Article published online: 2023-08-11



Breast Cancer

# Phase 1/2 Study of the Timing and Efficacy of 3 mg Peg-GCSF in Neo/Adjuvant Dose Dense Breast Cancer Treatment Protocols

Amol Patel[1] Abhishek Pathak[2] Arti Sarin[3] Divya Shelly[1] Richa Ranjan[2] Arashdeep Singh[1] Tripti Kala[4] Babitha PV[4]

[1] Indian Naval Hospital Ship, Asvini, Mumbai, Maharashtra, India
[2] Command Hospital, Kolkata, West Bengal, India
[3] Western Naval Command, Mumbai, Maharashtra, India
[4] Day Care Chemotherapy Centre, INHS, Asvini, Mumbai, Maharashtra, India

Address for correspondence Abhishek Pathak, MBBS, MD, DNB, Command Hospital, Kolkata 700 027, West Bengal, India (e-mail: drabhipat@gmail.com).

South Asian J Cancer 2023;12(3):238–244.

## Abstract

Amol Patel

**Background** Peg-GCSF has similar efficacy at a dose of 60 µg/kg and 100 µg/kg. The conventional 6 mg SC dose was based on the maximum tolerable dose. In Japan, 3.6 mg dose was approved on the basis of dose finding studies. Peg-GCSF is an integral part of dose-dense chemotherapy protocols. Dose finding and scheduling study of peg-GCSF have not been conducted in Indian patients.

**Materials and Methods** We conducted two-center phase 1/2 clinical study addressing the timing and efficacy of peg-GCSF in Indian breast cancer patients (CTRI no: 2021/07/034751). Three groups of timing administration were studied, namely 1, 6, and 24 hours post chemotherapy. The phase 2 part was the expansion of the best timing group. The primary objective was dose density, which was defined as receiving chemotherapy on $<3$ days of scheduled date. Adriamycin/epirubicin cyclophosphamide (AC/EC) was administered q2 weeks. The total leucocyte (TLC) and absolute neutrophil (ANC) kinetics were studied. Other outcomes were incidence of grade 4 neutropenia, febrile neutropenia (FN), and requirement of additional doses of G-CSF. Bone pain, fever, and myalgia were studied for adverse effects.

**Results** From November 20 to December 21, 36 patients were enrolled. Patient characteristics are depicted in Table 1. Initially, three patients received the peg-GCSF in each timing group. One patient in each 1-hour and 6 hours needed G-CSF support for maintaining the dose density. The 24-hour group was carried to phase 2 part. Dose density was maintained in 97% of patients. None of the patient in 24-hour group had FN. Also, 4/30 patients had grade 4 neutropenia and required an additional dose of GCSF. Grade 3 or 4 bone pain was not noticed by any of the patients. During the first cycle, the mean ANC (cells/µL) was 5284, 20704, 3010, 6954 on D0, D + 3, D + 7, and D + 13, respectively (Fig. 1A-TLC and 1B-ANC). The mean ANC (cells/µL) rise on D + 3 in cycles 1, 2, 3, 4 was 23810, 29209, 32428,22455, respectively.

**Keywords**

- 3 mg
- dose dense protocol
- Indian patients
- pegylated GCSF
- phase 2 study

DOI https://doi.org/10.1055/s-0042-1757599 ISSN 2278-330X

**How to cite this article:** Patel A, Pathak A, Sarin A, et al. Phase 1/2 Study of the Timing and Efficacy of 3 mg Peg-GCSF in Neo/Adjuvant Dose Dense Breast Cancer Treatment Protocols South Asian J Cancer 2023;12(3):238–244.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

**Conclusion** Dose density of AC/EC breast cancer protocol is maintained with peg-GCSF 3 mg. Post chemotherapy 24-hour timing of peg-GCSF administration remains as the standard. A phase 3 trial of 6 mg versus 3 mg is warranted.

