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Chemotherapy-induced Neutropenia in cancer patients with solid tumors in India

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ABSTRACT

The present study was aimed to evaluate the incidences of chemotherapy-induced neutropenia and febrile neutropenia in the patients with solid tumors in India. The patients with carcinomas of breast, lung, ovary, colon, head and neck, and liver were divided in two groups. Group 1 was for the patients who experienced grade 0-2 neutropenia and Group 2 was for the patients with grade 3-4 neutropenia. Different types of chemotherapeutic agents were administered to the patients according to the routine practice of the physicians. The study revealed that the incidences of grade 3-4 neutropenia were observed in the patients with the first time exposure of the chemotherapeutic agents as well as the age factor also played an important role in the occurrence of neutropenia and febrile neutropenia. The results of this observational study indicate that the proportion of grade 0-2 neutropenia does not significantly (P-value > 0.05) differ from the hypotheses value (i.e. 50%). Thus, we concluded that the proportion of incidence of grade 3-4 neutropenia is less as compared to proportion of grade 0-2 neutropenia. The grade of neutropenia and impaired chemotherapy delivery remain serious problems in most solid tumor carcinomas. Hence, proper preventive rather than reactive measures should be taken by the physicians, considering co-factors which are responsible for the occurrence of neutropenia, to avoid severe long-term implications.

Keywords: Chemotherapy-induced neutropenia, Febrile neutropenia, Solid Tumors.

INTRODUCTION

Cancers in all forms are causing about 12% of deaths throughout the world. In the developed countries, cancer is the second leading cause of death accounting for 21% (2.5 million) of all mortality. In the developing countries cancer ranks third as a cause of death and accounts for 9.5% (3.8 million) of all deaths.

Chemotherapy is the standard remedy for patients with cancer. Myelosuppression is a major side effect of anticancer chemotherapy. Consequences include potentially life-threatening febrile neutropenic episodes, intravenous antibiotic treatment and prolonged hospitalization[1].

Chemotherapy dose reductions and delays are common sequelae and may affect treatment outcomes adversely[2,3].

Neutropenia is a disorder characterized by an abnormally low number of neutrophills in the blood. Particularly, chemotherapy-induced neutropenia (CIN) is the most common side effect associated with the administration of anticancer drugs. Up to 25% of patients treated with chemotherapy are likely to develop a febrile neutropenia (FN) episode [4] although this percentage could increase up to 96% in some particular type of tumors [5].

Neutropenia is defined as an abnormally low number of circulating neutrophils in the peripheral blood. It is an important dose-limiting toxicity of anticancer agents and is the most common cause of chemotherapy dose reduction and delay, which in certain tumour types has been reported to be associated with reduced treatment outcomes. Patients with neutropenia are at risk of developing febrile neutropenia, which can be life-threatening and usually leads to hospital admission and requires intravenous anti-infectives, disrupting the daily lives of patients, their families and carers, and reducing patients' quality of life.

The Common Toxicity Criteria of the National Cancer Institute established a scale of four grades for neutropenia, according to the absolute neutrophil count (ANC): grade 1, ANC ≥1.5 to <$2x10^9$/l; grade 2, ANC ≥1.0 to <$1.5x10^9$/l; grade 3, ANC ≥0.5 to <$1x10^9$/l; grade 4, ANC <$0.5x10^9$/l.

Neutropenia and resultant infections are potentially life-threatening side effects of cancer chemotherapy. The use of dose intensive chemotherapeutic regimens makes the management of myelosuppression increasingly important. The use of colony stimulating factor (CSF) in patients with established neutropenia after chemotherapy is mostly routine. Chemotherapy can exacerbate the development and progression of anemia in cancer patients. The incidence of transfusion-dependent anemia induced by chemotherapy ranges from 9% to 40%. Treatment with recombinant human erythropoietin (rhEPO) increases hemoglobin levels, reduces transfusion requirements and promotes negative side effects.

In Europe, it is common practice in many hospitals to delay or reduce chemotherapy doses in an effort to minimize this risk or in response to the occurrence of a myelosuppressive event or low neutrophil nadir. For example, Chirivella et al (2009) reported that, in their hospital it was standard protocol to delay chemotherapy by 5–7 days even at lower grades of neutropenia, if the neutrophil count was <$1.5×10^9$/L or if the platelet count was <$100×10^9$/L [6].

