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Chemotherapy-induced neutropenia and its determinants in patients with solid malignancies: A prospective observational study

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ABSTRACT

Background: Chemotherapy-induced neutropenia (CIN) is a significant dose-limiting toxicity of chemotherapy that can lead to severe infection and treatment disruption. Febrile neutropenia (FN) has an in-hospital mortality rate of 2–7% in adults with solid tumors. **Aims and Objectives:** This study evaluated the incidence, risk factors, and outcomes of CIN and FN in patients with solid malignancies in India. **Materials and Methods:** In this hospital-based prospective observational study conducted at Tirunelveli Medical College Hospital, 1,252 adult patients with solid tumors underwent chemotherapy over a 12-month period. Among these patients, 142 developed CIN and were included in the analysis. Demographic data, cancer stage, nutritional status, laboratory parameters, and radiotherapy and chemotherapy histories were recorded. CIN and FN were defined according to the common terminology criteria for adverse events v5.0. Patients were monitored for neutropenia and FN. Chemotherapy modifications, infection rates, and mortality were also recorded. Risk factor associations were analyzed using Chi-square and logistic regression analyses. **Results:** Among 142 patients (66.2% women), severe neutropenia (grade 3–4) occurred in 37.3% of patients, and FN occurred in 2.2% of patients, mostly during the initial chemotherapy cycle. Independent CIN risk factors included age >60 years (odds ratio [OR]: 2.21, P = 0.043), male sex (OR: 2.93, P = 0.005), underweight body mass index (OR: 2.35, P = 0.086), smoking (OR: 3.54, P = 0.003), comorbidities (OR: 3.08, P = 0.02). Prophylactic granulocyte colony-stimulating factor (G-CSF) significantly lowered FN incidence (13.2% vs. 28.8%, P = 0.038). The clinical consequences included dose delays (18.3%), reductions (17.6%), FN-related hospitalizations, and FN-related mortality (4.9%), predominantly in elderly patients. **Conclusion:** CIN and FN significantly affected the chemotherapy outcomes. Older age, malnutrition, comorbidities, and aggressive regimens increase the risk of developing this disease. Nutritional assessment and selective prophylactic G-CSF administration are critical for optimizing cancer care outcomes in resource-limited settings.

Key words: Chemotherapy-induced neutropenia; Febrile neutropenia; Solid tumors; Risk factors; Nutritional status

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INTRODUCTION

Chemotherapy-induced neutropenia (CIN) is a significant dose-limiting toxicity in cancer treatment, and up to half of patients with solid tumors receiving chemotherapy may develop febrile neutropenia (FN), which can cause serious infections and mortality.[1] FN has an in-hospital mortality rate of 2–7% in adults with solid tumors.[2,3] CIN often necessitates reductions or postponements in chemotherapy dosing, which can decrease relative dose

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intensity and potentially affect survival outcomes.[1,2] Thus, effective prevention and management of CIN are crucial for ensuring optimal treatment outcomes in oncology.

Several factors influence the risk of developing CIN/FN. Patient factors, including age >60 years, female sex, poor performance status, comorbidities, and poor nutritional status, are associated with a higher FN risk.[4] Factors related to the disease (advanced cancer stage and bone marrow involvement) and treatment (chemotherapy regimen and intensity) are important.[4] Regimens containing anthracyclines, taxanes, or high-dose platinum often cause severe neutropenia. Younger patients without comorbidities who received less myelosuppressive regimens had a lower risk of developing CIN/FN. According to guidelines, granulocyte colony-stimulating factor (G-CSF) prophylaxis is advised when the risk of FN is high (≥20%) or in the intermediate range (10–20%) and additional patient risk factors are present.[4] In many resource-limited settings, routine G-CSF prophylaxis is not utilized because of cost, leading to higher rates of CIN and FN.[5]

India has a growing cancer and chemotherapy burden; however, data on CIN determinants are limited. One observational study found grade 3–4 neutropenia in 43% of patients with solid tumors and an FN incidence of 15%.[6] We conducted a prospective observational study to determine the incidence of CIN and FN among patients with solid malignancies at a South Indian tertiary care center and analyzed the associated patient and treatment factors. We evaluated the effect of CIN on chemotherapy delivery and outcomes to guide risk-adapted interventions for improving patient safety and the quality of cancer care.

