prone to life-threatening infections. Chemotherapy-related FN is linked with increased mortality rates, increased costs of hospitalization also affect patient outcome by delaying chemotherapy doses or reducing dose intensity. Major risk factors for the development of FN include older age, comorbid conditions, the type of cancer, and the type and number of myelosuppressive chemotherapy agents used [3]. Infection in neutropenic cancer patient often can be difficult to identify due to the lack of neutrophils and associated clinical symptoms and signs. The febrile response also can be blunted in some immunosuppressed cancer patients due to reduced circulating leukocytes producing interleukin 1 (IL-1), IL-6, and tumor necrosis factor-alpha [4-6]. The major strategies for decreasing the risk of FN and its complications include the prophylactic use of a myeloid growth factor and the selective prophylactic use of antimicrobial agents. In a meta-analysis of 17 randomized controlled trials, there was a significant reduction in FN and other infection with primary granulocyte colony-stimulating factor (G-CSF) prophylaxis [7]. According to the MASCC scoring system, the patients are divided into low- and high-risk groups. Higher risk rates are associated with greater complications and mortality rate [8]. High-risk patients mandate inpatient treatment with wide-spectrum I.V. antibiotics effective against *Pseudomonas aeruginosa* and Gram-negative pathogens [9]. To evaluate, episodes of FN in patients with solid tumors, also to find out the association of FN with various chemotherapeutic regimens, identify the microorganisms and the factors affecting the outcome (recovery, morbidity, and mortality).

METHODS

The study was a prospective observational study conducted at a tertiary care government hospital in North India from May 2019 to March 2021. The Institutional Ethics Committee clearance was obtained before initiating the study. All admitted patients diagnosed with malignancies, including lymphomas, were confirmed histologically. The informed consent form was obtained in the regional language from all the participants. The patients receiving either chemotherapy or radiation therapy or concurrent chemoradiotherapy with FN were enrolled. Patients developing second or subsequent episodes of neutropenia will be counted as separate episode. The exclusion criteria were hematological malignancies, patients with HIV infection, receiving stem cell or bone marrow transplantation or concurrent participation in other trials, or pregnant patients on alternative drugs. All patients with FN were admitted and treated as inpatients with adequate neutropenic precautions. A detailed history was taken, and a thorough clinical evaluation was carried out with a focus to determine the source of the infection. Blood, urine, and throat swab cultures and cultures from any other clinically evident site of infection would be sent to all the patients. The study subjects also underwent the necessary radiological investigations (Chest X-ray, ultrasound [USG] abdomen, computed tomography scan) to aid in diagnosis and follow-up. All patients were administered G-CSF and started on antibiotics as per the clinical decision. The data collected were statistically analyzed using IBM SPSS Statistics for Windows, version 27.0.

RESULTS

In this study, 100 patients with histologically confirmed diagnosis of malignancies, including lymphomas in adults were enrolled. The mean age of the patients was 45.7 years with median age was 49 years. The majority of the patients were female with a female: male ratio of 1.5:1. In our study, the most common diagnosis was Ca breast and non-Hodgkin's lymphoma in 13 (13%) patients, respectively, followed by Ca ovary – 12 (12%). The majority of the patients were stage in clinical Stage IV in 76 (76.0%), followed by Stage III – 21 (21%) and Stage II – 3 (3%) patients (Fig. 1).

The ECOG performance status of 2 was seen in 61% of patients, while 27.0% of patients had a performance status of 3. The FN episode (11%) was seen in patients with Ca cervix, Ca esophagus, Ca ovary, and in patients receiving carboplatin plus paclitaxel. This was followed by BFM 90 protocol which caused 5% of the total episodes of FN in patients with adult lymphoblastic lymphoma and non-Hodgkin's lymphoma, and 4% of the episodes were seen in liposomal doxorubicin regimen in patients with Ca pancreas. Sixty-six percentages patients reported previous chemotherapy history and 22 (22%) patients reported previous radiotherapy history. The mean ± standard deviation body surface area (BSA) of the patients was 1.72±0.11 (Range: 1.37–1.95) and median (interquartile range [IQR]) body mass index was 1.75 (IQR: 1.65–1.79). Out of 100 patients, 42% showed evidence of focus of infection. Table 1 shows the involvement of various systems in patients with FN.

Mucositis was present in 22% of patients. In our study, 11%, 10%, and 4% organism growth were seen in blood, urine, and throat swab cultures, respectively. Fig. 2 shows the growth of various types of micro-organisms in blood, urine, and throat swab culture.