Myelosuppression (bone marrow suppression) is the most important toxic side effect of most chemotherapeutic agents and typically is the dose-limiting factor. Death occurring after chemotherapy usually results either from infection related to drug-induced leucopoenia or from bleeding related to thrombocytopenia. Chemotherapeutic agents affect the rapidly proliferating pool of blood precursors in the marrow leading to a predictable decrease in the peripheral white blood cell count at approx. 7-14 days after the drug is administered depending on the type and intensity of chemotherapy [7]. Incidence of severe infection rises dramatically when the absolute neutrophil count drops below 1000 cells/mm^3. Some possible predictors include a 49% risk of FN if the absolute lymphocyte count is less than 700 mm^3 [8]. In general, febrile neutropenia is treated with immediate hospitalization and the administration of intravenous antibiotics [9]. In Addition to the impact on patient's quality of life, episodes of FN may result in subsequent chemotherapy dose delays or reductions.

A patient with febrile neutropenia is very susceptible to suffer life-threatening complications including death, and this is related to the duration and severity of the FN episode [10]. Moreover, the higher the duration of neutropenia, the higher infection risk, so it is fundamental to determine the CIN duration at the onset of a febrile neutropenic episode.

Colony-stimulating factors (CSFs) are widely used in adjunct to standard-dose chemotherapy and in febrile neutropenic patients. Routine use of CSFs for primary prophylaxis of FN for any common disease in previously untreated patients can reduce the incidence of FN as much as 50% [11], but has minimal impact on freedom from disease and overall survival [12]. The rationale for secondary CSF administration in patients with a prior episode of FN, pre-existing neutropenia due to disease, and a history of neutropenia while receiving earlier chemotherapy of similar or lesser dose-intensity is two-fold. First, according to the American Society of Clinical Oncology (ASCO) 2000 guidelines, this group of patients is most likely to benefit from CSF support, and second, the use of CSF, a relatively expensive treatment with several side effects, would shorten the duration of neutropenia.

Neutropenia was found in 51% of patients who were treated for lymphoma or solid tissue malignancy [13]. The degree and duration of neutropenia is determined by the intensity of the chemotherapy regimen [14].

No such data have been published so far on chemotherapy-induced neutropenia and febrile neutropenia in Indian population. So our objective is to assess the incidence and risk of chemotherapy-induced neutropenia, febrile neutropenia in patients with solid tumors undergoing chemotherapy in India.

MATERIALS AND METHODS

The study was carried out at Shyam Hem-Onc Clinic, Ahmedabad and Medisurge Hospitals, Ahmedabad, Gujarat, India. The study design was observational and treatment was as per normal institutional clinical practice. Records were kept of all blood counts taken during each patient's chemotherapy treatment. The protocol was approved by the Institutional Ethics Committee. All the participants provided written informed consent before participation in the study. Data release forms were filled for the patients. Baseline demographic details as well as details of their Complete Blood Count (CBC) were collected. Patient's oncology related history was also recorded.

2.1 Study Population

2.1.1 Inclusion Criteria

1. Patients with histologically confirmed diagnosis of malignancy
2. Adult participants (age 18 or older, without upper age limit) who start a new myelosuppressive chemotherapy regimen sequence
3. ECOG Performance status ≤ 2 and life expectancy ≥ 3 months
4. Prior or concurrent radiation therapy will be allowed
5. To sign data release form

2.1.2 Exclusion Criteria

1. Active infection within 72 hour prior to start of chemotherapy
2. Malignant conditions with myeloid characteristics
3. Use of antibody-based or cell-based immunotherapies (with the exception of rituximab)
4. History of stem cell or bone marrow transplantation
5. Concurrent participation in other trials
6. Pregnancy and lactation
7. Patients with any other serious concurrent illness
8. Patients with continuing history of alcohol and/or drug abuse

2.1.3 Withdrawal Criteria

1. The patient suffers from significant intercurrent illness
2. Any patient found to have entered the study in violation to this protocol
3. If it is felt in Investigator's / Medical Expert's opinion that it is not in the patient's best interest to continue
4. Any patient / relative who wishes to withdraw his / her consent for participation in the study

2.2 Study end points:

The efficacy end points were as follows:

1. Incidence of grade 3 (ANC $<1.0x10^9$/L) and grade 4 neutropenia (ANC $<0.5x10^9$/L)
2. Incidence of FN (ANC $< 1.0 \times 10^9$/L and temperature $\geq 38\ ^0$C)

2.3 Blood Collection and Sample analysis

The blood samples were collected from each patient for the estimation of Complete Blood Count (CBC) in each follow-up visit. The follow-up schedules were different for different patients based on the type of cancer they were associated with. The samples were analyzed at the College of American Pathologists (CAP) & National Accreditation Board for Testing and Calibration Laboratories (NABL**)** accredited labs.