## Background

The granulocyte colony stimulating factor (G-CSF) is in common use for the last 30 years. They are used commonly for the prevention and treatment of febrile neutropenia (FN)[1] and also for mobilizing the harvest before stem cell transplant. The use of these factors is increased remarkably over the last one decade after the dose-dense protocol in adjuvant or neoadjuvant breast cancer treatment became the standard of care for maintaining the dose density.[2–4] The pegylated-GCSF (Peg-GCSF) was introduced into clinical practice in 1999 and has changed the conventional practice of use of daily GCSF.[5]

The dose of 100 µg/kg of Peg-GCSF was based on phase 1 pharmacokinetic study in mice and human volunteers of age 18 to 45 years. The median absolute neutrophil count (ANC) max ($\times 10^6$/mL) was 30.4, 31.2, 36.7, and 50.8 with doses of 30, 60, 100, and 300 µg/Kg, respectively.[5] Similarly, the median duration of response in days (range) was 5.79 (4.75–9.88), 8.79 (3.83–13.9), 8.29 (4.67–8.92), 8.79 (6.83–13.8) for 30, 60, 100, and 300 µg/kg, respectively. There was no significant difference between 60 µg/kg and 100 µg/kg for ANCmax. The duration of response was better with 60 µg/kg. The kinetics studies of G-CSF have shown that the duration of response might not prolong with increasing doses. The adverse effects of Peg-GCSF are fever, bone pain, and muscle pains. Bone pain has been reported in 25 to 60% of patients. The life-threatening adverse effects such as splenic rupture is rare but of real-world concern.[6] The use of colony-stimulating factors is also associated with significant risk of secondary malignancies especially for acute myeloid leukemia and myelodysplastic syndromes.[7]

Apart from the above known common side effects of G-CSF, there have been several reports of acute respiratory failure during G-CSF-induced neutropenia recovery.[8] It is believed to enhance cytokine production and activate the oxidative burst within circulating or resident alveolar neutrophils and macrophages leading to lung damage. During and postCOVID-19 pandemic, these risks are to be addressed.[9] De-escalating the dose might prevent such complications.

In Japan, peg-GCSF has been approved at a dose of 3.6 mg.[10] The dose finding study on GCSF and/or peg-GCSF has not been conducted in Indian patients. The average weight of Indian females is around 20 kg lesser than their western counterparts. With this background, we hypothesized that reduction of dose to half will not affect the neutrophil recovery and it will maintain the dose intensity chemotherapy protocol in breast cancer patients. The timing of peg-GCSF post chemotherapy has lacuna in the literature.[11]

A phase 1/2 study has been designed to test the timing, safety, tolerability, and efficacy of a lower dose of peg-GCSF (3 mg) in patients who are receiving chemotherapy with dose dense adriamycin/epirubicin cyclophosphamide (dd-AC/EC) protocol. Side effects of peg-GCSF would reduce and there is a scope of reducing financial burden of health care.

## Materials and Methods

This phase 1/2 trial was conducted at two centers of armed forces hospitals located in Mumbai (Center A) and Kolkata (Center B). The trial was registered at the Clinical Trial Registry India (CTRI 2021/07/034751). All patients were informed about the procedure and written informed consent was obtained. The Helsinki code of ethical conduct was followed.

### Objectives of the Study

The primary objective of the study was to maintain dose intensity, and a delay in scheduled day of chemotherapy $> 3$ days was considered as an event. Secondary objectives were to analyze the total leucocyte count (TLC) and ANC kinetics, side effects profile will be as per the common terminology criteria for adverse event (CTCAE) version 4[12] to estimate the incidence of FN and the need of additional dose of G-CSF and grade 3 and 4 neutropenia.

### Patients

All consecutive patients were enrolled after establishing the early and locally advanced breast cancer diagnosis. Staging work up was done as per the institutional protocol. The study started after obtaining the ethics committee approval and study registration. Inclusion criteria were patients having ECOG Performance status $< 2$, age of 18 to 75 years, adequate baseline bone marrow function reflected as hemoglobin $> 8$ g/dL, TLC $> 3{,}500/\text{mm}^3$, ANC $> 1{,}500/\text{mm}^3$), and platelets $> 100{,}000/\text{mm}^3$, serum creatinine $< 1.5$ mg/dL, serum bilirubin $< 3$ mg/dL, liver enzymes (AST and ALT) within 3 times the upper normal limit. Patients must not have exposed to previous chemotherapy and have active autoimmune disease. Exclusion criteria were lactating and pregnant women, history of previous carcinoma in last 5 years and active hepatitis B, C, or HIV infection. Echocardiography was done for all patients before the start of chemotherapy.