Aims and objectives

To evaluate the incidence, risk factor (including clinical & treatment-related factors), & clinical outcomes of chemotherapy-induced Neutropenia (CIN) & Febrile Neutropenia (FN) in adult patients with solid malignancies receiving chemotherapy at a tertiary care center in South India.

MATERIALS AND METHODS

This prospective observational study, conducted at Tirunelveli Medical College Hospital, involved 142 out of 1,252 patients who were treated with chemotherapy and subsequently developed CIN between January and December 2024. Adult patients (≥18 years) with histologically confirmed solid malignancies, receiving adjuvant, neoadjuvant, or palliative chemotherapy with an Eastern Cooperative Oncology Group performance status of 0–2 and adequate organ function, were included. Patients with pre-existing significant neutropenia (grade ≥2), hematological malignancies, active infections, or concurrent marrow-suppressive treatment were excluded.

Patients received standard chemotherapy protocols based on cancer type, including doxorubicin and cyclophosphamide, followed by paclitaxel or docetaxel for breast cancer; platinum doublet combinations for lung cancer; oxaliplatin and fluoropyrimidine combinations for gastrointestinal cancers; cisplatin-based regimens for head and neck cancers; and standard treatments for gynecologic cancers. Primary prophylaxis with G-CSF during the first cycle was used at the oncologist's discretion, particularly for regimens with a high risk of FN or in patients with multiple risk factors for FN. G-CSF was administered for FN or severe neutropenia, and broad-spectrum antibiotics were used according to institutional protocols. Patients were educated about neutropenia and advised to report fever or other symptoms between cycles.

Neutropenia was graded according to the National Cancer Institute common terminology criteria for adverse events version 5.0, from grade 1 (absolute neutrophil count [ANC] 1.5–<2.0×10^9/L) to grade 4 (ANC <0.5×10^9/L). CIN was defined as neutropenia occurring after chemotherapy, whereas FN was defined as a temperature ≥38.0°C with ANC <0.5×10^9/L expected to decline below 0.5×10^9/L. Each cycle was assessed for neutropenia and FN, and although multiple episodes were documented, each patient was counted once in the overall incidence.

Baseline data included age, sex, cancer diagnosis and stage, complete blood counts (hemoglobin, leukocyte, and platelet counts), and biochemical parameters, including renal function. Nutritional status was evaluated using body mass index (BMI), categorizing patients as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), or overweight (≥25 kg/m^2). Blood counts were performed before each cycle, and nadir ANC was recorded when available. Episodes of fever or infection were documented based on the clinical presentation, microbiological findings, treatment, and outcomes. Data on chemotherapy modifications, including dose delays, reductions, and discontinuations, were recorded using pre-designed forms.

The primary outcomes were the incidence of CIN and FN. The secondary outcomes included the identification of factors associated with CIN and FN and the evaluation of CIN's impact of CIN on chemotherapy delivery and patient outcomes, including infections, hospitalizations, and mortality. CIN and FN incidences were expressed as the percentages of affected patients.

Categorical variables were analyzed using the Chi-square or Fisher's exact test; variables with P<0.05 in the univariate

analysis were evaluated using multivariate logistic regression to identify independent predictors of CIN, expressed as odds ratios (OR) with 95% confidence intervals. Statistical significance was set at $P<0.05$. Statistical analyses were performed using SPSS software.

This study was approved by the hospital's Ethics Committee (Protocol ID 20232793) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent, and patient data were anonymized. This study received no external funding and had no conflicts of interest.