2.4 Statistical Analysis

Patients were stratified into two groups based on the grade of neutropenia they experienced (grades 0-2 versus grades 3-4). Exact binomial test was used to test the significant proportion rate of incidence of grade 0-2 neutropenia and grade 3 (ANC $<1.0x10^9$/L) or grade 4 neutropenia (ANC $<0.5x10^9$/L). All demographic data was presented using the descriptive statistics (like N, Mean, SD, and Median). SAS software version 9.1 was used for statistical analysis.

RESULTS AND DISCUSSION

3.1 Demographics

For present study, one hundred patients were selected based on inclusion and exclusion criteria with median age of 56 years (range 28-78 years) and male: female ratio was 51:49. Table 1 shows the statistical calculation like mean, median, and standard deviation (SD) for different categories of cancer.

Table 1: Demography of all patients

		Diagnosis						
		Ca Colon	Ca Breast	Ca H & N	Ca Lung	Ca Liver	Ca Ovary	Total
Age (in Years)	N	11	37	11	20	10	11	100
	Mean	55.55	52.51	54.18	56.09	51.7	54.18	54.08
	SD	13.44	11.64	9.34	9.52	12.41	9.34	10.97
	Median	61	55	55	58.5	55.5	55	55.50
Height (in cm)	N	11	36	11	20	10	11	100
	Mean	165.64	159	166.45	170.77	168.5	166.45	164.74
	SD	7.31	7.22	6.56	6.87	8.37	6.56	8.44
	Median	164	158	166	168.5	166	166	165.00
Weight (in kg)	N	11	36	11	20	10	11	100
	Mean	61.97	67.4	52.39	59.75	59.67	52.39	61.48
	SD	11.76	12.32	6.52	12.06	15.86	6.52	12.54
	Median	61	68.3	56.4	58.5	56.4	56.4	58.45
BSA (m2)	N	11	36	11	20	10	11	100
	Mean	1.69	1.69	1.57	17.53	1.67	1.57	3.45
	SD	0.17	0.16	0.11	38.97	0.23	0.11	17.61
	Median	1.71	1.67	1.62	1.68	1.62	1.62	1.65