### Peg-GCSF

The 6 mg/0.6 mL peg-GCSF pre-filled syringe was used. The pre-filled syringe was emptied in insulin syringe (1 mL) until the 0.3 mL mark. Next, 3 mg of peg GCSF was administered by insulin syringe. A vial of 6 mg was used as per the availability at Center A. The enrolled patients received peg-GCSF 3 mg on

 

as per timing group. Peg-GCSF was administered after 1 hour, 6 hours, and 24 hours of chemotherapy completion. After assessment of the response in nine patients, the second part of the study conducted as phase 2 design and 30 consecutive patients were enrolled. One hour and 6-hour groups were studied at centers A and B, respectively. The 24-hour group was studied at both centers.

### Chemotherapy

Dose dense adriamycin (60 mg/m$^2$) cyclophosphamide (600 mg/ m$^2$) (AC) and epirubicin (90 mg/m$^2$) cyclophosphamide (600 mg/m$^2$) (EC) every 2 weeks for four cycles were allowed at standard doses at the discretion of treating medical oncologists.

### Procedures

Initially, three patients were studied for pharmacokinetics of peg-GCSF in each 1-hour, 6-hour, and 24 -hour group. Complete blood count was monitored on D + 0, D + 3, D + 7, and D + 13. Patients having ANC below 500/mm$^3$ were treated with additional doses of GCSF for maintaining the dose density. During weekly paclitaxel, CBC monitored weekly, one day prior of chemotherapy and no peg-GCSF was used unless indicated.

Fever in neutropenic (ANC < 500 cells/mm$^3$) patients was defined as a single oral temperature of ≥ 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) sustained over a 1-hour period.[1] The total leucocyte count measured by an autoanalyzer and whenever required counts were confirmed by slide method.

### Statistics

As per the pharmacokinetic study stated above, we hypothesized that 3 mg of peg-GCSF will be equivalent to 6 mg peg-GCSF with a margin of 5%. Also, 3 mg dose was chosen for ease of administration and round off as compared to 3.6 mg considering the average weight of Indian breast cancer patients is below 60 kg. Next, 95% of patients completed the assigned dose dense protocol on or within 2 days of the scheduled date. This assumption is based on previous established literature.[2] The relative dose intensity has been used as the primary outcome in a previous study.[10] The rate of grade 4 neutropenia in the Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741 was 6% in dose dense trial. The treatment delays were 6% in dose dense arm, and 15% were attributed to hematological toxicities.[2] In the landmark trial of adjuvant weekly paclitaxel (dose dense), all 12 doses were permitted to complete within 15 weeks from the initiation of Taxane therapy, considering holidays, vacation, and toxicities.[13] Descriptive statistics was used to study the variables. The association of variables was studied by Chi-square test or Fisher's exact test wherever needed. STATA statistical software version 13 was used for data analysis. Phase 1 patients were planned to include in the combined analysis.

### Sample Size

For alpha error of 0.05, beta error of 80%, and the largest response probability of 95% for phase 2 design (Fleming's phase II procedure), a predetermined sample size of 30 was considered adequate.

### Safety Monitoring

If rates of FN exceeded > 5% at 3 months or at 25% accrual, the trial would have stopped.

## Results

This study was conducted at two centers of armed forces hospital located in Mumbai and Kolkata from July 2021 to December 2021. The baseline characteristics of patients are depicted in ►Table 1. All patients were female with a median age of 50 years (range: 31–72).

### Outcomes

In phase 1 part, one patient each in 1-hour and 6-hour groups had grade 4 neutropenia and none in the 24-hour group. Then, six patients in the 24-hour group and one patient had grade 4 neutropenia. Then, the 24-hour group was expanded as phase 2 part.

Primary objective (maintenance of dose density) – In all patients, dose density was maintained except one patient who received on D + 3 of scheduled day. Another three and two patients received on D + 1 and D + 2 of scheduled date, respectively.

### ANC/TLC Kinetics

All four days' kinetics were available for 27 patients and is shown in ►Fig 1A and 1B. During the first cycle, the mean ANC (cells/µL) was 5,284 (SD 1,616), 20,704 (SD 10,354), 3,010 (SD 2,191), 6,954 (SD 12,050) on D0, D + 3, D + 7, and D + 13, respectively. The mean ANC (cells/µL) on D + 3 in cycles 1, 2, 3, 4 was 23,810, 29,209, 32,428, and 22,455, respectively. All four days and all four cycles information was available for 18 patients and percentile distribution is shown in ►Table 2 (box plot distribution is shown in ►Fig 2A–D). A few patients tend to show a remarkable response to peg-GCSF. Such outliers were not studied separately.