RESULTS

Most patients (66.2%) were <60 years of age, and 66% were female. Malignancies included breast carcinoma (32.4%), lung cancer (7%), head and neck cancer (16.9%), gastrointestinal malignancies (13.4%), gynecological/urogenital cancer (19.7%), and other solid tumors (10.5%). At baseline, 86% had advanced disease (Stage III-IV), 8.5% had bone metastasis, and 14% had early-stage disease. BMI showed that 21.8% were underweight, 47.2% were of normal weight, 23.9% were overweight, and 7% were obese. Comorbidities included diabetes (16.1%), hypertension (12.6%), and vascular events (5%), with 11.3% of patients having one and 16.2% having multiple comorbidities. A total of 31% of patients had received prior chemotherapy, and 24.8% had received prior radiotherapy. The most common chemotherapy regimens were paclitaxel/carboplatin (16.2%), AC (9.9%), and paclitaxel monotherapy (6.3%). Other regimens included cisplatin/5-fluorouracil (7%), carboplatin/5-fluorouracil (4.9%), pemetrexed/carboplatin (4.9%), and TPF (4.9%). Patients were classified as high-risk (40.8%), intermediate-risk (31%), or low-risk chemotherapy (28.2%) (Table 1).

CIN incidence was significantly higher in patients aged >60 years (52.1%) than in those aged ≤60 years (33%) ($P=0.043$). Males showed a higher CIN incidence (54.2%) than females (28.7%), with significance ($P=0.005$). Patients with a BMI below 18.5 kg/m^2 had a higher CIN incidence (61.3%) than those above 18.5 kg/m^2 (30.6%), with a significant difference ($P=0.042$). The presence of one or more comorbidities was significantly associated with a higher CIN incidence (65.2%) than that in patients without comorbidities (36.1%) ($P=0.018$). Smokers had a higher CIN incidence (60.6%) than non-smokers (30.3%) ($P=0.003$). Patients without primary G-CSF prophylaxis showed a significantly higher CIN incidence (28.8%) than those who received it (13.2%) ($P=0.041$). Similarly, the incidence of CIN was significantly higher among anemic

Table 1: Distribution of patient demographic, clinical, and chemotherapy-related characteristics

Variables	n (%)
Age	
<60	94 (66.2)
>61	48 (33.8)
Gender	
Female	94 (66.2)
Male	48 (33.8)
BMI	
Underweight	31 (21.8)
Normal weight	67 (47.2)
Overweight	34 (23.9)
Obese	10 (7)
Smoking history	
No	109 (76.8)
Yes	33 (23.2)
Alcohol consumption	
No	116 (81.7)
Yes	26 (18.3)
Comorbidities	
No	103 (72.5)
One comorbidity	16 (11.3)
More than one comorbidity	23 (16.2)
Previous history of FN	
No	100 (70.4)
Yes	42 (29.6)
Type of solid malignancy	
Breast	46 (32.4)
Lung	10 (7)
Head and neck	24 (16.9)
Genitourinary	28 (19.7)
Germ cell tumor	5 (3.5)
Miscellaneous	10 (7)
GI malignancy	19 (13.4)
TNM stage	
Stage 1	5 (3.5)
Stage 2	13 (9.2)
Stage 3	65 (45.8)
Stage 4	59 (41.5)
Advanced disease stage (III/IV)	
No	19 (13.4)
Yes	123 (86.6)
Prior chemotherapy	
No	98 (69)
Yes	44 (31)
Previous radiotherapy	
No	106 (75.2)
Yes	35 (24.8)
Chemotherapy regimen	
AC	14 (9.9)
Paclitaxel/carboplatin	23 (16.2)
Docetaxel/carboplatin	3 (2.1)
TPF	7 (4.9)
CAPOX	4 (2.8)
Cisplatin/5FU	10 (7)
Gemcitabine/5FU	2 (1.4)
TCH	4 (2.8)
IA	3 (2.1)
Lipodox/carboplatin	4 (2.8)
Docetaxel	4 (2.8)
FOLFOX	3 (2.1)
VAC	4 (2.8)

(Contd...)

