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RESEARCH PAPER

Neutropenia in breast cancer patients receiving Paclitaxel as chemotherapy: a study in a tertiary care centre in Northeast India

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Background and aims: *Chemotherapy-induced neutropenia (CIN) is one of the most common side effects in breast cancer patients receiving myelosuppressive chemotherapy like Paclitaxel which adversely affect patient outcomes.* ***Materials and methods:*** *A single centre, retrospective, observational study was conducted on 210 breast cancer patients with prior adequate bone marrow, hepatic and renal functions, receiving Paclitaxel as neoadjuvant or adjuvant or palliative chemotherapy from January 2018 to April 2019 at State Cancer Institute (SCI), Guwahati, Assam, India. Patients with a history of taking immunosuppressive agents, immunodeficiency states, hematological disease and any intercurrent illness were excluded from this study. Paclitaxel was given two weekly for four cycles at a dose of 175mg/m2 in each cycle. A total of 836 cycles were observed for 210 patients, while four patients did not complete the last cycle due to peripheral neuropathy.* ***Results:*** *The average age of the patients was 49.44±9.13 years. Among 210 patients, 82 patients presented with neutropenia (39.02%), while total neutropenia episodes were 128 (15.31%). Seven patients presented with febrile neutropenia (FN) out of 82 patients who received Paclitaxel (8.54 %). Prior incidence of CIN, advanced age, poor performance status and lower baseline Hb% were found as risk factors for CIN.* ***Conclusion:*** *The incidence of CIN and CIN episodes was 39.02% and 15.31%, respectively, in our study. Hence judicious use of Granulocyte colony-stimulating factor (G-CSF) as prophylaxis in our populations with close monitoring and as needed may be undertaken. However, the limitations of our study were the small sample size. Hence, further studies are necessary for a large scale population to confirm the findings of our research.*

Keywords: *Chemotherapy-induced neutropeni; Paclitaxel; North-East India.*

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INTRODUCTION

Breast cancer is the most commonly occurring cancer in women in developed and developing countries like India and the second most common cancer worldwide after lung cancer. According to Global Burden of Cancer (GLOBOCAN) study 2018, there were over 2 million new breast cancer cases were reported in 2018 worldwide.[1]

Indian Council for Medical Research [ICMR] has reported 1.5 lakhs of new breast cancer cases in India per year. Chemotherapy is one of the mainstays in the management of

breast cancer. Paclitaxel is an effective anticancer agent derived from the bark of Taxus brevifolia Nut (Taxaceae) and forms one of the most commonly use chemotherapeutic agents in breast cancer management in various settings like neoadjuvant, adjuvant or palliative setting.[2]

Myelosuppression is a significant dose-limiting side effect of Paclitaxel manifested as anemia, neutropenia, thrombocytopenia or a combination of any of these. Paclitaxel induces troublesome neutropenia of grade 3-4 in the dose range of 150-250 mg/m^2 in more than 50% of the patients. According to the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v 4.0), neutropenia is defined by a granulocyte count below 1.5×10^9/L (**Table 1**). CIN increases the risk of infection which is typically manifested by fever. When neutropenic patients develop fever, i.e. FN, the likelihood of infection and serious consequences often necessitates immediate hospitalization for urgent evaluation, ongoing monitoring, and empirical administration of broad-spectrum intravenous antibiotics.[3]

The management of CIN often mandate the use of G-CSF other than chemotherapeutics dose reduction, dose delay and discontinuation of chemotherapeutic agents, which seriously interfere with the delivery of optimal treatment and possibly adversely aûecting patient outcome.[4,5]

SCI, Guwahati is one of India's North-Eastern region's tertiary care oncology centers, providing comprehensive oncology services to the patients of this regions; however, data regarding neutropenia in breast cancer patients from this part of India is limited. With the knowledge from the existing literature, we have aimed to investigate the profile of CIN in breast cancer patients receiving Paclitaxel; use of G-CSF in neutropenic breast cancer patients of North-east populations receiving Paclitaxel as chemotherapy and to evaluate the association of CIN with other baseline patient characteristics.

MATERIALAND METHODS

The present study is a single centre hospital-based retrospective observational study done at SCI, Guwahati, Assam, India.

Study population:

All breast cancer patients with adequate baseline bone marrow, hepatic and renal functions who develop neutropenia after receiving Paclitaxel as neoadjuvant or adjuvant or palliative chemotherapy under the Medical Oncology department at SCI Guwahati from January 2018 to April 2019 over 16 months were included in the study. Patient with a history of taking immunosuppressive drug or patient with immunodeûciency status or any hematological diseases or any intercurrent illness were excluded from the study.