### Toxic Deaths

No toxic death or treatment-related mortality during this study was seen.

### Febrile Neutropenia

One patient had FN in post fourth cycle at center A in the 1-hour group. She had a temperature of 100.4°F and ANC was 120 cells/µL. She recovered with two doses of G-CSF 300 µg over 2 days and received antibiotics as per the institutional policy. None of the patients in the 24-hour group had FN.

### Grade 3/4 Neutropenia

In this study, 6/29 patients had grade 3 neutropenia and 4/29 had grade 4 neutropenia.

### Requirement of Additional Doses of GSCF

A total of six patients received an extra dose or doses of G-CSF 300 µg. Details of these patients are shown in ►Table 3. At

 

**Table 1** Baseline characteristics of patients ($n = 36$)

| Variable | *N* | % |
|---|---|---|
| **Center*** | | |
| A | 7 | 19.44 |
| B | 29 | 80.55 |
| **Age (y)** | | |
| Median (range) | 50(31-72) | |
| **Sex** (female) | 36 | 100 |
| **Weight** | | |
| Median (range) | 61.3 (47.9-82) | |
| BMI ≥ 25 kg/$m_2$ | 22 | 59.46 |
| Weight > 60 kg | 18 | 50 |
| **Menopausal status** | | |
| Pre | 14 | 37.84 |
| Peri | 2 | 5.4 |
| Post | 20 | 54.05 |
| **Comorbidities** | | |
| DM2 | 3 | 8.33 |
| DM2 + hypertension | 1 | 2.77 |
| Hypertension | 1 | 2.77 |
| Hypothyroidism | 1 | 2.77 |
| **Therapy** | | |
| Adjuvant | 16 | 44.44 |
| Neoadjuvant | 20 | 55.55 |
| **Stage** | | |
| Early | 16 | 44.44 |
| Locally advanced | 19 | 52.77 |
| Oligometastatic | 1 | 2.77 |
| **Receptor** | | |
| ER +/PR+ | 19 | 52.77 |
| Her2neu + | 0 | 0 |
| Triple-negative | 15 | 41.66 |
| **Chemotherapy** | | 88.88 |
| AC | 32 | |
| EC | 4 | 11.11 |
| **Surgery**** ($n = 17$) | | |
| MRM | 12 | 33.33 |
| BCS | 5 | 13.88 |
| **Baseline** | | |
| Median (range) | | |
| Hb (gm/dL) | 11.45 (8.5-13.5) | |
| Platelet count (lakh/mm ) | 2.43 (0.72-5.12) | |
| Total proteins (g/dL) | 7.55 (5.9-9.1) | |
| Albumin (g/dL) | 4.05 (3-5.2) | |

*Centre A – located at Mumbai, B at Kolkata, ** As the study is ongoing, as on 15.1.2022, 17 patients completed surgery, AC/EC: adriamycin epirubicin cyclophosphamide, ER: estrogen receptor, PR: progesterone receptor.

center B, patients were admitted and monitored for ANC. Three patients received the GCSF during second cycles and one patient received during the first cycle. At center B, one patient needed an additional dose of G-CSF during the first cycle. Another patient at center A also received additional two doses of G-CSF in the fourth cycle.

## Discussion

In a retrospective Japanese study of 97 patients of breast cancer treated with dose dense AC protocol, peg-GCSF 3.6 mg prevented the occurrence of FN and maintained a relative dose intensity of 97.9%. In our study, 97.3% of patients completed the assigned treatment in time. The rate of treatment delay by 1 week was seen in a study by Burstein et al in 4.9% of cases though the reasons for delay were not exclusive to hematological toxicity.[14]

Peg-GCSF 3 mg was used in lung cancer in China with positive results in terms of reducing acute lower respiratory tract infection and reducing FN.[15] Similarly, 3.6 mg was used in colon cancer patients treated with the FOLFIRI regimen.[16] Intense chemotherapy protocols, such as docetaxel, adriamycin, and cyclophosphamide (TAC) were studied with 3.6 mg peg-GCSF support and compared with 6 mg. The duration of severe neutropenia was equal in 3.6 and 6 mg groups.[17] Similarly, one large retrospective study from China evaluated the role of 3 and 6 mg peg-GCSF in docetaxel plus cyclophosphamide-treated breast cancer patients. The rates of FN were similar, i.e., 7.3 versus 8.3% in both the groups.[18] There is a prospect of studying the low-dose peg-GCSF in other conditions.