Table 1: *(Continued)*

Variables	n (%)
Carboplatin/5FU	7 (4.9)
Gemcitabine/carbo	6 (4.2)
Bleomycin	5 (3.5)
Doceaqualip	2 (1.4)
Cisplatin/etoposide	6 (4.2)
EOF	3 (2.1)
Pemetrexed/carboplatin	7 (4.9)
Palbociclib	6 (4.2)
IROX	1 (0.7)
TAC	5 (3.5)
Paclitaxel	9 (6.3)
Chemotherapy risk	
Low risk	40 (28.2)
Intermediate risk	44 (31)
High risk	58 (40.8)

BMI: Body mass index, TNM: Tumor, node, metastasis, FN: Febrile neutropenia, GI: Gastrointestinal

Table 2: Association between baseline characteristics, treatment factors, and CIN

Characteristics	CIN (%)	P-value
Age (in years)		
>60 (n=48)	25 (52.1)	0.043
≤60 (n=94)	31 (33)	
Sex		
Male (n=48)	26 (54.2)	0.005
Female (n=94)	27 (28.7)	
BMI (kg/m^2)		
<18.5 (n=31)	19 (61.3)	0.003
>18.5 (n=111)	34 (30.6)	
≥1 comorbidity		
Yes (n=23)	15 (65.2)	0.018
No (n=119)	43 (36.1)	
Smoking history		
Yes (n=33)	20 (60.6)	0.003
No (n=109)	33 (30.3)	
Primary G-CSF prophylaxis		
Yes (n=68)	9 (13.2)	0.041
No (n=73)	21 (28.8)	
Anemia		
Yes (n=108)	35 (32.4)	0.015
No (n=33)	3 (9.09)	

G-CSF: Granulocyte colony-stimulating factor, BMI: Body mass index, CIN: Chemotherapy-induced neutropenia

patients (32.4%) compared to non-anemic individuals (9.09%) (P=0.015) (Table 2).

In the multivariate analysis, patients aged >60 years had a higher risk of developing CIN (OR: 2.21, 95% CI: 1.09–4.50, P=0.043). Male patients showed an increased risk (OR: 2.93, 95% CI: 1.42–6.04, P=0.005). The presence of more than one comorbidities was associated with a higher risk of CIN (OR: 3.08, 95% CI: 1.20–7.92, P=0.02). Patients with a smoking history were more likely to develop CIN (OR: 3.54, 95% CI: 1.58–7.95, P=0.003). G-CSF prophylaxis was associated with a reduced risk of CIN (OR: 0.38, 95% CI: 0.16–0.90, P=0.038) (Table 3).

Table 3: Multivariate logistic regression analysis of independent predictors of CIN

Predictors	Adjusted OR (95% CI)	P-value
Age >60 years	2.21 (1.09–4.50)	0.043
Male sex	2.93 (1.42–6.04)	0.005
Underweight (BMI <18.5 kg/m^2)	2.35 (0.98–5.60)	0.086
≥1 comorbidities	3.08 (1.20–7.92)	0.02
Smoking history	3.54 (1.58–7.95)	0.003
Primary G-CSF prophylaxis	0.38 (0.16–0.90)	0.038

BMI: Body mass index, G-CSF: Granulocyte colony-stimulating factor, CIN: Chemotherapy-induced neutropenia

Table 4: Incidence of CIN, FN, and associated outcomes

Outcomes	n (%)
Severe neutropenia (Grade 3–4)	53 (37)
FN incidences	30 (2.2)
Associated outcomes	
Due to CIN	
≥1 delayed chemotherapy cycle	26 (18.3)
Dose reduction	25 (17.6)
FN episodes	
Requiring hospitalization	30 (100)
With documented infection	12 (40)
Related deaths	7 (23.3)
Received G-CSF at any point (therapeutic)	69 (48)

G-CSF: Granulocyte colony-stimulating factor, CIN: Chemotherapy-induced neutropenia, FN: Febrile neutropenia

Among the 1252 patients, 142 experienced neutropenia during chemotherapy, resulting in an 11.3% incidence of CIN. FN was observed in 30 patients, corresponding to a 2.2% incidence, all of whom exhibited grade 4 neutropenia. Severe neutropenia, classified as grade 3–4, was present in 53 patients, accounting for a 37.3% cumulative incidence of CIN grade ≥3 (Table 4).