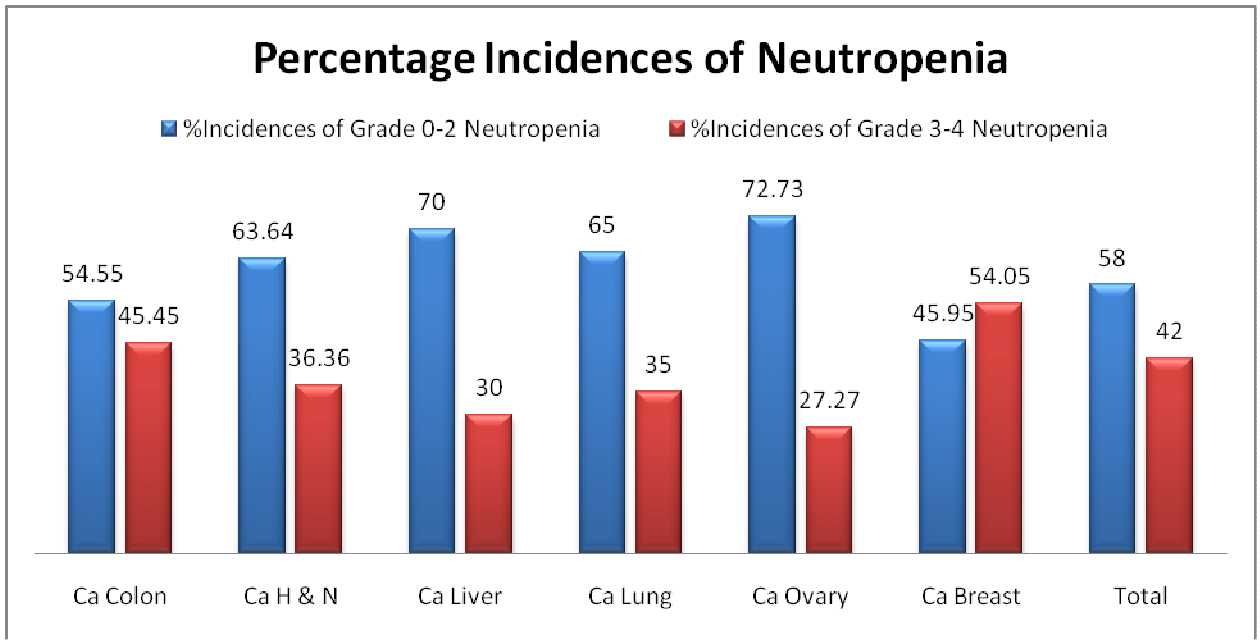
3.2 Types of solid tumor carcinoma

Patients with carcinomas of breast, lung, colon, ovary, head & neck, and liver were studied**.**

Table 2: Incidences of Grade 0-2 and Grade 3-4 Neutropenia

	Diagnosis						Total
	Ca Colon	Ca H & N	Ca Liver	Ca Lung	Ca Ovary	Ca Breast	
Grade	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Grade 0-2	6 (54.55)	7 (63.64)	7 (70)	13 (65)	8 (72.73)	17 (45.95)	58 (58)
Grade 3-4	5 (45.45)	4 (36.36)	3 (30)	7 (35)	3 (27.27)	20 (54.05)	42 (42)
P-Value	1.000	0.549	0.344	0.263	0.227	0.743	0.133

Chart 1: Percentage Incidence of Grade 0-2 and 3-4 Neutropenia



3.3 Rates of Neutropenia

The rates of grade 3 or 4 neutropenia in the whole study were 43% (43/100). The rates of Grade 3 or 4 neutropenia in different cancers were 54% (20/37) in breast cancer patients, 35% (7/20) in lung cancer patients, 36% (4/11) in

ovarian cancer patients, 46% (5/11) in colon cancer patients, 36% (4/11) in head and neck cancer patients, and 30% (3/10) in liver cancer patients. The median age of experiencing grades 0-2 and 3-4 neutropenia was 49 years (range 28-78) and 56 years (range 36-74). Table 2 shows the calculation of p-value for grade 0-2 and 3-4 neutropenia for different types of cancers and Chart 1 shows the percentage incidences of Grade 0-2 and 3-4 neutropenia.

3.3 Febrile Neutropenia

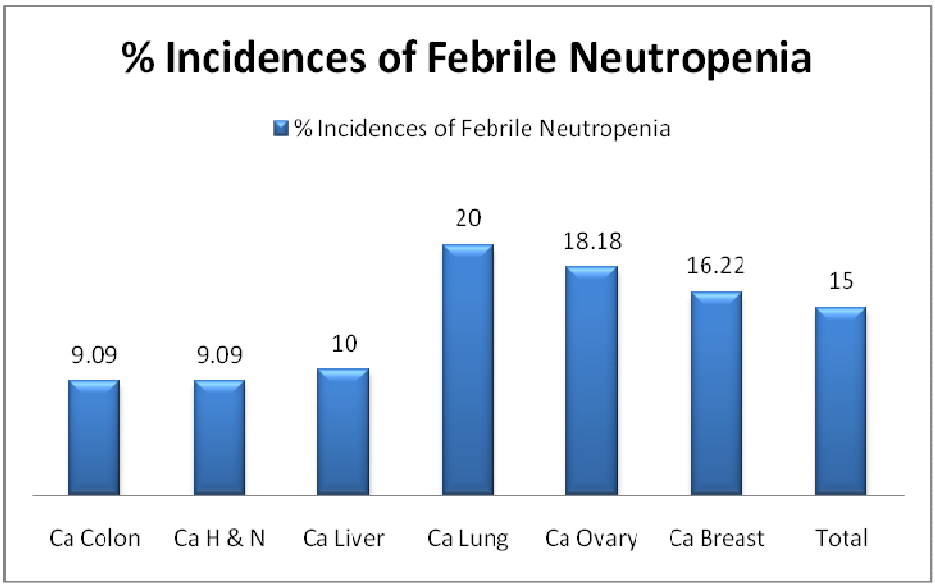
The incidence of febrile neutropenia in the whole study was 15% (15/100). This incidence was 16.22% (6/37) in breast cancer patients, 20% (4/20) in lung cancer patients, 18.18% (2/11) in ovarian cancer patients, 9.09% (1/11) in colon cancer patients, 9.09% (1/11) in head and neck cancer patients, and 10% (1/10) in liver cancer patients. No statistical test was performed due to insufficient data available for statistical calculations. However, data are presented in tabular form in Table 3 for patients who experienced febrile neutropenia. Graph 2 shows percentage incidences of febrile neutropenia.