Paclitaxel was given two weekly for four cycles at a dose of 175mg/m2/cycle. Long-acting G-CSF, like injection pegfilgrastin 6 mg, was used subcutaneously for both primary and secondary prevention of neutropenia. In contrast, short-acting G-CSF, like injection filgrastin 300 mcg, was used to treat neutropenia for 7-10 days or till absolute neutrophil count (ANC) > 3000/dl.

Data were collected on following parameters:

i) Patient's characteristics: age, sex, menopausal status, Eastern Co-operative Oncology group Performance Status (ECOG-PS), chemotherapy setting, hormone receptor (HR) status and other laboratory parameters like baseline haemoglobin, total count and platelet count.

ii) Neutropenic status: symptomatology, grade of neutropenia, episodes of FN.

iii) Subsequent dose reduction, dose delay or suspension of chemotherapy in neutropenic patients.

iv) Use of G-CSF.

Table 1: Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v 4.0) grading of Chemotherapy-Induced Neutropenia (CIN)

Grade of Neutropenia	Absolute Neutrophil Count
Grade 1	Lower Limit of Normal -1500/µL
Grade 2	1000-1500/µL
Grade 3	500-1000/µL
Grade 4	<500/µL

Statistical analysis:

Baseline characteristics of the study participants are expressed in mean ±SD. Correlations were observed by using Pearson's correlation co-eûcient. The results were considered signiûcant when the probability (p-value) was less than 0.05% of the observed values of "t" at a particular degree of freedom. Statistical analysis was done using GraphPad InStat version 3.00. All the statistical graphs were prepared using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA). Prior ethical clearance was taken from the institute's ethics committee SCI of GMCH, Guwahati, Assam Vide Ref. No. SCI/ECR/2020/02 dated 02/05/2020.

RESULTS

A total of 210 breast cancer patients were included in the study, with a mean age of 49.44± 9.13 years at diagnosis. The female to male ratio was 208:2. The majority of female patients were postmenopausal (56.19%). Total 836 cycles of Paclitaxel were observed in 210 patients, with four patients who did not complete the last cycle due to peripheral neuropathy. (Table 2 and 3)

Incidence of CIN:

Among 210 breast cancer patients who received paclitaxel, 82 patients (39.05%) developed CIN. A total of 128 (15.24%) episodes of CIN were documented. The majority of

neutropenic breast cancer patients had the triple-negative disease (n=27, 32.93%), and a majority (n=48 episodes, 38.28%) received Paclitaxel in palliative setting followed by adjuvant (31.42%) and neoadjuvant (29.52%) setting. Grade I neutropenia (51.22%) was most common among neutropenic patients, followed by Grade III (18.29%) and Grade II neutropenia (17.07%). A total of 7 (8.54%) patients presented with FN. Among seven FN patients, six had grade IV neutropenia, while one patient had grade III neutropenia. (**Figure 1** and **Table 3**)

Table 2 Baseline clinical characteristics

Serial No.	Parameters	Number (%)
1.	Total number of patients Included	210
2.	Age of presentation (years)	49.44±9.13 years
3.	Sex:	
	Male	2
	Female	208
4.	Menopausal status:	
	Premenopausal	43.81%
	Postmenopausal	56.19%
6.	Baseline receptor Status	
	HR positive	117 (55.71%)
	Her2neu positive	65 (31.42%)
	TNBC	43 (20.47%)
	Combined HR & Her2neu positive	83 (39.52%)
7.	Baseline hematological parameters	
	Hemoglobin (gm %)	11.2±2.1 gm%
	Total count (109/L)	7.6±3.3 ×109/L
	Platelet count (109/L)	2.8±1.45 × 109/L

Incidence of CIN:

Among 210 breast cancer patients who received paclitaxel, 82 patients (39.05%) developed CIN. A total of 128 (15.24%) episodes of CIN were documented. The majority of neutropenic breast cancer patients had the triple-negative disease (n=27, 32.93%), and a majority (n=48 episodes, 38.28%) received Paclitaxel in palliative setting followed by adjuvant (31.42%) and neoadjuvant (29.52%) setting. Grade I neutropenia (51.22%) was most common among neutropenic patients, followed by Grade III (18.29%) and Grade II neutropenia (17.07%). A total of 7 (8.54%) patients presented with FN. Among seven FN patients, six had grade IV neutropenia, while one patient had grade III neutropenia. (Figure 1 and Table 3)