The median hospital stay was 6 days (range, 4–20 days). Broad-spectrum antibiotics and G-CSF therapy were administered to all patients. Microbiologically documented infections occurred in 12 FN episodes (40% of episodes). The most common infection sites were the respiratory tract (10 cases), neutropenic colitis (eight cases), and cellulitis (five cases). Three patients had urinary tract infections (*Escherichia coli*), and no fungal infections were documented. Neutropenia resolved after a median of 3 days of G-CSF treatment. Seven patients (23.3% of FN cases, 4.9% of the total patients) died from sepsis despite receiving ICU care. Five patients were elderly (>60 years) and had significant comorbidities. All other patients with FN recovered and resumed chemotherapy with adjustments as required (Table 5).

The intensity of the chemotherapy regimen strongly influences the risk of neutropenia. In patients with breast cancer who received anthracycline-taxane combinations,

Table 5: Management and outcomes of FN

Management and outcomes	n (%)
Empiric broad-spectrum antibiotics are administered	30 (100)
G-CSF therapy was initiated for the FN episode	30 (100)
Microbiologically documented infection complications	
Respiratory tract (pneumonia)	10 (33.3)
Neutropenic colitis	8 (26.7)
Cellulitis	5 (16.7)
Urinary tract infection (*Escherichia coli*)	3 (1)
Invasive fungal infections	0
Patients recovered and resumed chemotherapy	23 (76.7)
Median length of stay (days) (range)	6 (4–20)
Median time to neutropenia resolution with G-CSF (days)	3

G-CSF: Granulocyte colony-stimulating factor, FN: Febrile neutropenia

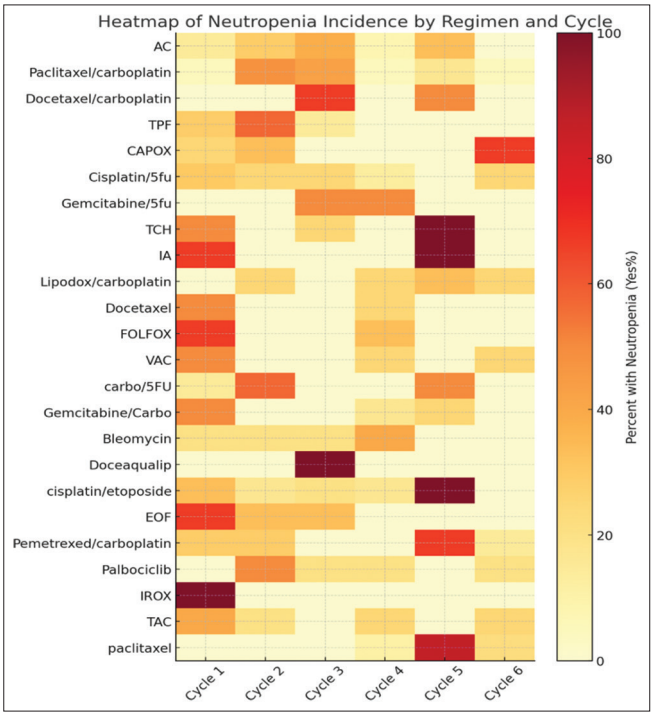

Figure 1: Heatmap of neutropenia and incidence

71.4% developed neutropenia. High CIN rates have been observed with platinum-based doublet therapies for lung cancer (66.7% with cisplatin-etoposide). Patients receiving less myelosuppressive treatment had a lower incidence of CIN (<20%) (Figure 1).

DISCUSSION

This study examined the burden of CIN in Indian patients with solid tumors. We found high rates of severe neutropenia (37%) and FN (2.2%) in patients with good performance status who received standard-dose chemotherapy. These findings align with regional reports, although population differences affect comparisons. Doshi et al. reported 43% grade 3–4 neutropenia, similar to our rates.[6] Our FN incidence was lower than that of Rapoport et al., 9.5%, likely due to G-CSF prophylaxis. The clinical impact of neutropenia is significant.[7] Other studies reported that one-third of patients with CIN require changes in their chemotherapy schedule. Maintaining dose intensity is crucial for survival in curative settings.[1] Patients with FN receive a lower dose intensity, potentially affecting tumor control. These findings emphasize the importance of preventing neutropenia to avoid treatment alterations.