Table 2 shows the mean and median range of blood investigation report of the present study population. The liver function test/renal function test was normal in all patients.

On imaging investigations, 23% of patients showed the infective focus on chest X-ray and 9% of patients were abnormal on USG abdomen (Table 3).

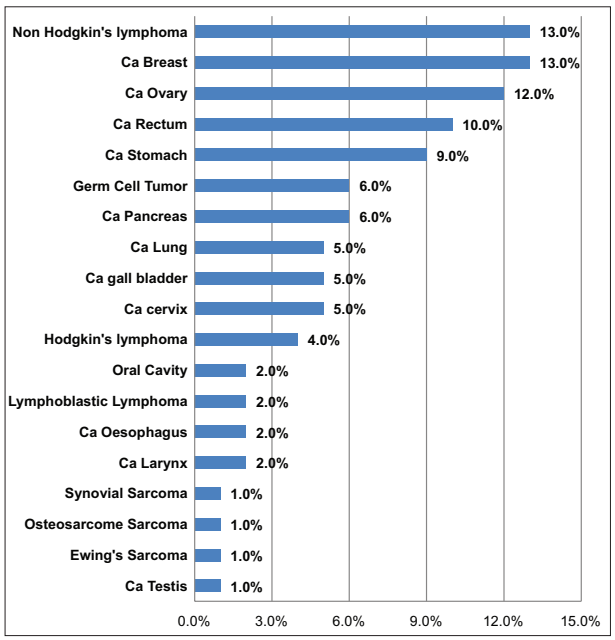

Fig. 1: Malignancies where febrile neutropenia was encountered in the study population

The mean number of antibiotics infusion days was 9.1 and median (IQR) days was 8. The Mean number of chemotherapy days after which patients reported to have FN was 3.6 and median (IQR) days was 2. G-CSF was administered in all patients in this study. The mean value of days required for recovery of the patients was 4.9 and median (IQR) days was 4.

Table 1: Depicting sites of infection seen in various patients of febrile neutropenia (n=100)

Systemic involvement	Number of patients (%)
Chest	16 (16.0)
GI tract	10 (10.0)
Genitourinary	4 (4.0)
Cellulitis	4 (4.0)
Urine	2 (2.0)
Hickman infection	1 (1.0)
PTBD insertion site infection	1 (1.0)
Central venous catheter	1 (1.0)

PTBD: Percutaneous transhepatic biliary drainage, GI: Gastrointestinal

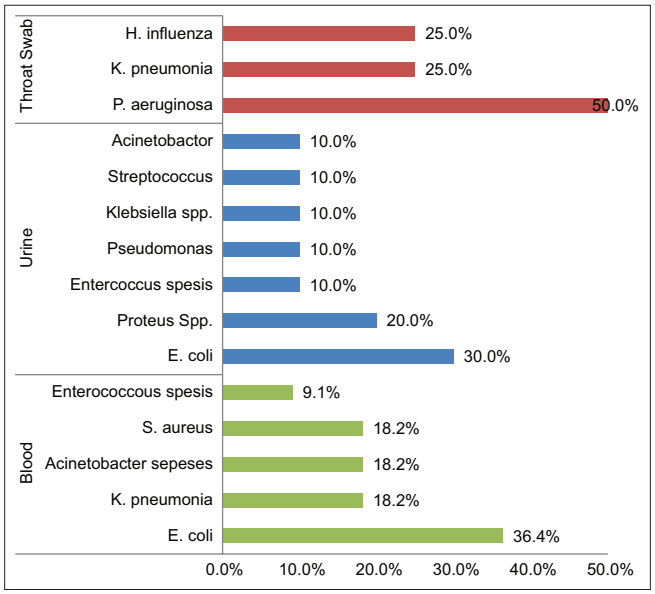

Fig. 2: Details of micro-organisms grown in febrile neutropenia patients in the study

Table 2: Summary of hemogram in study population

Parameters	Mean±SD (range)	Median (IQR)
Nadir Hb	9±2 (4–14.5)	9 (7.8–10)
Nadir TLC	1356.1±624 (260–2970)	1200 (900–1895)
ANC	328.6±157.8 (0–600)	355 (200–485)
Nadir platelets	82,880±42,321 (4000–183,000)	80,000 (48,000–100,500)

SD: Standard deviation, IQR: Interquartile range, Hb: Hemoglobin, TLC: Total leukocyte count

Table 3: Imaging findings in cases of febrile neutropenia in this study (n=100)

Imaging findings	Chest X-ray (%)	USG abdomen (%)
Infective focus seen	23	9
Infective focus not seen	77	91