The average weight of females in India, Japan, China, and USA is 52.5, 54.8, 62.2, and 77.1 kg.[19] In a study by Masuda et al on peg-GCSF 3 mg, BSA was 1.55 $m^2$ and the body weight was $>$ 60 kg in 38% of cases in the 3.6 mg group.[17] In our study, 50% of patients had a weight of more than 60 (range: 47.9–82) kg. As the primary objective was met, weight in this series would have minimal effect on outcomes. However, this area remains an active field of research in respect of diverse Indian populations and applicability to the western population.

Overall, the rates of FN remain low (1.5–3%) in dose dense protocols.[2,14,20] In our study, in the 24-hour phase 2 part, none of the patients had FN. Grade 4 neutropenia of 13% was higher in our patients. The rate of grade 4 neutropenia was 6% in seminal work by Citron et al[2] and grade 3 and 4 neutropenia was 11.8% in a Japanese study.[10] The duration of grade 4 neutropenia usually lasts for $\leq$ 3 days.[10,20]

The remarkable higher response to peg-GSCF is not studied in the literature. Such responses are unpredictable. Further studies should analyze such patients separately and long-term follow-up of such patients should be done for the development of bone marrow-related toxicity.

### Strength of the Study

For the first time, Indian breast cancer patients were studied systematically for timing and dose of peg-GCSF. All four cycles were analyzed for ANC kinetics for all D0, D + 3, D + 7 and D + 13 days, which are not studied before.

 