Our study identified key CIN determinants that aligned with known risk factors. Advanced age was correlated with a higher FN risk in Western studies by Bachlitzanaki et al., and Schwenkglenks et al.[3,8] Patients >60 years of age showed a higher incidence of neutropenia, possibly due to reduced bone marrow reserves and comorbidities.[9]

In our study, poor nutrition was a significant predictor of neutropenia. Underweight patients had threefold higher odds of severe neutropenia than patients with normal BMI. Malnutrition impairs immune function and bone marrow reserve. Xiao et al. showed that pre-operative nutritional status predicted grade ≥3 neutropenia in patients with gastric cancer.[10] Nutritional support before chemotherapy may reduce the risk of CIN. A Thai study by Neesanun found that obese patients had higher severe neutropenia during lung cancer chemotherapy, suggesting that both under- and over-nutrition affect chemotherapy tolerance.[11] BMI could help refine CIN risk stratification.

In our study, chemotherapy intensity influenced the risk of neutropenia, similar to the study by Bow.[12] Myelotoxic combination regimens show high CIN rates, supported by Schwenkglenks et al.'s study.[8] Our findings showed that 32% of patients with breast cancer receiving G-CSF prophylaxis experienced grade 4 neutropenia. Hutajulu et al. reported 78% grade 4 neutropenia without prophylaxis.[5] Anthracycline-plus-taxane regimens increase severe neutropenia risk 3.6-fold, supported by Schwenkglenks et al.'s study.[8] These align with guidelines advocating G-CSF prophylaxis for treatments with 20% or higher FN risk.[3]

In our study, the pre-treatment neutrophil count predicted CIN, and patients who started chemotherapy with a low-normal ANC had a higher risk of severe neutropenia, consistent with the findings of Lyman et al., and Lyman et al.[13,14] When assessing risk, consider baseline ANC of 1.8×10^9/L versus 5×10^9/L; lower values provide less cushion during marrow suppression.

Our study advocates the identification of high-risk patients (those receiving myelotoxic regimens, especially elderly

or malnourished individuals) for G-CSF prophylaxis in resource-constrained settings. Selective G-CSF administration can cost-effectively prevent FN, as treatment costs often exceed prevention costs.[15]

In our study, the 4.9% FN-related mortality rate matches historical ranges for solid tumors (2–7%), indicating successful treatment with inpatient care and antibiotics.[2] FN episodes require week-long hospitalizations, disrupting cancer treatment schedules. Studies have shown that Gram-negative bacterial infections are prevalent in neutropenic patients.[3] Fungal infections are rare because of the shorter duration of neutropenia in solid tumor chemotherapy compared to hematologic malignancies.

Limitations of the study

Our single-center study with a modest sample size limits generalizability. Although we found associations between factors and CIN, our observational design cannot prove causation. Confounding factors were adjusted for, but unmeasured variables could have affected the results. We did not use the MASCC or CISNE risk scoring systems, which could be explored in future studies. The incidence of FN may have been underestimated if patients sought care elsewhere.

CONCLUSION

Our study concluded that 11.3% of the patients developed CIN, with 37% experiencing severe neutropenia. Key predictors included advanced age, low BMI, low hemoglobin level, and intensive chemotherapy regimens. These findings highlight the need for risk assessment and preventive strategies in high-risk populations. Adequate nutrition and prophylactic G-CSF can reduce the risk of FN and maintain the intensity of chemotherapy. Strengthening supportive care measures, especially in resource-constrained settings, can improve cancer treatment safety. Patient risk stratification, proactive care, and guideline-based prophylaxis can enhance treatment continuity and outcomes in patients with solid tumors.

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