USG: Ultrasound

DISCUSSION

Despite numerous trials and studies, FN remains one of the most notorious complications of cancer chemotherapy. FN is responsible for considerable morbidity as 20%–30% of patients present with complications that require in-hospital management, with an overall in-hospital mortality of ~10% [10]. Initial cycles of chemotherapy carry the highest risk of neutropenia at a rate of 50%–75%. Moreover, the risk of recurrence increases in patients who have experienced an initial neutropenic event. Factors associated with poor outcome in FN include advanced age, low albumin, deranged renal functions, and presence of chronic inflammatory states [11]. Guidelines from the American Society for Clinical Oncology suggest that antibiotic prophylaxis is to be used in patients with a high risk of FN [12].

In the present study, *Staphylococcus aureus* was the most common Gram-positive organism and *Klebsiella pneumoniae, Escherichia coli,* and *Acinetobacter* the most common Gram-negative organisms isolated in patients with FN. A study done by Haupt *et al*. showed a hike of 3.4% per year in the incidence of Gram-negative bacteremia in children with solid malignancies over a 10-year period study [13]. Similar results were observed in a study carried out by Gaytan-Martınez *et al*. where they also found that *E. coli* was the most common causative pathogen in FN [14]. According to the study done by Siddaiahgari *et al*, out of 89 isolates of neutropenic patients with cancer, majority of them represented with blood and urinary tract infections. Moreover, extended spectrum beta-lactamases, carbapenem resistant, and pan-resistant organisms were seen in 28 (31.4%), 5 (5.6%), and 2 cases (2.3%), respectively. Overall, Gram-positive isolates were 13/89 (12.3%). *Staphylococcus* was the most common Gram-positive organism and methicillin-resistant *S. aureus was* seen in 5 each, which correlated with our findings [15].

In the present study, the most common diagnosis was Ca breast (13%), non-Hodgkin's lymphoma (13%), and Ca ovary (12%). According to Ahn *et al.* [16], out of the 396 cases, 71.5% of patients were solid tumors. Among solid tumors, breast cancer was the most common followed by lung cancer, renal cell carcinoma, and gastric cancer. And 28.5% of patients had hematologic malignancies, where non-Hodgkin's lymphoma (19.4%) and acute leukemia (5.8%) were most common. These study findings are correlated with our study results.

Initially, antimicrobials were used to prevent episodes of FN. Most standard-dose chemotherapy regimens are associated with neutropenia, lasting for almost 1 week. Neupogen® (filgrastim) was the product of one of the pioneer clinical trials conducted by the U.S Food and Drug Administration in 1991. Filgrastim is an approved drug for managing patients receiving cancer chemotherapy with fever and neutropenia [17-19]. The recombinant hematopoietic colony-stimulating factor is a promoter of neutrophil maturation and their survival. It plays an important role in inducing granulopoiesis and plays a key role in preventing chemotherapy-related neutropenia [20]. However, according to Ahn *et al.,* prophylactic antibiotics, treatment with G-CSF, and history of FN were not associated with outcome, while Roviello *et al*. reported 11 (12.5%) patients out of 25 to have FN among patients receiving G-CSF [16,21].

Roviello *et al*. [21] reported 12.5%, Sato *et al*. reported 5.1% [22], and Hashiguchi *et al*. [23] reported 20% of patients, respectively, having FN as opposed to our study, wherein FN episode (11%) was seen in patients with Ca cervix, Ca esophagus, Ca ovary, and in patients receiving carboplatin plus paclitaxel.

Limitation of study

This study does not include the pediatric population and patients with myeloid leukemia.

CONCLUSION

In this study, episodes of FN occurred mostly in patients with Ca breast, followed by non-Hodgkin's lymphoma, and Ca ovary. The majority of the patients were in ECOG performance status 4. The common chemotherapeutic agent that leads to FN was carboplatin plus paclitaxel in patients with Ca cervix, Ca esophagus, and Ca ovary, followed by BFM 90 protocol in patients with adult lymphoblastic lymphoma and non-Hodgkin's lymphoma. The majority of patients had focused on infection in the bloodstream, with *E. coli* being the most implicated organism. The recovery is within 2 weeks. For most patients, the G-CSF administration along with guidelines-directed antibiotic therapy was found to be useful.

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AUTHORS' CONTRIBUTION

Dr. Byomakesh Swain, Dr. Ravi Jain, and Dr. Harpreet Singh have designed the entire work. and Dr. Sandeep Mishra contributes to making necessary correction and revision of the manuscript. The final draft was checked by all the authors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Nil.

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