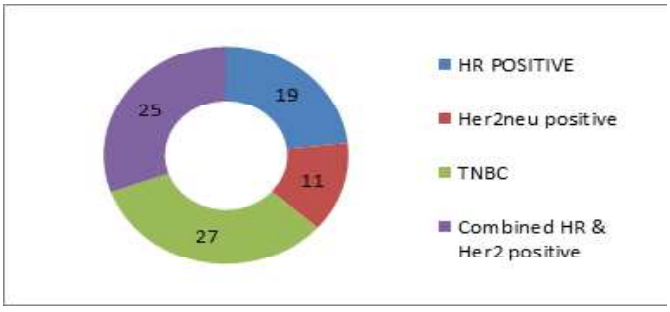

Figure 1 Receptor status in Neutropenic patients

Table 3 Neutropenic events in the present study

Sl. No.	Parameters	No.(n=210)
1.	Total no. of patients developing CIN	82 (39.05%)
2.	Grades of Neutropenia	
	Grade I	42 (51.22%)
	Grade II	14 (17.07%)
	Grade III	15 (18.29%)
	Grade IV	11 (13.41%)
3.	Total episodes of CIN	128 (15.24%)
4.	Patients presented with FN	7 (8.54%)
5.	Chemotherapy setting in Neutropenic patients	
	Neoadjuvant	37 (28.90%)
	Adjuvant	43 (33.59%)
	Palliative	48 (37.5%)

Abbreviations: HR- Hormone receptor; Her2neu- Human epidermal growth factor 2; TNBC- Triple-negative breast cancer]

Most of the CIN patients were asymptomatic at presentation, while 9 patients presented with fever and 3 patients presented with diarrhoea.

Risk factors of CIN: Patient with advanced age (>60 years), poor ECOG-PS (e"2), comorbidities like baseline anemia and neutropenia and disease in advanced stage (i.e. receiving chemotherapy in palliative setting) are at a higher risk of developing CIN, as shown in Table 4.

Table 4 Association of chemotherapy induced neutropenia with other baseline factors

Parameters		No. of CIN patients	p-value
Age group	< 40 years	12 (14.63%)	p=0.038
	40-60 years	26 (31.7%)	r=0.39
	>60 years	44 (53.65%)	
Baseline Hb status (%)	8-10 %	61 (74.39%)	p=0.022
	< 8gm %	21 (25.60%)	r=0.55
History of prior CIN		38 (46.38%)	

Impact of CIN on chemotherapy schedule and use of G-CSF: Patients with FN were hospitalized and treated with injectable antibiotics and G-CSF support as per institutional protocol with temporary withhold of chemotherapy. Patients with grade III CIN received G-CSF, and in them, the chemotherapy schedule was delayed. Patient with grade 2 CIN received chemotherapy at a reduced dose while there is no dose reduction or delay in grade I CIN.

Table 5 Neutropenic episodes following paclitaxel in the study

Following	Following Cycle 1	Following Cycle 2	Following Cycle 3	Following Cycle 4	Total (n)
Grade 1	2	19	17	4	42
Grade 2	2	7	4	1	14
Grade 3	1	4	8	2	15
Grade 4	1	3	6	1	11
Total	6	33	35	8	82

Among the 82 patients who developed CIN, 25 patients (30.49%) experienced dose delay while 14 patients (17.07%) experienced dose reduction. There was greater occurrence of neutropenia following the 3rd cycle followed by the 2nd cycle of Paclitaxel **(Table 5)**. The mean duration of neutropenia was 5±3 days. CIN was the most common cause of temporary suspension of chemotherapy **(Figure 2)**; a delay of about 7±2 days occurred between cycles. In no patient, chemotherapy was completely discontinued due to CIN.

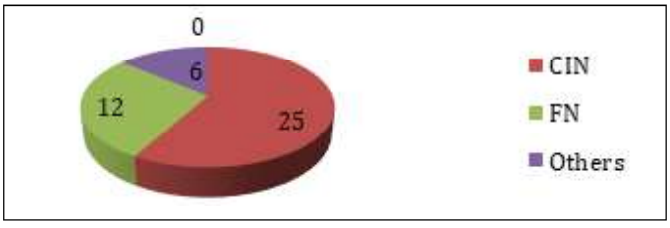

Figure 2 Reason for the delay between the chemotherapy cycles.