Table 3: Incidences of Febrile neutropenia

	Diagnosis						Total
	Ca Colon	Ca H & N	Ca Liver	Ca Lung	Ca Ovary	Ca Breast	
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Febrile Neutropenia	1 (9.09)	1 (9.09)	1 (10)	4 (20)	2 (18.18)	6 (16.22)	15 (15)

Note: Statistical test is not performed due to insufficient counts.

Chart 2: Percentage of Incidence of Febrile Neutropenia



3.4 Chemotherapy treatment

Depending upon the nature and stage of the disease, different chemotherapeutic agents were prescribed by the physicians. However, it has been observed that patients having the first time exposure to chemotherapeutic agents experienced higher grade of neutropenia (approx. 70%) while the repeated exposure lead to lower grade of neutropenia or no neutropenia. It was also observed that patients treated with Taxane or Platinum based chemotherapy, experienced higher grade neutropenia i.e. approx. 57% (21/37).

DISCUSSION

This study assessed the incidences of CIN and FN and their consequences for chemotherapy delivery in patients with carcinomas of breast, lung, colon, ovary, head & neck, and liver undergoing chemotherapy.

Neutropenia during chemotherapy has been studied as a surrogate marker for improved treatment outcomes in breast cancer [17-19], osteosarcoma [15], ovarian [16] and non small cell lung cancers [20].

A significant proportion of FN and grade 3-4 neutropenia occurred in the first cycle of chemotherapy for the majority of regimens considered. This finding is consistent with reports from other studies. The incidence of FN for the most frequently used breast cancer regimens was low (16%). However, grade 4 neutropenia occurred in a low proportion of patients (11%) but significantly impacted upon chemotherapy delivery.

Dose reductions and dose delay were observed frequently due to low ANC, age factor, and co-morbidities.
A certain underestimation of neutropenia rates and, to a lesser extent, FN rates may have occurred because the frequency of blood counts was according to local institutional practice (apart from the protocol-specified blood count taken at cycle 1 nadir). The FN risk of patients treated with anthracycline-based regimens was 20%-25%. Regimens with concomitant anthracyclines and taxanes that have a high (> 20%) generic FN risk were appropriately supported by primary CSF prophylaxis in most cases. In the present study, the overall FN rate for patients receiving primary CSF prophylaxis was lower as compared to those treated without prophylactic CSF support.

Choice of chemotherapy regimen is a key driver of adverse events including neutropenia and FN. Differing outcomes of patients who experience higher degrees of neutropenia could be due to several possible factors. Firstly, the anti-cancer drugs used to treat different types of cancers. It is possible that those patients with greater rates of myelotoxicity are those with greater plasma drug levels. Studies have shown various genetic polymorphisms may affect the metabolism of anti-cancer agents and it is possible that these factors may lead to subgroups of patients with higher active drug levels [21, 22]. Secondly, genetic polymorphisms are known to predict chemo-sensitivity of anti-cancer drugs in normal tissue and tumour. Thus, patients could respond differently to an anti-cancer drug despite having similar pharmacokinetic profiles [23, 24].

CONCLUSION

This observational study provides information about the occurrence of CIN and FN examines how neutropenic events and other factors impact upon chemotherapy delivery. The results of this observational study indicate that the proportion of grade 0-2 neutropenia does not significantly (P-value > 0.05) differ from the hypotheses value (i.e. 50%). Thus, we concluded that the proportion of incidence of grade 3-4 neutropenia is less as compare to proportion of grade 0-2 neutropenia. The grade of neutropenia and impaired chemotherapy delivery remain serious problems in most solid tumor carcinomas. Hence, proper preventive rather than reactive measures should be taken by the physicians, considering co-factors which are responsible for the occurrence of neutropenia, to avoid severe long-term implications.

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