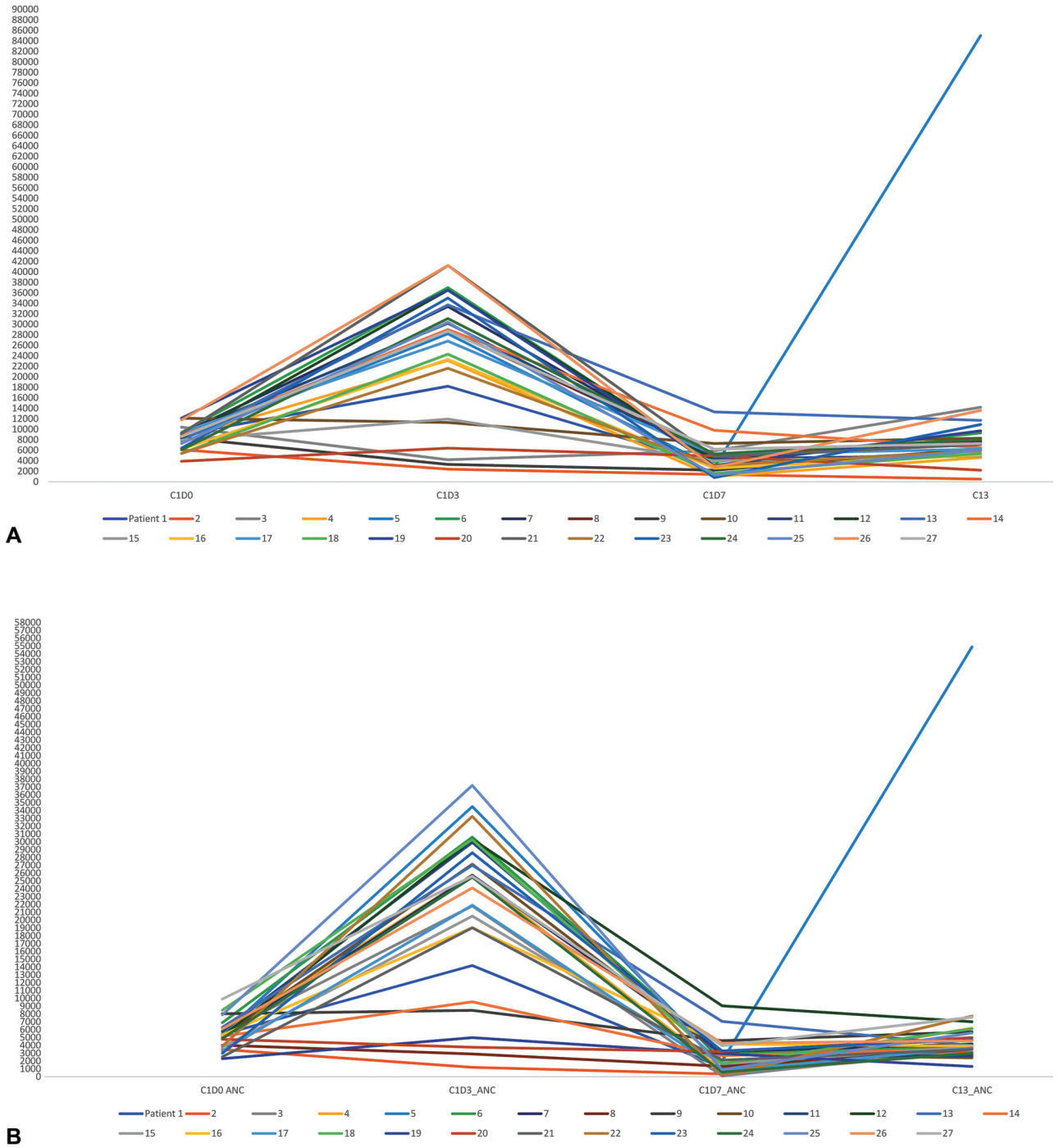


**Fig. 1** (**A**) Total leucocyte count: post first chemotherapy cycle (out of 36 patients, 27 had available information on ANC for all days). (**B**) Absolute neutrophil count: post first chemotherapy cycle (out of 36 patients, 27 had available information on ANC for all days).

## Limitations of the Study

Our study was limited to only breast cancer patients treated with dose dense protocol. The COVID-19 pandemic posed a real challenge to conduct the study. At center A, due to the second peak, enrollment was hampered and a smaller number of patients were recruited. Daily monitoring of counts was not done, which was impracticable during the pandemic. Some patients refused for admission and carried the peg-GCSF at home. It is possible that cold chain might not be maintained during the long 12-hour travel in one patient in the 1-hour group. We expanded the 24-hour group as per our initial experience and available literature. The rates of grade 4 neutropenia appeared to be the same; however, the increase in counts was less in 1-hour and 6-hour groups.

Challenges faced during the conduct of the trial – The majority of patients travelled far distances across the state. The cold chain maintenance is an integral problem in our country. In the 24-hour schedule, travelling to the center is a big hurdle for the conduct of such a trial. Autoinjectors availability would make a change in care of these patients.

 

**Table 2** Percentile distribution of ANC in respect of chemotherapy cycles ($n = 72$ doses, 18 patients)

| | Percentile distribution of ANC* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Days of chemotherapy** | **1%** | **5%** | **10%** | **25%** | **50% (median)** | **75%** | **90%** | **95%** | **99%** |
| **#Cycle 1** | | | | | | | | | |
| D0 | 2300 | 2300 | 2538 | 4784 | 5275 | 5800 | 8040 | 8500 | 8500 |
| D3 | 2900 | 2900 | 3760 | 9560 | 23810 | 29930 | 30600 | 34500 | 34500 |
| D7 | 90 | 90 | 750 | 1674 | 2808 | 3200 | 7056 | 9044 | 9044 |
| D13 | 1300 | 1300 | 2410 | 3500 | 3950 | 5727 | 7020 | 54900 | 54900 |
| **Cycle 2** | | | | | | | | | |
| D0 | 1300 | 1300 | 2410 | 3500 | 3950 | 5727 | 7020 | 54900 | 54900 |
| D3 | 3685 | 3685 | 3900 | 14520 | 29209 | 40570 | 53100 | 62360 | 62360 |
| D7 | 290 | 290 | 500 | 1020 | 1521 | 5148 | 7917 | 8800 | 8800 |
| D13 | 413 | 413 | 800 | 3150 | 5031 | 6808 | 7970 | 12240 | 12240 |
| **Cycle 3** | | | | | | | | | |
| D0 | 413 | 413 | 720 | 3100 | 4385 | 6120 | 7970 | 12240 | 12240 |
| D3 | 2925 | 2925 | 4980 | 20839 | 32428 | 43470 | 60630 | 67193 | 67193 |
| D7 | 1150 | 1150 | 1300 | 2240 | 3583 | 5313 | 13400 | 23800 | 23800 |
| D13 | 1200 | 1200 | 1700 | 2260 | 2818 | 4420 | 6310 | 10440 | 10440 |
| **Cycle 4** | | | | | | | | | |
| D0 | 1200 | 1200 | 1700 | 2260 | 2818 | 4420 | 6310 | 10440 | 10440 |
| D3 | 4300 | 4300 | 4450 | 7800 | 22455 | 46040 | 52400 | 57800 | 57800 |
| D7 | 786 | 786 | 1281 | 2000 | 3652 | 5865 | 20774 | 38294 | 38294 |
| D13 | 600 | 600 | 1780 | 2900 | 4611 | 5530 | 7030 | 7770 | 7770 |