[**Abbreviations:** CIN- Chemotherapy-induced neutropenia; FN- Febrile neutropenia]

In the present study, G-CSF was used in the highest number for secondary prevention (n=23, 28.05%) of neutropenia followed by treatment of neutropenia (n=15, 18.29%). Simultaneously, only one patient received G-CSF for primary prevention of neutropenia (**Table 6**).

DISCUSSION

Breast cancer is the 2nd most common cancer worldwide and the most common cancer in female. In general, breast cancer has been reported to occur a decade earlier in Indian patients than their Western counterparts. Although most

Table 6 Use of Granulocyte-Colony Stimulating Factor (G-CSF) in various setting in the study

Indication of G-CSF in Neutropenic patients	Number (%)
As primary prophylaxis of CIN	1 (1.22%)
As secondary prophylaxis of CIN	23 (28.04%)
Treatment of neutropenia	15 (18.29%)

patients with breast cancer in Western countries are postmenopausal and in their 60s and 70s, the picture is quite different in India.[6,7] More than 80% of Indian patients are younger than 60 years of age.[8] The average age of patients with breast cancer has been reported to be 50 to 53 years in various population-based studies done in different parts of the country.[9,10] In the present study, we have documented a median age of 49.33± 9.13 years which is similar to the survey by Gogia A et.[11] In studies from Western countries, the median age of presentation was 55-60 years.[6,7] The present study documented that approximately 43.81% of patients were premenopausal and 56.19% were postmenopausal, whereas researchers from the Western world recorded 70% to 80% postmenopausal patients.[6,7]

In this study, HR status was positive in 55.71% (n=117) of patients; previous studies documented approximately 49% to 68% of HR-positive status.[6,7,11] The incidence of TNBC in the present study was 20.47% (n=43) which is higher than the survey by Kunikullaya SU et al. (16%).[12]

The development of neutropenia during chemotherapy is influenced as much as by the characteristics of the drug used as by the conditions presented by the patient. Although the risk factors for neutropenia during chemotherapy with Paclitaxel in breast cancer patients is not well defined, current studies found advanced age (> 60 years), low ECOG PS (e"2), reduction in haemoglobin and total count before starting Paclitaxel as a significant risk factor for the development of subsequent CIN.

The incidence of neutropenia in the present study was 39.02% (n=82) which is quite different as reported by another researcher, i.e., 10-34% by Schwenkglenks M et al., and Chia VM et al., 46.4% by Xuan Ye et al., in Chinese patients, 50.50% by Yasunori Hashiguchi et al., in Japanese patients and 63.3% by Talita Gracia do Nascimento et al., in Brazilian patients.[13,14,15, 16, 17] Incidence of FN in the present study was 8.54%. In comparison, it was 6.9% in the survey by Yasunori Hashiguchi et al.[16] In our research, we found that neutropenia was more when Paclitaxel was used in a palliative setting, but Talita Gracia do Nascimento et al., in their study found that it was common in the adjuvant setting.[17] Among the 128 episodes of neutropenia, grade 1 neutropenia was most common, followed by grade 3 and grade 2, which was similar to the study by Talita Gracia do Nascimento et al.[17] There was greater occurrence of neutropenia following 2nd and 3rd of Paclitaxel in the present study. In contrast, Derek Weycker et al., in their research, found that it was common following 3rd cycle of chemotherapy.[18] In the current research, G-CSF was used in the highest number (n=23, 28.05%) for secondary prevention of neutropenia, which is similar to findings in the study by Derek Weycker et al. but Xuan Ye et al. in his research on Chinese patients found that use of G-CSF was highest in treatment of CIN and lowest for secondary prevention of CIN (1.9%).[18,15] CIN was the most common cause of temporary suspension of chemotherapy (28.05%) which is similar to the study by Xuan Ye et al.[15] The mean duration of neutropenia was 5±3 days which is identical to the survey by Yasunori Hashiguchi et al.[16]

CONCLUSION

In the study, we have found that most of the patient were younger age and premenopausal at presentation and in the productive years of their life. CIN is fairly common in breast cancer patients receiving Paclitaxel, by identifying risk factors, such as elderly age group, baseline anemia, poor performance status, disseminated disease or distant metastatic disease, the safe management of chemotherapy-induced neutropenia may be possible in patients. Although delays or reductions of chemotherapy dose minimize the myelotoxicity, these actions can negatively impact the result of the treatment, on overall survival and must be avoided as much as possible.

Limitation of the study: A limitation in our study is that the study population was less, so we advocate for further studies with a large number of patients over a longer duration of the period.

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Conflict of interest: No conflict of interest associated with this work.