*ANC: absolute neutrophil count.
#Cycle: Adriamycin/epirubicin cyclophosphamide.

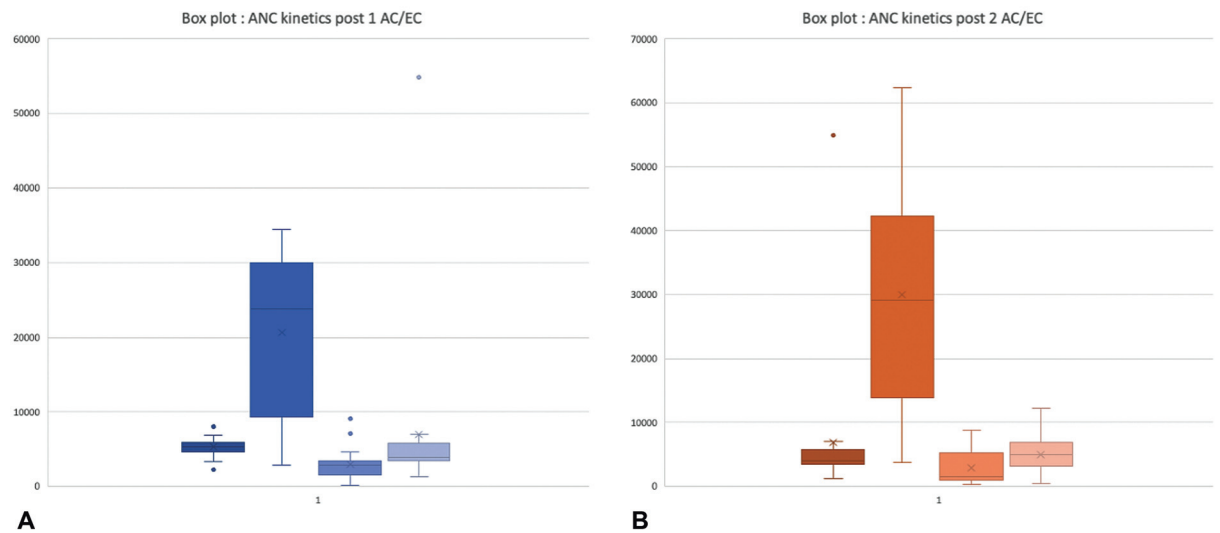


**Fig. 2** Graphical representation of the distribution of absolute neutrophil count post chemotherapy after peg-GCSF 3 mg administration, **A, B, C, D** post 1, 2, 3, 4 cycles, respectively.

 

**Table 3** Requirement of additional dose of G-CSF for maintaining dose density

| Patient | Age | Weight | Centre | Peg-GSCF group | Cycle needing extra dose | extra days G-CSF | Comorbidities |
|---|---|---|---|---|---|---|---|
| 1 | 50 | 76 | A | 1-hour | Fourth | 2 days | Hypertension |
| 2 | 47 | 48 | A | 24-hour* | First | 2 days | No |
| 3 | 45 | 60 | B | 6-hour | Second | 1 day | No |
| 4 | 61 | 53 | B | 24-hour | Second | 1 day | No |
| 5 | 49 | 77 | B | 24-hour | Second | 4 days | No |
| 6 | 44 | 72 | B | 24-hour | Second | 2 days | No |

*Patient carried the Peg-GCF-prefilled syringe home, G-CSF: granulocyte colony-stimulating factor, center A–located in Mumbai, B–located in Kolkata.

## Conclusion

Dose density of AC/EC breast cancer protocol is maintained with peg-GCSF 3 mg. Post chemotherapy 24-hour timing of peg-GCSF administration remains as the standard. A phase 3 trial of 6 mg versus 3 mg is warranted.

### Conflict of Interest

None declared.

### Acknowledgments

We thank all our patients who participated in this study. We also thank Late Prof. Gauri Shankar Bhattacharya who first introduced the low dose concept of Peg GCSF to the first author.

### References

1 Freifeld AG, Bow EJ, Sepkowitz KA, et al; Infectious Diseases Society of America. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis 2011;52(04):e56–e93
2 Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21(08):1431–1439
3 Citron ML. Dose-dense chemotherapy: principles, clinical results and future perspectives. Breast Care (Basel) 2008;3(04):251–255
4 Gray R, Bradley R, Braybrooke J, et al; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet 2019;393(10179):1440–1452
5 Molineux G, Kinstler O, Briddell B, et al. A new form of Filgrastim with sustained duration in vivo and enhanced ability to mobilize PBPC in both mice and humans. Exp Hematol 1999;27(12):1724–1734
6 Kuendgen A, Fenk R, Bruns I, et al. Splenic rupture following administration of pegfilgrastim in a patient with multiple myeloma undergoing autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2006;38(01):69–70
7 Lyman GH, Yau L, Nakov R, Krendyukov A. Overall survival and risk of second malignancies with cancer chemotherapy and G-CSF support. Ann Oncol 2018;29(09):1903–1910
8 Karlin L, Darmon M, Thiéry G, et al. Respiratory status deterioration during G-CSF-induced neutropenia recovery. Bone Marrow Transplant 2005;36(03):245–250
9 Lasagna A, Zuccaro V, Ferraris E, Rizzo G, Tancredi RJ, Pedrazzoli P. How to use prophylactic G-CSF in the time of COVID-19. JCO Oncol Pract 2020;16(11):771–772
10 Morita S, Kikumori T, Tsunoda N, et al. Feasibility of dose-dense epirubicin and cyclophosphamide with subcutaneous pegfilgrastim 3.6 mg support: a single-center prospective study in Japan. Int J Clin Oncol 2018;23(01):195–200
11 Gerberich AJ, Attilio MR, Svoboda A. Revisiting same day administration of pegfilgrastim in the age of biosimilars: a review of literature. J Oncol Pharm Pract 2020;26(08):1970–1976
12 Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP [Internet]. [cited 2020 Dec 3]. Accessed September 13, 2022, at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50
13 Sparano JA, Wang M, Martino S, et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. N Engl J Med 2008;358(16):1663–1671
14 Burstein HJ, Parker LM, Keshaviah A, et al. Efficacy of pegfilgrastim and darbepoetin alfa as hematopoietic support for dose-dense every-2-week adjuvant breast cancer chemotherapy. J Clin Oncol 2005;23(33):8340–8347
15 Ji X, Xu L, Pan P, Xu Z, Wang A, Li Y. Efficacy and safety of 3 mg pegylated recombinant human granulocyte colony-stimulating factor as support to chemotherapy for lung cancer. Thorac Cancer 2022;13(01):117–125
16 Osumi H, Shinozaki E, Wakatsuki T, et al. Is the PEG-G-CSF useful as the prevention for the severe neutropenia in metastatic colorectal cancer patients treated with FOLFOXIRI plus bevacizumab? Ann Oncol 2018;29:v62
17 Masuda N, Tokuda Y, Nakamura S, Shimazaki R, Ito Y, Tamura K. Dose response of pegfilgrastim in Japanese breast cancer patients receiving six cycles of docetaxel, doxorubicin, and cyclophosphamide therapy: a randomized controlled trial. Support Care Cancer 2015;23(10):2891–2898
18 Zhang Z, Li H, Zhang J, et al. Effect of 3 mg versus 6 mg pegfilgrastim on the prevention of febrile neutropenia in breast cancer patients receiving docetaxel and cyclophosphamide: a retrospective study. Ann Palliat Med 2021;10(05):5310–5315
19 Average height of men and women worldwide [Internet]. Worlddata.info. [cited 2021 Nov 23]. Accessed September 09, 2022, at: https://www.worlddata.info/average-bodyheight.php
20 Li X. Is PEGylated G-CSF superior to G-CSF in patients with breast cancer receiving chemotherapy? A systematic review and meta-analysis. Support Care Cancer 2020 Nov;28(11):5085–5097. doi: 10.1007/s00520-020-05603-w. Epub 2020 Jul 3. PMID: 32621264

 