Contributions of authors: We declare that we did the study, and we will bear all liabilities about claims relating to this article's content. **Conception and design:** Dr. Naba K. Kalita, Dr. Hitesh Deka. **Collection of data:** Dr. Naba Kumar Kalita, Dr. Pranjit Moral, Dr. Hitesh Deka. **Data analysis and interpretation**: Dr. Neelakshi Mahanta, Dr. Hitesh Deka, Dr. Naba K. Kalita. **Manuscript writing and final approval of manuscript:** All authors. **Accountable for all aspects of the work:** All authors.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 Nov;68(6):394-424.

2. Casper ES, Waltzman RJ, Schwartz GK, Sugarman A, Pfister D, Ilson D, Woodruff J, Leung D, Bertino JR. Phase II trial of Paclitaxel in patients with soft-tissue sarcoma. Cancer Invest. 1998;16(7):442-6.

3. Chang J. Chemotherapy dose reduction and delay in clinical practice. evaluating the risk to patient outcome in adjuvant chemotherapy for breast cancer. Eur J Cancer. 2000 Apr;36 Suppl 1:S11-4.

4. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006 Jul 1;24(19):3187-205.

5. Caggiano V, Weiss RV, Rickert TS, Linde-Zwirble WT. Incidence, cost, and mortality of neutropenia hospitalization associated with chemotherapy. Cancer. 2005 May 1;103(9):1916-24.

6. Dafni U, Grimani I, Xyrafas A, Eleftheraki AG, Fountazilas G. Fifteen-year trends in metastatic breast cancer survival in Greece. Breast Cancer Res Treat 2010 Feb;119(3):621-31.

7. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? Cancer 2004 Jan 1;100(1):44-52.

8. Agarwal G, Ramkant P. Breast cancer care in India: The current scenario and challenges for the future Breast care (Basel) 2008;3(1):21-7.

9. National Cancer Registry Programme: First All India Report: 2001-2002, Chapter 2: Overall planning and methods. 2010. Available from: URL:http:// www.ncdirindia.org/ncrp/ca/ map.aspx.

10. National Cancer Registry Programmme: First All India Report: 2001-2002, Chapter 4: Minimum incidence rates of cancer [all sites] in districts. 2010. Available from: URL:http:// www.ncdirindia.org/ncrp/ca/ chapter4_1.aspx.

11. Gogia A, Deo SVS, Sharma D. Thulkar S, Kumar R, Malik PS, et al.: Clinicopathologic characteristics and treatment outcomes of patients with up-front metastatic breast cancer: Single-centre experience in India. J Global Oncol 2019 Mar;5:1-9.

12. Kunikullaya SU, Poddar J, Sharma AD, Patel S. Pattern of distant metastasis in molecular subtypes of carcinoma breast: An institutional study. Indian j cancer 2017;54(1): 327-32.

13. Schwenkglenks M, Jackisch C, Constenla M, Kerger JN, Paridaens R, Auerbach L, Bosly A, Pettengell R, Szucs TD, Leonard R. Neutropenic event risk and impaired chemotherapy delivery in six European audits of breast cancer treatment. Support Care Cancer. 2006 Sep;14(9):901-9.

14. Chia VM, Page JH, Rodriguez R, Yang SJ, Huynh J, Chao C. Chronic comorbid conditions associated with risk of febrile neutropenia in breast cancer patients treated with chemotherapy. Breast Cancer Res Treat. 2013 Apr;138(2):621-31.

15. Ye X, Zhai Q, Wang ZY, Du Q, Zhu B, Yu B. Neutropenic complications in Chinese patients with breast cancer in a real-world setting. International journal of clinical and experimental pathology. 2017 Jan 1;10(1):651-660.

16. Hashiguchi Y, Kasai M, Fukuda T, Ichimura T, Yasui T, Sumi T. Chemotherapy-induced neutropenia and febrile neutropenia in patients with gynecologic malignancy. Anticancer Drugs. 2015 Nov;26(10):1054-60.

17. do Nascimento TG, de Andrade M, de Oliveira RA, de Almeida AM, Gozzo Tde O. Neutropenia: occurrence and management in women with breast cancer receiving chemotherapy. Rev Lat Am Enfermagem. 2014 Mar-Apr;22(2):301-8.

18. Weycker D, Edelsberg J, Kartashov A, Barron R, Lyman G. Risk and healthcare costs of chemotherapy-induced neutropenic complications in women with metastatic breast cancer. Chemotherapy. 2012;58(1):8-18.